UNIVERSITÀ DI TRENTO

Doctoral Thesis

Understanding Socio-Cognitive Impairments in Parkinson's Disease: from Behavioural to Neuroimaging Characterisation

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“It is imperfection — not perfection — that is the end result of the program written into that formidably complex engine that is the human brain, and of the influences exerted upon us by the environment and whoever takes care of us during the long years of our physical, psychological and intellectual development.”

Rita Levi-Montalcini

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy in the Doctorate in Cognitive and Brain Sciences, University of Trento.

Declaration of Authorship

I hereby declare that the contents and organization of this dissertation constitute original work and do not compromise in any way the rights of third parties, including those relating to the security of personal data.

Data

11 November 2024

Giulia Funghi

Thesis abstract

Parkinson's disease (PD) represents the second most prevalent neurodegenerative disorder. Despite notable advancements in the comprehension of its pathophysiology in recent years and the introduction of updated diagnostic criteria that reflect these developments, the comprehensive understanding of its intricate clinical presentation remains to be further investigated and more precisely delineated. A substantial body of evidence from existing literature has consistently demonstrated the presence of non-motor symptoms in patients with PD, including deficits in social cognition. Nevertheless, socio-cognitive dysfunctions in PD remain a relatively underexplored area, and the available tools for assessing these deficits are limited, particularly in the clinical setting. To address this gap in the existing literature, the present doctoral thesis is structured around three key objectives. The first aim is to improve the characterisation of socio-cognitive dysfunctions in PD in the clinical context. Secondly, the objective is to introduce and evaluate the clinical validity of a novel test designed to assess the ability to recognise complex mental states. Finally, the thesis aims to contribute to the elucidation of the neural correlates underlying deficits in mental state recognition in individuals with PD via magnetic resonance imaging. In order to achieve these aims, three behavioural studies (Study 1-3) and one neuroimaging study (Study 4) have been conducted. The results of this doctoral thesis posit that deficits in socio-cognitive processes can be observed in patients with PD from the early stages of the disease and are associated with structural and functional changes in brain areas involved in emotion understanding. Furthermore, this thesis suggests that a detailed characterisation of early socio-cognitive dysfunctions in PD may facilitate the definition of new cognitive phenotypes and potentially the development of new non-pharmacological interventions (Study 5) tailored to the individual's specific needs.

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The research studies presented here are the result of a collaborative effort. In particular, the Facial Complex Expressions (FACE) test was developed in collaboration with Stefano Terruzzi, joint first author of the manuscript. Moreover, the magnetic resonance imaging results were obtained in collaboration with Giuseppe Rabini, Prof Luca Turella and Chiara Speranza, to whom I would like to

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Last but not least, I would like to dedicate a special thank you to my family and friends for supporting me every day during this journey. They all pushed me out of my comfort zone without ever making me feel far away, supported all my choices and offered valuable advice when I needed it.

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Sincerely thank you.

Giulia Funghi

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List of Abbreviations

ACC	Anterior Cingulate Cortex
Amyg	Amygdala
ATC	Anterior Temporal Cortex
BOLD	Blood Oxygenation Level Dependent
CON	Active Control Group
CRIq	Cognitive Reserve Index questionnaire
CU	Cognitively Unimpaired
dACC	dorsal Anterior Cingulate Cortex
dlPFC	dorsolateral Prefrontal Cortex
dmPFC	dorsomedial Prefrontal Cortex
DSM	Diagnostic and Statistical Manual of Mental Disorders
dTL	dorsal portion of the Temporal Lobe
EBA	Extrastriate Body Area
EK60F	Ekman 60-Faces test
ENG	English-speaking participants
EQ	Equivalent Scores
FACE	Facial Complex Expressions test
FBA	Fusiform Body Area
FC	Functional Connectivity
FDR	False Discovery Rate
FFA	Fusiform Face Area
fMRI	Functional Magnetic Resonance Imaging
GM	Grey Matter
HC	Healthy Controls
IFG	Inferior Frontal Gyrus
ILFC	Inferior Lateral Frontal Cortex
Ins	Insula
iPD	idiopathic Parkinson’s Disease
IPL	Inferior Parietal Lobe
ISELS	Italian Social and Emotional Loneliness Scale
ITA	Italian-speaking participants
LEDD	Levodopa Equivalent Daily Dose

MCI	Mild Cognitive Impairment
MDS	Movement Disorder Society
Mini-SEA	Mini-Social cognition & Emotional Assessment battery
MNI	Montreal Neurological Institute
MoCA	Montreal Cognitive Assessment
mPFC	medial Prefrontal Cortex
MRI	Magnetic Resonance Imaging
mTL	medial Temporal Lobe
OFA	Occipital Face Area
OFC	Orbitofrontal Cortex
PCC	Posterior Cingulate Cortex
PCu	Precuneus
PD	Parkinson’s Disease
PD-CU	PD patients cognitively unimpaired
PDD	Parkinson's Disease Dementia
PD-IMP	PD patients classified as impaired on the FACE test
PD-MCI	Parkinson’s Disease – Mild Cognitive Impairment
PD-UN	PD patients classified as unimpaired on the FACE test
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
pSTS	Posterior Superior Temporal Sulcus
RAVLT	Rey Auditory Verbal Lists Test
RBD	REM Sleep Behaviour Disorder
REM	Rapid Eye Movement
RMET	Reading the Mind in the Eyes Test
ROC	Receiver Operating Characteristic curve
ROCF	Rey-Osterrieth Complex Figure
ROI	Region of Interest
RRC	ROI-to-ROI Connectivity
rs-fMRI	Resting-state functional MRI
S1/S2	Primary and Secondary Somatosensory Cortices
SBC	Seed-based Connectivity
SCD	Subjective Cognitive Decline
SCOT	Social and Cognitive Online Training

SET	Story-Based Empathy task
SET-CI	SET-Causal Inference
SET-EA	SET-Emotion attribution
SET-IA	SET-Intention attribution
SPECT	Single-Photon Emission Computed Tomography
STS	Superior Temporal Sulcus
TIV	Total Intracranial Volume
ToL	Tower of London
ToM	Theory of Mind
TPJ	Temporo-Parietal Junction
UPDRS	Unified Parkinson's Disease Rating Scale
vACC	ventral Anterior Cingulate Cortex
VBM	Voxel-Based Morphometry
vlPFC	ventrolateral Prefrontal Cortex
vmPFC	ventromedial Prefrontal Cortex
vTL	ventral portion of the Temporal Lobe

List of Publications

Papers in peer-reviewed journals

Included in this thesis

Funghi, G., Meli, C., Cavagna, A., Bisoffi, L., Zappini, F., Papagno, C., & Dodich, A. (2024). The Social and Cognitive Online Training (SCOT) project: A digital randomized controlled trial to promote socio-cognitive well-being in older adults. *Archives of gerontology and geriatrics*, *122*, 105405. https://doi.org/10.1016/j.archger.2024.105405

Terruzzi, S.*, **Funghi**, G.*, Meli, C., Barozzi, N., Zappini, F., Papagno, C., & Dodich, A. (2023). The FACE test: a new neuropsychological task to assess the recognition of complex mental states from faces. *Neurological sciences: official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, *44*(7), 2339–2347. https://doi.org/10.1007/s10072-023-06697-w **co-first authors*

Dodich, A., **Funghi**, G., Meli, C., Pennacchio, M., Longo, C., Malaguti, M. C., Di Giacopo, R., Zappini, F., Turella, L., & Papagno, C. (2022). Deficits in Emotion Recognition and Theory of Mind in Parkinson's Disease Patients With and Without Cognitive Impairments. *Frontiers in psychology*, *13*, 866809. https://doi.org/10.3389/fpsyg.2022.866809

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Chapter 1 : General introduction

As many students who enter university with a clear trajectory in mind, only to find that their academic journeys take unexpected turns and lead them into areas of study they had not initially anticipated, neuropsychology happened to cross my path by chance and has immediately exhibited an incredible attraction. Neuropsychology is a relatively recent branch of science that investigates the physiological processes that underpin the relationship between the nervous system and both cognition and behaviour. This field of study focuses on the examination of brain functioning, encompassing both normal processes and those disrupted by brain damage or pathology (American Psychiatric Association, 2013). The study of brain architecture and the heterogeneity of clinical manifestations resulting from minor or massive changes in the brain, as well as their impact on everyday life, has historically stimulated the interest of both clinicians and researchers and continues to exert a strong appeal. Furthermore, neuropsychology encompasses both experimental and clinical dimensions. The experimental approach focuses on elucidating the neural correlates of behaviour and cognitive processes in both healthy subjects and patients through the use of controlled laboratory experiments. In contrast, the clinical dimension is oriented towards the application of knowledge about the relationship between the brain and behaviour and cognition to the "*diagnosis of brain disorders, the assessment of cognitive and behavioural functioning, and the design of effective treatments"* (American Psychiatric Association, 2013). Collaboration and joint efforts between experimental and clinical neuropsychology are essential for advancing our understanding of the relationship between the brain and behaviour/cognition, since experimental research provides the basic knowledge that informs clinical practice, while clinical evidence helps to refine experimental hypotheses and methods. For a considerable period of time, clinical neuropsychology was based entirely on the objective examination of behaviour by the clinician, supported by a few practical tests and anecdotal reports from informants (who are now referred to as "carers" or "caregivers"). However, over the time, the necessity for more precise, standardised, and quantitative procedures became evident. This

resulted in the development of a wide range of assessment tools, including paper-and-pencil tests and rating scales, designed to more accurately characterise cognitive deficits and assist clinicians in formulating diagnoses. The advent of new technologies has subsequently led to the development of innovative tools that have transformed the field and shaped contemporary scientific research. A major contributor to this revolution has been the advent of magnetic resonance imaging (MRI), which has enabled the non-invasive measurement of biological indicators in the brain (*neuroimaging biomarkers*), including grey matter volume, cortical thickness, blood flow, resting-state functional connectivity, white matter integrity, receptor activity and metabolism. These indicators have the potential to provide insight into the diagnosis, the disease progression, the response to treatment and the underlying mechanisms of neurological and psychiatric disorders. Combined with sophisticated data processing techniques and other biological markers (e.g., cerebrospinal fluid), MRI facilitates a deeper understanding of brain structures and functions in a completely non-invasive manner, significantly advancing both basic neuroscience and clinical diagnostics. In the field of neurocognitive disorders, the recent advances in the development of biomarkers have resulted in a paradigm shift in the diagnostic framework, moving away from a clinical-neuropsychological approach towards a clinical-biological one (Dubois et al., 2010). Nevertheless, neuropsychological testing is still crucial for confirming the presence of cognitive difficulties, orienting the diagnostic hypothesis, deciding upon the use of potentially invasive and/or expensive biomarkers, phenotyping neurocognitive disorders, reliably monitoring and staging the clinical progression of diseases (not yet fully captured by biomarkers), designing and monitoring the efficacy of interventions (Frisoni et al., 2024). Therefore, despite the paradigm shift in the diagnostic framework, a comprehensive neuropsychological assessment remains essential for the identification of neurocognitive disorders prior to proceeding with in vivo confirmation of the diagnosis through the use of biomarkers.

Similar to other neurocognitive disorders such as Alzheimer's and Huntington's diseases, a significant shift in the diagnostic approach towards a biological definition has recently been advocated in

Parkinson's disease (PD). This transition aims to facilitate earlier diagnosis and disease course-modifying therapy (Kulcsarova et al., 2024). However, despite the recent proposal of two biological classification and/or staging systems for PD (both of which focus on alpha-synucleinopathy and evidence of neurodegeneration) (Höglinger et al., 2024; Simuni et al., 2024), the current status of biological markers in PD only allow for indication of the presence or absence of a particular characteristic or condition associated with PD, rather than providing more nuanced or graded information on disease progression, or response to treatment of the disease (Kulcsarova et al., 2024). Consequently, the definition of PD today remains clinically based, focusing on the core symptoms and supportive/exclusive criteria. Moreover, the clinical manifestations of the disease remain a fundamental aspect of PD phenotyping.

PD is clinically characterised by the presence of distinct motor and non-motor symptoms. It is now widely acknowledged that among the non-motor symptoms, cognitive impairment has a significant impact on the quality of life of people affected by the disease. While cognitive impairment has been extensively investigated in PD individuals (Aarsland et al., 2021; Poewe et al., 2017), social cognition has only recently attracted the attention of researchers and clinicians interested in the study of PD. This is particularly the case with regard to the identification of early markers of the disease. Social cognition can be defined as the ability to perceive, interpret and respond to the emotions, intentions and behaviours of others. This ability is crucial for successful social interactions, relationships and effective performance in social contexts. Conversely, socio-cognitive impairments can result in social withdrawal, a reduction in communication, and difficulties in maintaining personal and professional relationships (Dickerson, 2015).

Despite its importance for optimal functioning in everyday life, socio-cognitive dysfunctions in PD remain under-researched and poorly understood. Even though social deficits have been previously reported in individuals with PD, the extent of these impairments remains unclear. Moreover, social cognition is still excluded from the cognitive domains considered in the current criteria for mild

cognitive impairment (MCI) in PD (PD-MCI) (Litvan et al., 2012) and it is not commonly included in the routine clinical assessment (Cerami et al., submitted). In this context, the present thesis aims to enhance the characterisation of socio-cognitive dysfunctions in PD in clinical setting, as well as to investigate the extent, clinical relevance, early manifestations, and neural underpinnings of these deficits. Finally, this thesis will suggest a potential intervention that may effectively target these impairments.

Structure of the Thesis

This thesis is presented as a collection of articles, each addressing a specific research question related to socio-cognitive deficits in PD.

The opening section of the thesis (Chapter 2) will present a comprehensive introduction to PD, encompassing epidemiological data, pathological mechanisms, clinical features and diagnostic criteria. Subsequently, a description of the cognitive impairment associated with this clinical condition will be provided. The chapter will proceed with a detailed examination of the complex domain of social cognition and the neural substrates of its constituent processes, including social perception, emotion processing and understanding, theory of mind (ToM), empathy, and social behaviour. In conclusion, this section will describe the social cognitive deficits that can be observed in PD individuals, as well as the results of the scarce existing literature on the neural correlates of these deficits.

This overview of the current state of research on PD, social cognition, and its alterations in affected patients will be followed by an examination of unresolved issues in the scientific literature, with a particular focus on their clinical implications. Indeed, it is the intention of this thesis to contribute to the narrowing of the gap between theoretical research and neuropsychological practice. While the gap remains considerable, it is hoped that these two fields will increasingly converge in order to

facilitate more effective diagnosis, assessment and intervention strategies for socio-cognitive impairments in PD.

In particular, three specific research questions will be addressed in Chapters 3, 4 and 5, respectively. The objective of **Study 1** (Chapter 3) is to ascertain whether socio-cognitive dysfunctions are clinically significant in PD. To this end, the social cognitive abilities of PD individuals with and without MCI are examined and compared with those of a group of healthy controls (matched for demographic variables). In order to interpret the performance clinically, social cognitive abilities are evaluated through tests that have been validated in Italy for emotion recognition and ToM. Nevertheless, a comprehensive characterisation of socio-cognitive dysfunctions in clinical populations is significantly constrained by the paucity of social cognition tests that have been adapted for clinical use (Cerami et al., submitted). The recognition of this limitation, together with the growing body of evidence indicating the importance of social cognition as an early marker in neurodegenerative diseases (Elamin et al., 2012), for distinguishing between disease subtypes (Ibañez et al., 2021) and for differential diagnosis in dementias (Christidi et al., 2018; Maresca et al., 2020; Setién-Suero et al., 2022), prompted the decision to develop a novel task with the objective of enhancing the characterisation of social cognitive abilities in clinical setting. To address this issue, the FAcial Complex Expressions (FACE) test was developed as a novel tool to assess the recognition of complex mental states from facial expressions. The primary objective of **Study 2** (Chapter 4) is to present this test, describing the methodology employed in its development, the standardisation procedure and its clinical validation in PD individuals. Furthermore, Study 2 seeks to ascertain whether emotional processing is affected early in PD, as preliminary evidence from the literature indicates that socio-cognitive impairments are present even in the early stages of the disease (Czernecki et al., 2021). Given the growing interest in the validity and reliability of neuropsychological diagnostic instruments in a linguistically and culturally rich context such as

Europe, **Study 3** (Chapter 4) presents the preliminary results of the cross-cultural validation of the FACE test in Italian and English-speaking healthy older adults.

The final research question addressed in this thesis concerns the neural correlates of emotional processing deficits observed in PD individuals. The aim of **Study 4** (Chapter 5) is to examine the relationship between deficits in the recognition of complex mental states and both structural and functional brain changes in PD individuals, classified as clinically impaired or unimpaired based on their performance on the FACE test (according to Italian normative data provided in Study 2). Specifically, Study 4 first examines the association between FACE test performance and both resting-state functional connectivity and grey matter volume in a selected group of brain regions, as described in the scientific literature as the emotion understanding network (Spunt & Adolphs, 2019). Subsequently, as an exploratory aim, this study investigates the association between FACE performance and functional/structural brain metrics at a whole-brain level. This could potentially extend our understanding of the network of regions involved in emotion dysfunction in these patients.

The thesis will conclude with a **general discussion** (Chapter 6) highlighting the importance of the overall research in addressing critical gaps in the study of socio-cognitive deficits in PD. Limitations of the research project and remaining open questions will also be critically examined in order to suggest avenues for future research.

By establishing the clinical relevance of these impairments, demonstrating their early manifestation, their clinical value and identifying their neural correlates, this thesis aims to provide a comprehensive framework for future research and clinical practice. Within this framework, the thesis will also present in the **Appendix** a potential intervention that may prove effective in targeting socio-cognitive deficits. Indeed, a comprehensive description of the early socio-cognitive deficits observed in clinical populations represents a valuable resource for the development of new non-pharmacological interventions, tailored to the specific needs of the individual. To the best of my knowledge, no previous studies have tested the effects of digital training programs targeting both social cognitive

and executive skills in healthy older people, nor in a PD clinical population. To address this gap in the literature, **Study 5** pilot tests the efficacy of the Social and Cognitive Online Training (SCOT) project in a sample of healthy older people. This study aims to compare the efficacy of a multidimensional online intervention with that of non-specific cognitive stimulation in improving socio-executive functioning. Although the study was conducted in healthy older participants, this research paves the way for the future implementation of similar interventions in PD individuals with early socio-cognitive and executive deficits (Guglietti et al., 2021), suggesting a potential avenue for mitigating these deficits through targeted training.

Chapter 2 : Parkinson's Disease and Social Cognition Deficits

2.1. Parkinson's Disease

2.1.1. Epidemiology

Parkinson's disease (PD) represents a significant socio-economic issue and a global priority (Ben-Shlomo et al., 2024), ranking as the second most common neurodegenerative disorder after Alzheimer's disease (Aarsland et al., 2021; Kulcsarova et al., 2024). Notwithstanding the global epidemiological variations observed over time, across different geographical regions, ethnic groups, ages and sex, the international prevalence has demonstrably increased beyond the influence of demographic changes (Ben-Shlomo et al., 2024). Indeed, the most recent prevalence estimates indicate that PD affects 1% of the population ≥60 years of age and 3% ≥80 years old (Balestrino & Schapira, 2020; Lee & Gilbert, 2016). This rising prevalence of PD can be attributed to several potential reasons, including a reduction in mortality from other competing causes, prolonged disease duration, exposure to industrial toxicants and global population ageing (Ben-Shlomo et al., 2024; Grotewold & Albin, 2024). Furthermore, given that age is the most significant risk factor for the disease (Ben-Shlomo et al., 2024; Lee & Gilbert, 2016), it is projected that prevalence will double by 2030 (Simon et al., 2020). The same overall trajectory of age-related prevalence increase was also observed in the Global Burden of Disease Study (Ray Dorsey et al., 2018), which lends support to an age-dependent PD model with maximal risk concentrated in the ninth decade of life (Grotewold & Albin, 2024).

In contrast, the evidence regarding whether the incidence of newly diagnosed PD is steadily increasing worldwide is less certain due to the lack of trend analyses over the centuries and the paucity of high-quality data from all countries (Ben-Shlomo et al., 2024). Overall, the age-adjusted incidence rate is approximately 13/100'000 new cases per year, with an annual increasing trend of 0.61% from 1990 to 2019 (Ou et al., 2021). Additionally, the incidence of the disease increases markedly from the sixth to the ninth decade of life (Simon et al., 2020), reaching its peak in the eighth decade

(Grotewold & Albin, 2024). Nevertheless, it remains unclear whether age-standardised PD incidence has changed over the last few decades, with several studies suggesting that incidence rates have been relatively stable, or have even declined modestly, over this period (Grotewold & Albin, 2024).

Epidemiological and clinical studies have indicated significant sex differences in PD in the prevalence, incidence, and mortality risk, with a male-to-female ratio of approximately 1,4:1 (Ben-Shlomo et al., 2024; Grotewold & Albin, 2024). While the estimated prevalence ratio has remained constant (Ray Dorsey et al., 2018) or exhibited a slight decline (Zirra et al., 2023) over the past two or three decades (Ben-Shlomo et al., 2024), the incidence ratio has increased over time in men and remained stable in women (Ben-Shlomo et al., 2024; Hirsch et al., 2016). The reasons for the observed sex differences in incidence remain unclear, but potential explanations include greater exposure of men to adverse environmental risk factors and the protective effect exerted by female hormones (Ben-Shlomo et al., 2024). Moreover, there seem to be variations in PD risk across different geographical regions, ethnicities, and races. Such discrepancies may be attributed to differences in accessibility to healthcare and educational resources, as well as differing levels of socioeconomic status within countries. For instance, occupational and passive exposure to pesticides may be a contributing factor in the observed rise in low- and middle-income countries, whereas air pollution may be a more significant issue in industrialised, high-income countries.

The integration of data from epidemiological and clinical studies is also crucial for the identification of causal determinants of PD. The aetiology of the disease is complex and multifactorial, involving a range of intrinsic and extrinsic factors (Ben-Shlomo et al., 2024). These include environmental agents (e.g., pesticides), lifestyle behaviours (e.g., dietary habits, physical activity or cigarette smoking), physical factors (e.g., traumatic brain injury whose sequelae may also depend on genetic vulnerability), individual genetic predisposition to the disease, metabolic status (for instance, elevated urates) and the presence of comorbidities (such as diabetes) (Ben-Shlomo et al., 2024). It is beyond the scope of this chapter to address all potential contributing factors to the onset of PD, however it is

important to note that genetic mechanisms often operate and interact with environmental factors, that certain determinants may exert a differential influence on disease risk in men and women, and that the majority of cases of PD result from a combination of environmental exposure and genetic predisposition (Ben-Shlomo et al., 2024; Bogers et al., 2023). Despite significant advancements in research, the aetiology of the disease remains unknown in the majority of cases (Balestrino & Schapira, 2020), clinically defined as idiopathic PD (iPD).

2.1.2. Pathology

Researchers and clinicians widely agree on the clinicopathological definition of PD as a slowly progressive multisystem neurodegenerative disorder (Kulcsarova et al., 2024). The pathological hallmarks of this disease are the loss of dopaminergic neurons in the substantia nigra (particularly in the pars compacta) and the widespread intracellular α-synuclein protein deposition (Poewe et al., 2017). These two major neuropathologic feature are specific for a diagnosis of iPD when applied together (Poewe et al., 2017).

The substantia nigra (divided into pars compacta containing dopaminergic neurons and pars reticulata containing GABA neurons), forms part of the basal ganglia along with the globus pallidus (externus and internus), the subthalamic nucleus and the striatum (comprising the nucleus accumbens, the caudate and the putamen) (Rocha et al., 2023). This cluster of subcortical nuclei is primarily involved in motor control, acting as a sophisticated gatekeeper for the initiation of motor movement by selecting actions to inhibit or disinhibit (Young et al., 2024). Additionally, the basal ganglia are implicated in cognitive, affective and motivational functions due to their projections to limbic and prefrontal regions (Obeso, Rodríguez-Oroz, et al., 2008; Young et al., 2024).

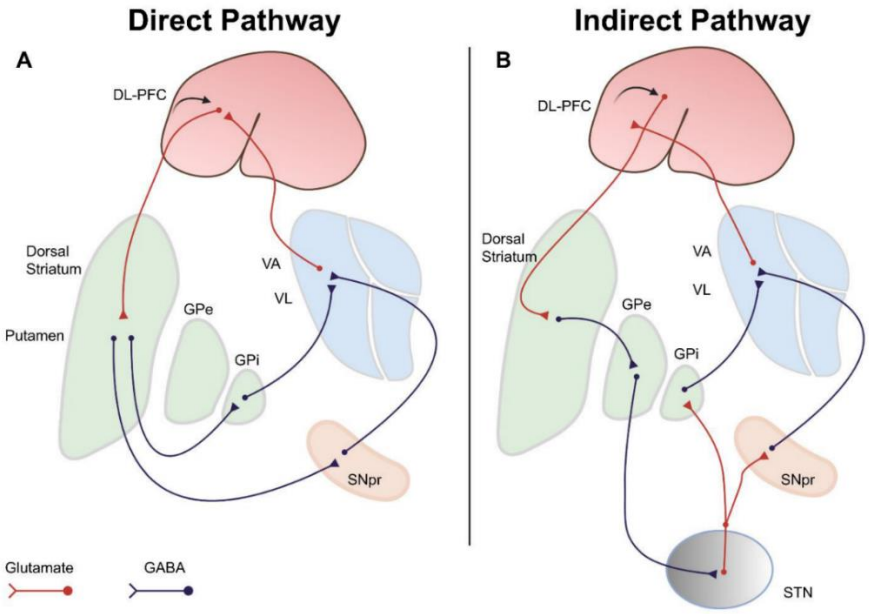
The contribution of the basal ganglia to both motor and non-motor functions is contingent upon their anatomo-functional organization. Indeed, each nucleus is topologically organised and has partially segregated connections to the motor, associative, and limbic areas (Obeso, Rodríguez-Oroz, et al.,

2008; Papagno & Trojano, 2018). Specifically, as *afferent nuclei*, the caudate nucleus and the putamen (dorsal striatum) receive corticostriatal inputs that are related to motor control and executive functioning, whereas the nucleus accumbens (ventral striatum) receives inputs related to emotions, reward and aversion from the cingulate and orbital cortices (Rocha et al., 2023; Young et al., 2024). The internal section of the globus pallidus and the substantia nigra pars reticulata (*efferent nuclei*) project primarily to the thalamus, which, in turn, send projections back to the cerebral cortex (mainly the frontal lobe) (Lanciego et al., 2012; Rocha et al., 2023). The external section of the globus pallidus, the subthalamic nucleus and the substantia nigra pars compacta (*intrinsic nuclei*) are implicated in circuits between the components of the basal ganglia, acting as a relay for information (Lanciego et al., 2012; Rocha et al., 2023; Young et al., 2024). Moreover, the basal ganglia are connected with subcortical structures, including the superior colliculus, the pedunculopontine nucleus, the periaqueductal grey, the pontine nuclei, and the medullary reticular formation (Papagno & Trojano, 2018).

The proper functioning of the basal ganglia system depends on the release of dopamine at the input nuclei, most notably the striatum (Lanciego et al., 2012). Consequently, the dopaminergic deficiency in the substantia nigra, which is a hallmark of PD, results in dysfunction in the basal ganglia and, subsequently, in cortico-striatal-thalamic-cortical circuits that underpin motor, cognitive and behavioural functions (Papagno & Trojano, 2018). Indeed, *the direct/indirect pathway model* proposed by DeLong (1990) posits that projections from the frontal cortex to the substantia nigra pars reticulata and the globus pallidus internus constitute the *direct pathway* of the cortico-striatal-thalamic-cortical loops. This pathway has the effect of disinhibiting the thalamic neurons that project back to the cortex, which in turn results in motor activation. In contrast, projections from the frontal cortex to the substantia nigra pars reticulata via the globus pallidus externus and the subthalamic nucleus constitute the *indirect pathway*. This pathway inhibits the thalamo-cortical projections, thereby reducing motor responses (DeLong, 1990; Papagno & Trojano, 2018). To clearly understand

the activity of both direct and indirect pathways is essential to mention the functioning of the *nigrostriatal dopaminergic system* (Rocha et al., 2023). Indeed, the dopamine released by the substantia nigra pars compacta acts throughout the striatum and, by binding both D1 and D2 receptors on neurons respectively projecting to the efferent nuclei and the globus pallidus externus, simultaneously activates the direct pathway and inhibits the indirect pathway (Gerfen & Surmeier, 2011). However, the activity of the nigrostriatal pathway is determined by excitatory projections from the cortex to the substantia nigra and inhibitory projections from the striatum to the nigra (Figure 1). The degeneration of dopaminergic neurons in the substantia nigra (pars compacta) caused by PD results in an imbalance between the two pathways (DeLong, 1990; Papagno & Trojano, 2018). Specifically, the direct pathway is continuously inhibited (resulting in a reduction in motor activation), while the indirect pathway is always active (thereby reducing motor responses) (Obeso et al., 2000; Rocha et al., 2023). Collectively, these mechanisms cause an excessive inhibition of thalamic neurons projecting to the cortex (DeLong, 1990; Papagno & Trojano, 2018; Rocha et al., 2023).

Figure 1. *Direct and indirect pathways in the basal ganglia*



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Although the model was originally formulated to understand the pathophysiology of movement (DeLong, 1990; Lanciego et al., 2012) and still offers a solid framework for interpreting PD and other motor disorders (Papagno & Trojano, 2018), subsequent research has demonstrated that parallel circuits within the basal ganglia are responsible for other functions (such as executive functions and emotions), through their engagement with associative and limbic areas (Lanciego et al., 2012; Obeso, Rodríguez-Oroz, et al., 2008). Indeed, while the nigrostriatal pathway plays a primary role in the execution of movements and decision-making processes, the dopaminergic neurons of the ventral tegmental area of substantia nigra extend their projections to both ventral regions of the striatum (nucleus accumbens) and the ventromedial prefrontal cortex, thereby constituting two distinct pathways: the mesolimbic and the mesocortical pathways (Haber, 2014; Trojano & Papagno, 2018). The mesocortical pathway projects from the ventral tegmental area to the prefrontal cortex and is involved in cognitive functions such as working memory, attention, and executive decision-making. The mesolimbic pathway, which projects to the nucleus accumbens and other limbic regions, is crucial for emotion and reward processing, as well as motivation and reinforcement of behaviours (Halliday et al., 2014). Although the loss of dopamine in the mesocortical and mesolimbic regions is less pronounced than that in the nigrostriatal projections (Barone et al., 2011), behavioural symptoms of PD may result from the disruption of these two pathways (Trojano & Papagno, 2018).

In light of the latest evidence from the scientific literature, the original functional model has been revised. It is now understood that the basal ganglia comprise multiple loops, in which cortical and subcortical projections interact with internal re-entry loops to form a complex network optimally designed for the selection and inhibition of concurrent events and signals (Lanciego et al., 2012).

A series of recent resting-state functional Magnetic Resonance Imaging (rs-fMRI) studies have consistently demonstrated a reduction in connectivity within the fronto-striatal pathways in patients diagnosed with PD (Papagno & Trojano, 2018; Xu et al., 2016). This reduction in connectivity has been observed to underlie not only the motor features associated with PD, but also the cognitive and

behavioural changes that are commonly observed in patients (Papagno & Trojano, 2018; Schapira et al., 2017). However, as the disease progresses, dysfunction of the fronto-striatal pathways may be associated with alterations in the posterior cortical regions, resulting in intricate rearrangements of cerebral activity (Papagno & Trojano, 2018).

Although some symptoms characteristic of PD (i.e., impairments in executive functions and other related cognitive changes) can be explained by the dopamine-dependent fronto-striatal dysfunction, several other cognitive and behavioural disturbances (such as long-term memory deficits, sleep disorders, hyposmia and depression), appear to be associated with the involvement of different neurotransmitter systems (Papagno & Trojano, 2018; Schapira et al., 2017). Indeed, the latest research suggests that *non-dopaminergic systems*, including *cholinergic, serotonergic and noradrenergic pathways*, also play a significant role in these non-motor symptoms (Aarsland et al., 2021; Bonnet et al., 2012; Papagno & Trojano, 2018; Wolters, 2009). In particular, with respect to cognitive decline, a dopaminergic deficit is observed in the initial stages of PD-MCI in the caudate nucleus, with subsequent progression to limbic and neocortical brain regions in Parkinson's disease dementia (PDD). Similarly, deficits in noradrenergic and cholinergic neurotransmission are observed in the brains of PD patients with normal cognition. However, these deficits become progressively more widespread with increasing severity of cognitive impairment in PD. Conversely, serotonin deficits have been identified in PD, though they are not directly related to cognitive decline (Aarsland et al., 2021). The involvement of different neurotransmitter systems in non-motor PD dysfunction is also supported by the limited effect of levodopa treatment on them (Papagno & Trojano, 2018) and their association with the progression of extra-nigral Lewy body pathology in PD (Wolters, 2009).

As previously stated, another hallmark of PD is the aggregation of abnormally folded α-synuclein protein in neuronal cell bodies (Lewy bodies) and processes (Lewy neurites) across multiple brain regions (Kalia & Lang, 2015; Obeso et al., 2017; Poewe et al., 2017). The Lewy pathology initially manifests in monoaminergic and cholinergic brainstem neurons, as well as in neurons within the

olfactory system. However, with disease progression, it is also observed in limbic and neocortical brain regions (Poewe et al., 2017).

Recent research has demonstrated that the pathology of PD is more intricate than was previously thought, extending beyond the neurodegeneration caused by Lewy bodies pathology. Proteins other than α-synuclein may interact with Lewy pathology, contributing to the clinical expression of PD. Additionally, the identification and characterisation of monogenic forms of PD have revealed that this clinical condition can occur in the absence of Lewy pathology (Kalia & Lang, 2015).

Lastly, neuroinflammation is another characteristic feature of PD pathology but whether it promotes or protects from neuro degeneration has yet to be established (Kalia & Lang, 2015).

2.1.3. Clinical features

Due to the involvement of cortical and subcortical regions involved in motor, cognitive and affective functioning, PD is clinically characterised by a heterogeneous constellation of motor and non-motor symptoms, which result in different clinical phenotypes (Balestrino & Schapira, 2020).

The cardinal *motor symptoms* are bradykinesia (slowness in initiating voluntary movements and a reduction in the amplitude or speed of movements as they continue), rest tremor, muscular rigidity, and in more advanced stages postural instability (not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction) (Hughes et al., 1992; Jankovic, 2008; Lees et al., 2009; Poewe et al., 2017). Empirical clinical observations indicate the existence of two principal subtypes of PD: a tremor-dominant subtype, characterised by the absence of other motor symptoms, and a non-tremor-dominant subtype, which encompasses phenotypes such as akinetic-rigid syndrome and postural instability gait disorder. An additional subgroup of patients with PD presents with a mixed or indeterminate phenotype, exhibiting a combination of motor symptoms of comparable severity. The course and prognosis of the disease differ between the subtypes, with the former often associated with

a slower rate of progression and less functional disability than the latter (Kalia & Lang, 2015). However, other secondary motor symptoms may also be observed, including gait disturbances and freezing, dysarthria, alterations in blinking and eye movements, hypomimia and micrographia (Balestrino & Schapira, 2020). The onset of motor symptoms is typically unilateral, with the asymmetry persisting throughout the disease course (Poewe et al., 2017). The mean age of onset is the late fifties, with a broad range from 40 to over 80 years old. Nevertheless, there are cases of young-onset PD, defined as onset at less than 45 years of age, which have typically genetic basis (Poewe et al., 2017). Furthermore, the efficacy of levodopa treatment in alleviating motor symptoms is a crucial aspect of PD, and it is also necessary to satisfy the diagnostic criteria (Balestrino & Schapira, 2020; Kulcsarova et al., 2024).

Although PD has historically been defined as a movement disorder, *non-motor symptoms* represent an important aspect of the clinical picture (Schapira et al., 2017). These latter comprise neurobehavioural disturbances (such as apathy, anxiety, depression, impulse control disorders, psychoses, hallucinations, fatigue, disorders of emotion processing), sensory impairment (mostly hyposmia), sleep disorders (such circadian rhythm alterations, excessive daytime sleepiness, rapid eye movement (REM)-sleep behaviour disorder (RBD)), autonomic dysfunction, pain, fatigue and cognitive deficits (Kalia & Lang, 2015; Papagno & Trojano, 2018; Poewe et al., 2017; Trojano & Papagno, 2018). Non-motor features are frequently observed in patients with *early-stage PD* (Kalia & Lang, 2015; Postuma et al., 2015) and some of these may precede the onset of classic motor dysfunction by more than a decade (*premotor or prodromal PD*) (Kalia & Lang, 2015; Poewe et al., 2017). As the pathology progresses, non-motor disturbances become increasingly evident, affecting the quality of life, influencing the overall disability and prompting institutionalization (Poewe et al., 2017; Schapira et al., 2017). It is therefore crucial to detect them early and intervene promptly to reduce their negative impact on patients' independence, as well as on cognitive and social functioning.

It is hypothesised that the pathogenic process which causes PD is already underway during the *premotor or prodromal phase*, involving the dopaminergic neurons of the substantia nigra pars compacta along with regions of the peripheral and central nervous system. Consequently, this prodromal phase represents a window of opportunity for the administration of disease-modifying therapies, with the objective of preventing or delaying the development and progression of the disease (Kalia & Lang, 2015). However, while a response to dopaminergic treatment is initially a requisite criterion for diagnosing PD (Kulcsarova et al., 2024), complications arise due to long-term symptomatic treatment as the disease progresses. This presents significant a challenge in the clinical management of late-stage patients and in predicting hospitalisation and mortality (Kalia & Lang, 2015).

In cases where patients manifest the complete and fully-developed motor characteristics associated with PD, the clinical diagnosis may appear relatively straightforward (Poewe et al., 2017). However, at the early stages of the disease, there is a considerable risk of misdiagnosis (Poewe et al., 2017). The accuracy of a clinical diagnosis of PD can be enhanced by the rigorous application of established clinical criteria. Nevertheless, even with these measures, the diagnostic accuracy at the initial visit remains only marginally above 80% (Rizzo et al., 2016). These findings emphasise the necessity for research efforts to enhance diagnostic accuracy in early disease stages or to facilitate the diagnosis of PD in its prodromal phases (Poewe et al., 2017).

2.1.4. Clinical diagnosis

Over time, several sets of clinical diagnostic criteria have been proposed in the scientific literature for the diagnosis of PD. These criteria have been refined to reflect a more comprehensive understanding of the disease and to improve diagnostic accuracy (Kulcsarova et al., 2024).

The UK Brain Bank Criteria (Hughes et al., 1992) proposed the first set of criteria for iPD, focusing on the presence of bradykinesia together with at least one of rigidity, postural instability or resting tremor as essential features for diagnosis.

Gelb's diagnostic criteria (Gelb et al., 1999) further refined these guidelines by incorporating additional elements such as asymmetric onset of symptoms, a good response to levodopa, and the absence of atypical features to support the diagnosis of PD. Gelb's criteria also outlined three levels of diagnostic confidence: possible, probable, and definite PD. These levels assist clinicians in assessing the certainty of a PD diagnosis based on specific clinical manifestations and therapeutic responses.

In 2015, the Movement Disorder Society (MDS) introduced its own clinical diagnostic criteria for PD (Postuma et al., 2015), initially designed for research but also applicable in clinical settings. These criteria define parkinsonism by the presence of bradykinesia, together with either rigidity or resting tremor. The authors proposed two levels of diagnostic certainty: clinically established PD and probable PD.

The principal benefit of the MDS criteria is that they outperformed the UK Brain Bank criteria in differentiating iPD from atypical or secondary parkinsonism (Malek et al., 2017). On the other hand, no specific indication has been provided to detect PD patients in the preclinical or prodromal disease stage.

To address this limitation, the MDS proposed research criteria for *prodromal PD* in 2015 (Berg et al., 2015), with an update in 2019 (Heinzel et al., 2019). These new criteria emphasise the importance of assessing a range of risk factors and prodromal markers for PD, including motor and non-motor symptoms, sex, exposure to toxic agents, response to dopaminergic therapy, and neuroimaging findings. They have gained considerable acceptance and are oriented towards clinical practice. Furthermore, they accord greater significance to non-motor symptoms and show satisfactory specificity in validation studies conducted with a selected cohort. It should be noted, however, that

they are not without limitations. These criteria do not fully reflect the underlying biological processes, as they lack histopathological confirmation and molecular markers. Moreover, they demonstrate low sensitivity in the general population unless specific markers (such as DaTscan or polysomnography-confirmed RBD), are included. Lastly, these criteria are weighted towards RBD-positive prodromal subtypes, which limits their applicability to other prodromal PD subtypes (Kulcsarova & Skorvanek, 2024).

These different sets of clinical diagnostic criteria have played a pivotal role in standardising the diagnosis of PD, providing clinicians with a framework for identifying key features and differentiating iPD from other causes of parkinsonism, atypical forms (multiple system atrophy, corticobasal degeneration, progressive supranuclear palsy), secondary forms (e.g., vascular, infectious, drug or toxin-induced, metabolic, post-traumatic or related to normo-pressure hydrocephalus), and hereditary neurodegenerative disorders with parkinsonism as one of possible manifestations (e.g., Wilson's or Huntington's disease), recognising a relevant role for both motor and non-motor symptoms. As our understanding of the pathophysiology of PD has advanced, the limitations of relying solely on clinical symptoms for diagnosis have become apparent, prompting a shift towards advocating for a biological definition of PD, similar to approaches taken in other neurodegenerative diseases (i.e., Alzheimer's and Huntington's diseases). Such efforts aim to improve early detection of the disease, possibly including pre-symptomatic stages, and to classify of patients on the basis of biological markers rather than just clinical symptoms detection. This would facilitate the development of personalised treatment approaches and improve overall disease management (Kulcsarova et al., 2024).

Despite the extensive revisions made to the diagnostic criteria for PD over time, the Hoehn & Yahr scale (1967) remains the most widely used for staging PD. The scale distinguishes between unilateral disease (stage I) and bilateral disease (stages II–V), with the onset of postural reflex impairment (stage III) representing a pivotal turning point in the disease's clinical trajectory (Hoehn & Yahr, 1967).

Although it is commonly employed to quantify the overall motor burden and the progression of functional disability, it should be noted that the scale is primarily focused on a limited subset of PD symptoms, predominantly symmetry and gait (Kulcsarova et al., 2024). Consequently, it is not specifically useful for capturing motor complications or non-motor symptoms (Martinez-Martin et al., 2018). Moreover, its application is limited to the final stages of PD, when clinical parkinsonism is evident, making it more suitable for evaluating motor impairment rather than for staging PD-related neurodegeneration (Kulcsarova et al., 2024).

In recent decades, neuroimaging techniques have made a substantial contribution to the advancement of clinical detection and characterisation of PD. The field has evolved from the utilisation of positron emission tomography (PET) scans with ^{18}F-labelled L-dopa in the early 1980s to the 123I-ioflupane single-photon emission Computed Tomography (SPECT) (also known as DaTscan) to visualise striatal dopamine depletion (Poewe et al., 2017). The latter, which is now routinely used in clinical practice, enables the differentiation of PD from other clinical conditions (i.e., essential tremor) that do not involve presynaptic nigrostriatal terminal dysfunction (Poewe et al., 2017). It is important to note, however, that dopaminergic imaging with PET or SPECT will yield abnormal results solely when there is a considerable loss of dopaminergic neurons in the substantia nigra pars compacta, whereas the ultimate objective is to diagnose the disease before this degeneration occurs (Kalia & Lang, 2015). Furthermore, dopamine imaging techniques solely are inadequate for diagnosing PD as they are unable to accurately differentiate between this condition and other parkinsonian syndromes that are characterised by nigral degeneration (i.e., atypical parkinsonism) (Kalia & Lang, 2015). In this context, high and ultra-high-field structural MRI plays a pivotal role in the early diagnosis of PD, enabling the detection of specific alterations in the basal ganglia and other cerebral structures (Kalia & Lang, 2015; Poewe et al., 2017). Additionally, the use of advanced MRI techniques and post-processed data analyses (including diffusion-weighted imaging, volumetric imaging, automated

subcortical volume segmentation, and multimodal imaging), can improve the diagnostic precision between PD and other forms of parkinsonism (Poewe et al., 2017).

2.2. Cognitive Impairment in Parkinson's Disease

Among the non-motor dysfunctions previously prescribed, cognitive impairment represents one of the most relevant, given its importance in terms of daily functioning and quality of life (Leroi et al., 2012; Obeso et al., 2017; Postuma et al., 2015). The risk of developing cognitive impairment is up to six times higher in individuals with PD compared to the non-affected population (Aarsland et al., 2001; Perez et al., 2012). Cognitive alterations can be observed in these patients across the full spectrum, from subjective cognitive decline (SCD) to PD-MCI and PDD (Aarsland et al., 2021).

SCD is defined as a self-perceived decline in cognitive functions despite normal age-, sex- and education-adjusted performance on neuropsychological tests and no evidence of impact on daily functioning (Jessen et al., 2020). In contrast, individuals with PD-MCI demonstrate a gradual decline in cognitive abilities when performing complex functional tasks. This decline is not simply attributable to age, is confirmed by objective cognitive measures and it has a minimal effect on daily functioning and it is not accompanied by dementia (Litvan et al., 2012; Petersen et al., 2014; Petersen et al., 2009). PDD, on the other hand, is typified by deficits in at least two of the four cognitive domains (memory, attention, executive, and visuospatial abilities), to the extent that it significantly affects the routine functions of daily living (Dubois et al., 2007; Emre et al., 2007).

Cognitive impairment in PD shows some variability in terms of the time of onset, the pattern of progression, the domains involved, and overall severity (Aarsland et al., 2021; Martinez-Horta & Kulisevsky, 2019). However, MCI has been estimated to occur in approximately 20-50% of PD patients (Aarsland et al., 2021; Goldman et al., 2018; Pedersen et al., 2017), although very recent

reviews and meta-analyses have reported a prevalence up to 70% (Baiano et al., 2020; Jellinger, 2022).

Despite the variability in clinical presentation, previous and recent literature consistently identify a typical neuropsychological profile of PD mainly characterised by deficits in executive functioning, attention and working memory, visuospatial skills, long-term memory, and language (Barone et al., 2011; Kehagia et al., 2010; Martinez-Horta & Kulisevsky, 2019; Muslimović et al., 2005).

A recent study by Barvas and colleagues (2021) described different cognitive phenotypes in PD by applying latent profile analysis. This resulted in a three-cluster *severity-based model*, which appears to be related to functioning in daily life, yet independent of disease stage, motor functioning, as well as anxiety, and depression. In particular, one cluster comprised individuals (21.54%) with either unimpaired cognition or relatively mild cognitive decline in executive functions and memory. In contrast, another group (53.85%) included patients exhibiting an intermediate level of cognitive impairment, while a last cluster (24.61%) consisted of patients with the most severe cognitive dysfunctions. Interestingly, these individuals showed a more pronounced deficit than other groups in executive functions and in tasks that predominantly engage posterior cortical areas, such as naming and visuospatial abilities. The heterogeneity of cognitive impairment in PD can be explained according to the "*Dual syndrome hypothesis*" (Kehagia et al., 2013), which suggests that cognitive deficits may result from two independent, still partially overlapping syndromes in PD: 1) a frontal-striatal network dysfunction present at the early stage of the disease, due to dopaminergic loss in the basal ganglia circuitry, leading to deficits in attentive-executive functions; 2) an additional, more posterior cortical degeneration, which is associated with cholinergic loss, impairment in cognitive tasks with a predominantly posterior cortical basis and a higher risk of progression to dementia (Barvas et al., 2021; Biundo et al., 2016; Kehagia et al., 2013). Further evidence in support of the Dual syndrome hypothesis has been provided by recent findings that demonstrate a dissociation between the resting-state networks of the frontal "dysexecutive" and posterior cortex cognitive

subtypes in patients diagnosed with PD (Lang et al., 2019). However, with regard to progression to dementia, other recent longitudinal neuroimaging studies have highlighted the relevance of frontal atrophy in the conversion from PD-MCI to PDD (Chung et al., 2019; Lee et al., 2014), along with the impairment in multiple cognitive domains (Williams-Gray et al., 2009).

In view of the considerable heterogeneity of cognitive symptoms observed across the spectrum of global impairment in PD, an alternative approach to cognitive subtyping in PD is *domain-based* (Pourzinal et al., 2022). This approach identifies subtypes based on the specific cognitive domains affected, such as memory, executive function, or a combination of these. Although the number of domain-based subtypes varies between studies, common phenotypes do emerge. In particular, subtypes characterised by memory deficits, executive deficits, global impairment or cognition intact have been observed across studies (Pourzinal et al., 2022). In addition, neuroimaging evidence has provided insights into the neural correlates of these domain-based subtypes, with the amnestic subtype primarily associated with dysfunction and atrophy of temporal and posterior cortical regions of the brain, whereas the executive-impaired phenotype shows alterations in some posterior and subcortical regions (Pourzinal et al., 2022).

Notwithstanding the absence of consensus regarding the optimal subtyping methodology, the review by Pourzinal and colleagues (2022) suggests the necessity for further revision of the criteria for PD-MCI.

Indeed, approximately 80% of PD-MCI patients will ultimately develop dementia (Aarsland & Kurz, 2010; Hely et al., 2008; Pedersen et al., 2017). This highlights the importance of early recognition of PD-MCI for several reasons. Firstly, early diagnosis allows patients at an increased risk to be identified and referred for timely intervention. Secondly, it facilitates the investigation of the disease's pathogenesis in the earlier stages (Litvan et al., 2012). In light of this, ten years ago the MDS provided specific guidelines for the clinical characterisation and diagnosis of cognitive alterations in PD (Litvan et al., 2012). The clinical, cognitive, and functional diagnostic criteria were derived from the

current methods of defining MCI in the general population (American Psychiatric Association, 2013; Petersen, 2004; Winblad et al., 2004), but modified to address PD-specific issues. Furthermore, they were devised in alignment with the aforementioned criteria for PDD (Dubois et al., 2007; Emre et al., 2007). According to these guidelines, PD-MCI classification requires a clinically established diagnosis of PD - based on UK PD Brain Bank Criteria (Hughes et al., 1992) - and the presence of disease-related cognitive impairment, as reported by either the patient/caregiver or detected by the clinician. Furthermore, the presence of cognitive deficits must be demonstrated by obtaining scores below the established cut-off on neuropsychological tests However, these deficits do not affect the patient's functional autonomy at this stage (Litvan et al., 2012).

In addition, the MDS task force proposed a two-level operational scheme for PD-MCI diagnosis that differs in terms of the neuropsychological assessment (first vs second level assessment), the degree of diagnostic certainty (possible vs probable PD-MCI), and the extent of clinical characterisation (i.e., subtyping PD-MCI) (Litvan et al., 2012). Specifically, Level I criteria rely on an abbreviated evaluation through a scale of global cognitive abilities validated for use in PD or a limited battery of neuropsychological tests. Conversely, Level II criteria require a comprehensive neuropsychological assessment that comprises at least two tests (i.e., one impaired test in two different cognitive domains or two impaired tests in one cognitive domain). In both cases, the relevant cognitive domains tested are attention and working memory, visuospatial abilities, executive functions, language, and long-term memory (Litvan et al., 2012).

Although the MDS criteria represented the first step towards a universally accepted definition of MCI in PD across multiple clinical and research realities, with noticeable benefits in terms of increased diagnostic validity (Boel et al., 2022; Postuma et al., 2018), they also acknowledged the need for additional research to optimise the neuropsychological assessment. For instance, a still open issue is represented by the lack of assessment of one of the core neurocognitive domains as identified in the fifth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American

Psychiatric Association, 2013): social cognition. This domain has received increasing attention in recent years (Boccardi et al., 2021; Van den Stock, 2021), with significant impairments observed in PD patients. Despite this, socio-cognitive assessment is still not routinely performed (Dodich, Boccardi, et al., 2022). This could lead to the non-detection of some PD-MCI patients who may be misclassified as not cognitively impaired, thus underestimating the presence of non-motor symptoms.

2.3. Social Cognition and its neural correlates

Social cognition represents a complex and multifaceted cognitive domain that underpins everyday social interactions and it is closely related to mental health, individual functioning, and quality of life. It comprises various cognitive processes that, collectively, enable individuals to perceive, recognise and interpret signals from the social environment, understand their own and others' behaviour, generate appropriate responses and adapt them according to social needs (Frith, 2008; Happé et al., 2017; Lewis & Ricciardi, 2021). As an umbrella term, there is still debate among scholars about which processes are included in social cognition and the relationships between them (Happé et al., 2017). However, there is a general consensus about four main components of social cognition: social perception, ToM or "mentalising", empathy and social behaviour (Alonso-Recio et al., 2021; Happé et al., 2017; Henry et al., 2016; Lewis & Ricciardi, 2021).

- *Social perception* can be defined as the ability to recognise and respond to a range of social and emotional cues, including facial expressions, body language, and voices (Alonso-Recio et al., 2021; Henry et al., 2016). A fundamental aspect of social perception, which is crucial for effective social interactions, is *emotion processing*. This encompasses two key elements: *emotion understanding* (the ability to recognise and represent emotions) and *emotion regulation* (the ability to control emotions, affect and motivation) (Decety, 2010). Subsequently, Enrici and colleagues (2015) enriched the description of *emotion understanding* by distinguishing between *emotion recognition*, considered as a low-level perceptual process involved in identifying emotionally salient

information in the environment, and *emotion representation*, a higher-level ToM inferential process involved in integrating and inferring social information (both emotional and intentional) (Enrici et al., 2015). According to this model, the more complex the emotion, the higher the level of ToM required to decode it, because basic emotions are culturally recognised and situational, whereas social emotions are belief-based and depend on what other people feel or think (Enrici et al., 2015).

- *ToM* refers to the ability to attribute mental states to oneself and others, to recognise that these may differ from one's own, and to deploy them correctly to understand and predict others' behaviour (Abu-Akel & Shamay-Tsoory, 2011; Henry et al., 2016). A key distinction within this component is the differentiation between the attribution of mental and affective states, which are respectively referred to as cognitive and affective ToM. In particular, the former pertains to inferences about the cognitive states, beliefs, thoughts, and intentions of others, while the latter refers to inferences about others' emotions, affective states or feelings (Abu-Akel & Shamay-Tsoory, 2011; Arioli et al., 2018; Coundouris et al., 2020).

- *Empathy* can be defined as the capacity to understand and share what another person is feeling. A further distinction has been made in this domain between cognitive and affective sub-components. Specifically, cognitive empathy refers to the ability to understand what others are feeling and overlaps with the affective ToM, as both involve attributing an emotional state to another person. On the other hand, affective empathy describes one's emotional response to a situation perceived by another. This response may be experienced as the same emotion as that felt by the other person (emotional contagion or affective resonance or experience sharing) or distinct from the other's experience (Coundouris et al., 2020; Henry et al., 2016).

- *Social behaviour* refers to the set of social interactions between individuals, social sensitivity and moral cognition. It also includes the ability to establish non-affiliative contacts with strangers and to adhere to standards of good manners and interpersonal boundaries (Alonso-Recio et al., 2021; Lewis & Ricciardi, 2021).

With regard to the neural correlates of social cognition, lesion and functional MRI studies have demonstrated that the "*Social Brain*" (Adolphs, 2009) encompasses a substantial number of brain structures. In recent years, however, the approach based on the involvement of a single area in the social brain functioning has been superseded by a network-based approach. Indeed, the complexity of signals to be processed in the social environment requires the activation of a distributed neural network (Adolphs, 2009; Christidi et al., 2018; Desmarais et al., 2018).

In particular, a central area of the neural pathways underlying social perception is the occipitotemporal cortex, where specific regions have been associated with the analysis of faces and bodies. Specifically, the Occipital Face Area (OFA) in the inferior occipital gyrus and the Fusiform Face Area (FFA) in the fusiform gyrus are activated in face processing. On the other hand, a different portion of the fusiform gyrus (Fusiform Body Area – FBA) and the Extrastriate Body Area (EBA) in the lateral occipitotemporal cortex are entailed in the processing of bodies and body parts. Besides these regions, a crucial hub of the brain network underlying social perception is the posterior superior temporal sulcus (pSTS) in the posterior-lateral temporal cortex. The pSTS processes the changeable features of biological stimuli and their action-related motion patterns and it is also implied in the processing of the affective value of observed stimuli thanks to its connection to the amygdala and orbitofrontal cortex (OFC). Finally, diffusion imaging studies have also recently emphasised the pivotal function of the inferior longitudinal fasciculus and the inferior fronto-occipital fasciculus in connecting the nodes previously mentioned for face processing (Arioli et al., 2018).

However, in addition to perceptual processing (i.e., the identification of the geometric configuration of facial features), emotional face perception also involves the ability to recognise the emotional meaning of a stimulus (Adolphs, 2002; Fusar-Poli et al., 2009). Functional brain imaging studies indicate that the processing of emotional faces is associated with increased activation of the visual cortex, the limbic system, the temporoparietal regions, the prefrontal cortex, as well as the putamen and the cerebellum (Fusar-Poli et al., 2009). In particular, the amygdala was found to be specifically

activated by happy, fearful, and sad faces, whereas insula activation was selectively detected during the processing of disgusted and angry faces. A more detailed examination of the differential sensitivity of these two brain areas to specific emotional conditions revealed that the amygdala exhibited greater sensitivity to fearful than to happy and sad faces, whereas the insula demonstrated greater sensitivity to disgusted than to angry faces. In contrast, the neural response in the occipital cortex and the cerebellum was observed in response to all different emotions (Fusar-Poli et al., 2009; Phan et al., 2002).

In regard to ToM, the neurobiological model proposed by Abu-Akel & Shamay-Tsoory in 2011 posit that the ability to represent cognitive and affective mental states to both self and others is subserved by cortical and subcortical areas that are functionally organized into distinct yet interacting networks. Specifically, the processing of cognitive ToM engages the dorsomedial prefrontal cortex (dmPFC), the dorsolateral prefrontal cortex (dlPFC), the dorsal anterior cingulate cortex (dACC), dorsal portion of the temporal lobe (dTL) (which projects to mPFC and OFC) and the dorsal striatum (caudate and putamen). On the other hand, the affective ToM network primarily engages the OFC, the inferior lateral frontal cortex (ILFC), the ventromedial prefrontal cortex (vmPFC), the amygdala, the ventral anterior cingulate cortex (vACC), the ventral portion of the temporal lobe (vTL) (which projects to mPFC and OFC) and the ventral striatum (nucleus accumbens) (Abu-Akel & Shamay-Tsoory, 2011; Fortier et al., 2018; Molenberghs et al., 2016).

Although the cognitive and affective components of the ToM engage dissociable circuits within the broader mentalisation network, they interact and influence each other through the anterior cingulate cortex (ACC). Indeed, although the ACC is anatomically divided into ventral and dorsal regions, these are reciprocally connected with both cognitive and affective regions and their output counterparts within the PFC (Abu-Akel & Shamay-Tsoory, 2011).

Other brain areas involved in mentalising include the temporo-parietal junction (TPJ) (comprising the inferior parietal lobe – IPL, and the pSTS), the posterior cingulate cortex (PCC)/precuneus (PCu),

and superior temporal sulcus (STS). However, these areas do not show a preference for affective or cognitive ToM processing but contribute to assigning agency to mental states (Abu-Akel & Shamay-Tsoory, 2011).

Recent evidence from neuroimaging and lesion studies has identified two discrete systems also for the cognitive and affective components of empathy. In particular, a neural network comprising the inferior frontal gyrus (IFG), the IPL, the amygdala, the insula, and the ACC appears to be involved in emotional/affective empathy (and emotion recognition). On the other hand, the vmPFC, the TPJ, and the medial temporal lobe (mTL) have been identified as key regions for the cognitive component. Neuroimaging studies have indicated that the brain activations associated with cognitive empathy mainly overlap to those observed for affective ToM. This finding lends support to the hypothesis of an overlay between these two subcomponents (Abu-Akel & Shamay-Tsoory, 2011; Dvash & Shamay-Tsoory, 2014).

Although specific social cognition components have been linked to distinct set of regions, social interactions frequently require the involvement of several networks to effectively process the rich amount of information to which individuals are exposed (Desmarais et al., 2018). Moreover, the complexity of neural circuits is compounded by the fact that a singular social stimulus can be processed through several parallel pathways and by the intertwining of social cognition with other cognitive domains (especially executive functions) (Desmarais et al., 2018).

2.4. Social cognition deficits in Parkinson's Disease and their neural correlates

In recent years, a growing body of evidence has shown that different neurodegenerative diseases (such as frontotemporal lobar degeneration, Alzheimer's and Parkinson's diseases, amyotrophic lateral sclerosis, etc.) are associated with impairment in social cognition (Christidi et al., 2018; Elamin et al., 2012; Fortier et al., 2018; Kumfor et al., 2017; Maresca et al., 2020). Moreover, there has been

a recent rising interest in studying how this set of cognitive processes can contribute to the clinical characterisation of neurodegenerative diseases associated with dementia and aid differential diagnosis (Bertoux et al., 2013; Dodich et al., 2016; Dodich, Boccardi, et al., 2022; Dodich, Crespi, Santi, Luzzi, et al., 2021; Palmeri et al., 2017; Van den Stock, 2021). As proposed by Lewis & Ricciardi (2021), PD represents a compelling pathological model for investigating the underlying mechanisms of social cognition and its various components. Indeed, deficits in different social cognition sub-domains have been demonstrated in PD (Palmeri et al., 2017) and it has been hypothesized these deficits are secondary to alterations in the mesocorticolimbic (Blonder & Slevin, 2011) and frontostriatal (Bodden, Dodel, et al., 2010) circuits.

Several reviews and meta-analyses have synthesised the evidence pertaining to social-cognitive dysfunctions in PD patients, analysing specifically emotion processing (Argaud et al., 2018; Gothwal et al., 2022; Gray & Tickle-Degnen, 2010; Mattavelli et al., 2021; Palmeri et al., 2017; Péron et al., 2012), ToM (Bodden, Dodel, et al., 2010; Bodden, Mollenhauer, et al., 2010; Coundouris et al., 2020; Palmeri et al., 2017) and empathy (Coundouris et al., 2020).

Emotion processing in PD has been widely examined, concerning both different emotion components (e.g., physiological arousal, feelings, motor expressions) and input modalities (e.g., faces, voices).

Literature reviews and meta-analyses (Argaud et al., 2018; Assogna et al., 2008; Coundouris et al., 2019; Gothwal et al., 2022; Gray & Tickle-Degnen, 2010; Péron et al., 2012) mostly agreed on the impairment of emotion recognition in PD patients (with around 64% of studies reporting a global deficit) which depends on the disease severity but sometimes appears from the onset of the condition, on its cross-modal nature (affecting both faces and voices) and on a greater deficit for negative emotions than positive ones (i.e., 54% for fear, 44% for anger, 27% for happiness) (Argaud et al., 2018). Nevertheless, the existing literature in this field continues to yield contradictory results, and several key questions remain unanswered. For instance, with regard to the selectivity of the deficit for specific emotions, 30% of the studies examined in the meta-analysis conducted by Argaud and

colleagues (2018) considered only an overall score, without distinguishing between different emotions. Moreover, even studies that examined performance in the recognition of single emotions reported conflicting results. For example, Mattavelli and colleagues (2021) observed that approximately one-third of their patients scored below the cut-off in fear recognition, which contrasts with previous studies reporting a disproportionate deficit in anger recognition (Clark et al., 2008; Lawrence et al., 2002, 2007). Furthermore, although several studies have indicated that negative emotions are predominantly impaired in PD patients, others have observed that this specific deficit is primarily evident in the early stages of the disease, with positive emotions being affected later (Lin et al., 2016).

The inconsistencies observed in these results may be driven by a number of confounding factors, including high inter-individual variability in emotion recognition ability, heterogeneity in assessment measures, and patients cognitive status (Argaud et al., 2018; Fortier et al., 2018). With regard to this latter point, a recent study has provided further evidence of impaired facial emotion recognition in PD patients without cognitive impairment (Pietschnig, Aigner-Wöber, et al., 2016). Unlike previous studies, PD patients were divided into groups according to the criteria set forth by Petersen's (2004) and Litvan's (2012). The former (Petersen, 2004) categorises patients as either cognitively intact MCI, amnestic MCI (aMCI), non-amnestic MCI (non-aMCI), while the latter (Litvan et al. 2012) distinguishes between cognitively intact MCI, single-domain MCI (sMCI), and multi-domain MCI (mMCI). The findings indicate that deficits in facial emotion recognition were presents even in PD patients with intact cognitive functions, suggesting that this dysfunction may precede the onset of overt cognitive decline (Pietschnig, Schröder, et al., 2016). Similarly, eye movement behaviour during a facial emotion recognition task was analysed in a sample of PD patients with preserved cognitive function and MCI (according to Litvan's Level II criteria, 2012), compared to healthy individuals (Waldthaler et al., 2019). Results confirmed PD-MCI patients' impairment in facial emotion recognition (specifically for anger) and showed that an ineffective visual exploration strategy

may be associated with their reduced performance. Indeed PD-MCI demonstrated a tendency to focus their gaze on the centre of the face and spent significantly less time fixating the mouth than both healthy subjects and cognitively intact PD patients. However, eye movements during visual exploration of emotional faces were also altered and restricted (though not significantly different from those of healthy controls) in PD patients cognitively intact without facial emotion recognition deficits. Collectively, these results suggest that the progression to PD-MCI may result in further deterioration of visual scanning behaviour and impairment in facial emotion recognition (Waldthaler et al., 2019), although oculomotor alterations can already be evident in PD patients without cognitive and facial emotion recognition deficits.

In the context of studying emotion processing in PD, it is noteworthy to mention a study conducted by Enrici and colleagues (2015), which investigated emotional processing in PD by comparing the three previously described levels: emotion recognition, representation, and regulation. The findings of this study indicated that individuals with PD exhibited an overall impairment in emotion recognition, as well as a deficit in emotion representation. Nevertheless, no specific impairment was identified in emotion regulation among the PD cohort.

Furthermore, research has indicated a correlation between impaired facial emotion perception and reduced emotional expressivity (hypomimia) in individuals with PD (Argaud et al., 2016; Prenger & Macdonald, 2018; Ricciardi et al., 2015, 2017). This non-motor symptom of PD is linked to a hypodopaminergic state, resulting in hypokinesia and bradykinesia of the facial muscles. This causes PD patients to be perceived as "cold" or "unhappy" (Gothwal et al., 2022). The observation and imitation of facial emotional expressions, which is essential for the recognition of emotions, has been demonstrated to activate a number of brain regions, including the premotor cortex, superior temporal cortex, insula and amygdala (Carr et al., 2003; Gothwal et al., 2022). The embodied simulation theory unifies these concepts and proposes that impairment in facial emotion perception may be associated

with diminished emotional expressivity and hypomimia (Argaud et al., 2016, 2018; Gothwal et al., 2022).

With regard to the neural correlates of the emotion recognition impairment in PD, neuroimaging studies indicate that the impairment in emotion identification observed in PD patients is likely attributable to dysfunction in frontostriatal pathways and mesolimbic areas, as well as in , amygdala, basal ganglia (i.e., striatum), and related dopaminergic pathways (Gothwal et al., 2022). Indeed, the available structural studies shown an association between reduced abilities in PD and grey matter loss in limbic regions such as the OFC, the amygdala, the ACC, the postcentral and the right occipital fusiform gyri, the subgenual cortex and the ventral striatum (Baggio et al., 2012; Diederich et al., 2016; Gothwal et al., 2022; Ibarretxe-Bilbao et al., 2009; Yoshimura et al., 2005). In addition, preliminary evidence from functional studies revealed that the impaired emotional facial recognition network is associated with reduced metabolic activity in the posterior cingulate gyrus (bilaterally), right superior frontal gyrus, and left superior frontal gyrus (Robert et al., 2014). More recently, Wabnegger and colleagues (2015) discovered that, in comparison to subjects without PD those with the disease exhibited heightened activation in the somatosensory cortices during emotion perception. These regions are involved in the decoding of emotional states through the generation of somatosensory representations that simulate the sensation of displaying a specific facial expression. Consequently, the authors suggest that they may play a significant role in emotion recognition. In a recent study, Moonen and colleagues (2017) observed a reduction in bilateral putamen activation and an increase in the right dmPFC in PD compared to controls. The authors posit that this may reflect a potential compensatory neural mechanism in PD patients during emotional processing, whereby increased mPFC activity may modulate emotional responsiveness via top-down cognitive control, thereby restoring emotional processing at the behavioural level, despite striatal dysfunction. Although emotional recognition is the most widely investigated domain of social cognition to date in PD,

further studies are needed to better address the still open issues, first of all, the neural correlates of this impairment.

Alongside the now well-documented deficits in emotion recognition, PD patients frequently manifest *ToM* impairments (Coundouris et al., 2020; Poletti et al., 2011; Trompeta et al., 2021). These deficits have been linked to the quality of life of PD patients (Bodden, Mollenhauer, et al., 2010; Santangelo et al., 2012) and executive functioning (in particular inhibition) (Foley et al., 2019). However, the results in this domain are also conflicting, particularly when examining the different subcomponents (i.e., cognitive and affective ToM) (Palmeri et al., 2017). As previously stated, these two aspects appear to depend on at least partly distinct networks (Abu-Akel & Shamay-Tsoory, 2011), which could then be differentially compromised in PD (Bodden, Mollenhauer, et al., 2010).

Initial studies in this clinical population reveled a greater deficit in the cognitive ToM component in PD patients, unlike outperformance inferring the emotions and the affective states of others (Péron et al., 2009; Roca et al., 2010). Conversely, later studies and meta-analyses found that both the cognitive and the affective components were equally compromised in PD (Bodden, Mollenhauer, et al., 2010; Bora et al., 2015a; Coundouris et al., 2020; Santangelo et al., 2012). These controversial results may be attributed to different methodological aspects in ToM assessment and/or the impact of confounding factors (such as the duration and onset of the disease, the patient's medication status, the influence of the cognitive status, and the presence of mood disorders), but they may also be due to the distinct networks involved in the different processes of cognitive and affective ToM (Palmeri et al., 2017; Trompeta et al., 2021).

To address this issue, in recent years, a few neuroimaging studies investigated the anatomical correlates of ToM performance in PD. Results reported damage in different frontostriatal circuitries possibly linked to the impairment of affective and cognitive ToM (Bodden, Mollenhauer, et al., 2010). Specifically, some authors proposed that early nigrostriatal degeneration affecting the dorsolateral-prefrontal-striatal circuitry in PD could determine cognitive ToM deficits. On the other hand,

alterations of the frontostriatal-limbic circuitry in more advanced PD stages could lead to OFC and vmPFC/ACC cortices dysfunctions, resulting in affective ToM deficits (Alonso-Recio et al., 2021; Bodden, Dodel, et al., 2010; Coundouris et al., 2020). However, recent studies on frontal, limbic, and striatal networks in PD patients have observed damage in white matter bundles involving both the nigrostriatal and mesolimbic circuits from the early stages of the disease (Nigro et al., 2016). A multi-modal imaging study (Díez-Cirarda et al., 2015) analysing both white and grey matter correlates of ToM deficits in PD at relatively early stages of the disease (compared to healthy controls) consistently identified reduced grey matter volume in the left inferior temporal gyrus (anterior and posterior) and the temporal fusiform gyrus, as well as white matter reduction in the right uncinate fasciculus (adjacent to insular cortex) and in the frontal lobe. Successively, Orso and colleagues (2020) conducted a study investigating the neural substrates of ToM abilities in unmedicated newly diagnosed PD patients. The results demonstrated that unmedicated *de novo* PD patients exhibited impaired performance on an advanced ToM test (i.e., the Reading the Mind in the Eyes Test) relative to controls. Furthermore, this impairment was found to be directly associated with cortical metabolic levels in the superior temporal gyrus and in the insula. A final study worth mentioning is that of Rabini and colleagues (2023), who observed alterations in resting-state functional connectivity within the ToM network in individuals with PD. In particular, these alterations follow a graded pattern, with a reduction in connectivity at an early stage of the disease, which then broadens to encompass a generalised increase with longer disease duration. In any case, as far as we know, the number of neuroimaging studies assessing ToM in PD patients is too narrow to draw any conclusion (Trompeta et al., 2021).

A further open issue is the involvement of the basal ganglia in ToM, as the neurobiological model proposed by Abu-Akel & Shamay-Tsoory (2011) (previously described) suggests a differential involvement of the dorsal and ventral striatum in cognitive and affective aspects, respectively. Given the progressive involvement of these portions in PD-related degeneration (with early impairment of

the dorsal striatum and subsequent involvement of the ventral striatum) (Dauer & Przedborski, 2003), this condition may prove to be a useful model for testing striatum involvement in mentalising processing (Bodden, Dodel, et al., 2010) according to disease stage.

In contrast to the well-documented deficits in emotion processing and ToM deficits in PD, the impact of the disease on *empathy* remains an under-explored area (Coundouris et al., 2020; Schmidt et al., 2017). In 2020 the first meta-analysis was published integrating both empathy and ToM findings in PD literature, distinguishing between the affective and cognitive subcomponents in both of them. The authors concluded that individuals with PD exhibited diminished abilities (compared to healthy subjects) in understanding others' mental states and emotional experiences, with a potentially preserved capacity to resonate affectively with others (no PD effects were evident for affective empathy) (Coundouris et al., 2020). It is important to note, however, that the studies included in this review are based on very small samples; moreover, in some cases, there was a reduced performance in patients compared to controls, while in others, scores were comparable between the two groups. Conversely, Schmidt and colleagues (2017) observed a reduction in empathy scores among PD patients, which they identified as a symptom associated with advanced disease stages. Nevertheless, these findings are still preliminary and further investigation through both behavioural and neuroimaging studies is required to gain insight into the underlying neural substrates of this deficit in PD.

Finally, it is also worth noting that, to the best of the author's knowledge, *social behaviour* has only been investigated to a limited extent. A study by Anderson and colleagues (2013) examined the ability to solve social problems in a cohort of PD patients with and without MCI, compared to healthy controls. The ability to understand the actions and sarcastic comments of others, provide and select optimal solutions to social problems, and self-perceive problem-solving skills were assessed. The results demonstrated deficits exclusively within the PD-MCI cohort, indicating that difficulties in solving social problems may be secondary to executive dysfunctions.

2.5. Open issues in the literature

In conclusion, the current scientific literature provides evidence for the presence of social cognitive dysfunctions in PD across the various subcomponents. These alterations appear to be associated with the well-documented impairment of mesocorticolimbic (Blonder & Slevin, 2011) and frontostriatal circuits that are typical of this disease (Bodden, Dodel, et al., 2010; Maresca et al., 2020; Palmeri et al., 2017). Moreover, it has been hypothesised that damage to distinct neural circuits may have a differential effect on cognitive and emotional processes in PD (Alonso-Recio et al., 2021; Bodden, Mollenhauer, et al., 2010; Kalbe et al., 2010; Shamay-Tsoory & Aharon-Peretz, 2007).

Notwithstanding the extensive theoretical and behavioural studies on social cognition in PD, the existing literature on this topic still lacks a comprehensive characterisation of socio-cognitive dysfunctions in PD, especially in the clinical setting, as well as their underlying neural correlates. In this regard, the extent of these impairments and their relationship to patients' cognitive status (as well as to mood, behaviour, dopaminergic medications, and motor severity) remains a topic of debate (Czernecki et al., 2021; Lewis & Ricciardi, 2021). Furthermore, the clinical relevance of these deficits must be more clearly established. Indeed, the potential identification of clinically significant social cognitive deficits in this population (particularly in the early stages of the disease) is of considerable importance, as it has the potential to inform the definition of the PD-MCI construct, which may be predictive of conversion to PD dementia (Hoogland et al., 2017). Finally, the neural correlates of emotional processing deficits observed in individuals with PD should be better elucidated.

Future research in these areas would facilitate a more in-depth comprehension of the disease, particularly with regard to the characterisation of social cognitive deficits in clinical settings.

Chapter 3 - Deficits in emotion recognition and theory of mind in Parkinson's Disease patients with and without cognitive impairments (Study 1)

The present study aims to analyse emotion recognition, affective and cognitive ToM in early PD patients classified according to Level II MCI criteria provided by the MDS (Litvan et al., 2012), and to evaluate the prevalence of socio-cognitive deficits in this sample. A total of 45 participants with PD were enrolled in the study and classified as either cognitively unimpaired (CU; n=32) or with MCI (n=13) based on the results of a standard neuropsychological assessment. The social cognitive abilities of the PD participants were evaluated through the administration of validated tests for emotion recognition (Ekman 60-faces test, Ek60 Test) and mental state attribution (Story-based Empathy Task, SET) and compared with those of a group of 45 healthy controls. This study highlights the relevance of early detection of isolated socio-cognitive deficits in PD patients without cognitive impairment. Furthermore, it emphasises the importance of assessing social cognition in this clinical population as a potential early marker of cognitive decline.

3.1. Introduction

Parkinson's disease (PD) is a progressive multisystem neurodegenerative disorder (Dickson, 2018) characterised at the clinical level by a constellation of motor and non-motor symptoms (Trojano & Papagno, 2018), among which cognitive impairments have received particular attention due to their consequences in everyday functioning (e.g., Leroi et al., 2012). Alongside the well-known deficits in executive functioning, visuo-spatial abilities and memory, recent evidence has underlined possible socio-cognitive impairments in PD. Social cognition is a complex cognitive domain, which refers to a set of different processes aimed at recognising and interpreting signals from the environment, understanding self and others' behaviours, and adapting the response based on social needs (Frith, 2008). As a multi-faceted domain, social processes required for successful social interaction include aspects of social perception (e.g., emotion recognition), theory of mind (ToM, also defined as mental states attribution)**,** empathy and social behaviour (Henry et al., 2016). Notwithstanding some controversial results, deficits of social cognition in PD have been previously reported, with the majority of studies showing significant emotion recognition deficits, particularly for negative emotions (Argaud et al., 2018; Coundouris et al., 2019; Gray & Tickle-Degnen, 2010). Interestingly, these deficits seem to be at least partially independent from depressive symptomatology (De Risi et al., 2018; Gray & Tickle-Degnen, 2010), executive dysfunctions (Enrici et al., 2015; Saenz et al., 2013) or early visual processing deficits (Mattavelli et al., 2021). From a neuroanatomical perspective, emotion recognition disorders have been previously related to neurodegenerative alterations in regions belonging to the mesocorticolimbic pathway (Baggio et al., 2012; Ibarretxe-Bilbao et al., 2009), including the amygdala (Diederich et al., 2016). Considering its role as a hub within neural networks responsible for multisensorial and affective processing, damage to this brain region is hypothesized to hamper not only emotion recognition in PD, but also the attribution of affective mental states to others (i.e., affective ToM) (Call & Tomasello, 2008; Diederich et al., 2016; Premack & Woodruff, 1978; Shamay-Tsoory et al., 2010). Consistently, ToM dysfunctions have been

recently described in PD patients (Bora et al., 2015b), although the extent to which these deficits involve cognitive (i.e., ability to infer other intentions or beliefs) or affective (i.e., ability to infer other emotions) subcomponents is still an open issue, with some evidence supporting an early impairment in the cognitive sub-component and a later involvement of affective processing (e.g., Poletti & Bonuccelli, 2012), and others supporting early alterations in both ToM aspects (e.g., Santangelo et al., 2012). Besides, to the best of our knowledge, only a few studies investigated both emotion recognition and affective ToM in PD (Alonso-Recio et al., 2021; Enrici et al., 2015; Foley et al., 2019), and the relationship between these two facets, as well as the presence of these deficits in the earliest disease stages, is still unclear.

Despite the above-mentioned evidence of socio-cognitive deficits in PD, social cognition is not included among the cognitive domains clinically assessed for the definition of PD cognitive status according to the 2012 Movement Disorder Society (MDS) criteria for the detection of mild cognitive impairment (MCI) (Litvan et al., 2012). These criteria include a two-level operational schema depending on the neuropsychological assessment. Together with an abbreviated evaluation (i.e., MDS Level I criteria), specific guidelines for a comprehensive cognitive assessment (i.e., MDS Level II criteria) were defined. According to these recommendations, a patient is classified as MCI when showing impairments on at least two neuropsychological tests (i.e., one impaired test in two different cognitive domains or two impaired tests in one cognitive domain) in specific cognitive domains (i.e., attention and working memory, executive function, language, memory and visuo-spatial functions). A recent study (Czernecki et al., 2021) evaluated the prevalence of socio-cognitive deficits in PD patients characterised by the MDS level I criteria. Notably, this study showed socio-cognitive dysfunctions in 30% of the sample, of which 20% was classified as cognitively unimpaired (CU). However, the narrow neuropsychological assessment, including only a measure of cognitive screening (i.e., MoCA) and a global measure of executive functioning (i.e., Frontal Behavioral Inventory) prevented a full MCI characterisation (Litvan et al., 2012). In this study, we aim to fill this

gap by investigating socio-cognitive deficits in PD patients characterised according to MDS Level II MCI criteria (Litvan et al., 2012). In order to analyse the prevalence of socio-cognitive dysfunctions in the clinical setting, we focused on tests validated for the Italian population assessing social perception (emotion recognition) and ToM.

3.2. Materials and Methods

3.2.1. Subjects

Forty-five patients with PD diagnosed according to the UK Parkinson's Disease Society brain bank criteria (Hughes et al., 1992) were enrolled at the Center for Neurocognitive Rehabilitation of the Center for Mind/Brain Sciences (University of Trento) from January 2020 to November 2021. Inclusion criteria were a diagnosis of idiopathic PD, Hoehn and Yahr score ≤3 (Hoehn & Yahr, 1967), age above 50 years old and being under anti-parkinsonian medication. Patients with evidence of dementia or other neuropsychiatric disorders were excluded. All patients underwent a baseline clinical evaluation performed by experienced neurologists and neuropsychologists and were tested while in their medication-on condition. To evaluate the possible effect of clinical features, levodopa equivalent daily dose (LEDD) was determined and correlation analyses have been performed considering socio-cognitive performance, LEDD, disease duration and Hoehn and Yahr stage.

Forty-five healthy controls (HC), matched for demographic variables to the patient group, were also enrolled for statistical comparison at social tasks. HC were included based on the absence of positive neuropsychiatric history, neurological disorders, or cognitive impairment evaluated through the Italian version of the Montreal Cognitive Assessment (MoCA, cut-off score <19.501) (Conti et al., 2015). The study was conducted in accordance with the ethical guidelines of the local ethics committee and the Declaration of Helsinki and written informed consent was signed by all participants.

3.2.2. Neuropsychological assessment

All patients underwent a standard neuropsychological evaluation including a test of global cognitive status (Conti et al., 2015), as well as two tests for each cognitive domain as suggested by MDS criteria (Litvan et al., 2012). Attentive matrices (Spinnler & Tognoni, 1987) and backward digit span (Monaco et al., 2013) were selected for attention and working memory, phonemic verbal fluency (Carlesimo et al., 1996) and Stroop task (Caffarra, Vezzadini, F., et al., 2002) for executive functions, line orientation judgment test and unknown face recognition test (Benton, 1983) for visuo-spatial abilities, and two naming tasks for language (Catricalà et al., 2013; Papagno et al., 2020). Long-term memory was assessed through delayed recall at verbal (Rey Auditory Verbal Lists test – RAVLT, Carlesimo et al., 1996) and non-verbal (Rey-Osterrieth Complex Figure ROCF, Caffarra, Vezzadini, Dieci, et al., 2002) tests (see Table 1 for a summary of the neuropsychological tasks included in the assessment). Based on Italian normative cut-off scores, patients were classified as CU or MCI following the MDS Level II criteria (Litvan et al., 2012). PD-MCI patients were also classified into subtypes based on the presence of abnormalities on two tests within a single domain (single-domain PD-MCI) or multiple deficits in different cognitive domains (multi-domain PD-MCI). Finally, the presence of mood disorders was evaluated through the Geriatric Depression Scale (Yesavage, 1988) and the Parkinson Anxiety Scale (Santangelo et al., 2016).

Table 1. *Neuropsychological tests used for PD profile classification according to PD-MCI Level II criteria*

Cognitive domain	***Cognitive tests***
Attention and working memory	• Attentive Matrices • Digit span backward
Executive functions	• Phonemic verbal fluency task • Stroop task
Visuospatial abilities	• Benton's Judgment of Line Orientation • Benton Facial Recognition Test
Long-term memory	• Rey Auditory Verbal List delayed recall • Rey-Osterrieth complex figure delayed recall
Language	• Naming of colored photographs • Naming verbs

3.2.3. Socio-cognitive assessment

Social-cognitive abilities have been evaluated through a test of emotion recognition (Ekman 60-faces Test – Ek60) (Dodich et al., 2014) and a test of mental state attribution (Story-based empathy task – SET) (Dodich et al., 2015). The Ek60 is a well-known test used to assess emotion recognition abilities from static images expressing six basic emotions (i.e., fear, disgust, anger, happiness, sadness, surprise), shown on a computer monitor each for 5 seconds according to the Italian normative procedure. No time limit was set for patients' responses. A global score, as well as scores for recognition of single emotions, can be computed. The maximum score is 60 for the whole test and 10 for each basic emotion. The SET is a non-verbal task developed to assess mental states attribution in neurodegenerative diseases associated with dementia (Cerami et al., 2015; Dodich et al., 2016; Dodich et al., 2021; Valera-Bermejo et al., 2021), which also provides supporting evidence in other neurological populations (Campanella et al., 2021; Realmuto et al., 2015). This test includes a sub-test of emotion attribution (SET-EA), as well as a condition of intention attribution (SET-IA) and causal inference (SET-CI). Each condition has a sub-score of a maximum of 6 points, with a global score of 18 indicating the best possible performance.

3.2.4. Statistical analysis

First, preliminary statistical analyses were performed to evaluate data distribution (Shapiro-Wilk test) and to compare demographic variables (i.e., age, education and sex) between groups (PD-CU, PD-MCI, HC) through one-way ANOVA and Chi-squared test.

Differences in basic neuropsychological tasks were evaluated between PD-MCI and PD-CU using t-student statistics or Mann-Whitney U based on data distribution.

Performances at social tasks (Ek60 test and SET adjusted scores) were compared between PD-CU, PD-MCI and HC using parametric or non-parametric (Kruskal-Wallis) one-way ANOVA. Post-hoc analyses were carried out through the Games-Howell test (for parametric statistics) and Dwass-Steel-Crotchlow-Fligner pairwise comparison (for non-parametric statistics). Since a significant difference between PD-CU and PD-MCI was found in education, analyses were performed on adjusted scores according to normative values. Then, partial correlation analyses controlling for global cognitive status (i.e., MoCA) were performed between the main neuropsychological variables of interest to assess the relationship between socio-cognitive abilities and clinical, cognitive and behavioural functioning in PD. Finally, we evaluated the number of patients with social-cognitive impairments in both MCI and CU subgroups based on Italian normative cut-off values for Ek60 global score, affective (SET-EA) and cognitive (SET-IA) mental states attribution. Notably, we used the approach of "equivalent scores" proposed by Capitani and Laiacona (1997). This method allows mapping patients' performance into an ordinal five-point scale (range 0-4), where "0" indicates a pathological performance, "1" a borderline performance, and "2-4" a normal performance. Statistical analyses were conducted using Jamovi 2 (Fox & Weisberg, 2020; Jamovi, 2021; R Core Team, 2021).

3.3. Results

3.3.1. Cognitive profile in PD patients

According to level II PD-MCI criteria, 32 patients were classified as PD-CU and 13 patients as PD-MCI (Table 2). All PD-MCI were classified as multiple-domain MCI. Among MCI patients, the most commonly affected cognitive domains were executive functions (85% of MCI patients), long-term memory (70%) and visuo-spatial abilities (46%). No significant differences emerged between patients and HC in demographic variables (Chi-squared test on sex variable: $X^2_{(2)}=1.15$, p=0.6; one-way ANOVA on age variable: $F_{2, 31.7}=0.11$, p=0.9), apart from education (PD-MCI<PD-CU: one-way ANOVA $F_{2, 39.8}=3.82$, p=0.03) (Table 2). At cognitive level, MCI patients showed lower performance than CU in long-term memory (RAVLT, p=0.002; ROCF, p<0.001), attention (attentive matrices, p<0.001) executive functions (Stroop time interference effect, p=0.002; Stroop error interference effect, p<0.001; verbal fluency on phonemic cue, p<0.001), language (naming of coloured photographs, p=0.005; naming of verbs, p=0.005) and visuo-spatial abilities (line orientation judgment test, p=0.003; unknown face recognition task, p=0.004).

Table 2. *Demographic, clinical and basic neuropsychological features of Parkinson's Disease (PD) patients and healthy controls (HC)*

Variable	***PD-MCI (n=13)***	***PD-CU (n=32)***	***HC (n=45)***	***Statistics***	***post -hoc***
DEMOGRAPHICS					
Sex (M/F)	9/4	17/15	24/21	$X^2(2)=1.15$, p=0.6	-
Age (years)	69±8.8	67.9±6.6	67.7±7.7	$F_{2, 31.7}$ =0.11, p=0.9	-
Education (years)	9.5±2.5	12.1±4.1	11.5±3.6	$F_{2, 39.8}$=3.82, **p=0.03**	MCI<CU*
CLINICAL					
Disease duration (months)	84 [48-120]	84 [45.5-117]	-	U=199, p=0.9	-
LEDD	527.8±176.3	571.6±289.7	-	t(39)=0.50, p=0.6	-
Hoehn & Yahr Scale	2.5 [2-2.75]	2 [1-2]	-	U=103, p=0.1	-
Geriatric Depression Scale	6 [2.5-13.5]	11 [8-14]		U=137, p=0.1	-
Parkinson Anxiety Scale	14±8.8	11.2±7.4		t(42)=1.03, p=0.3	-
NEUROPSYCHOLOGICAL					
MoCA	18.9±3.7	22.8±2.9	23.9±1.9	$F_{2, 84}$=18.29, **p<0.001**	MCI<CU**; MCI<HC***
Digit backward	4±0.7	4.3±0.8	-	t(43)=1.02, p=0.3	-
Attentive Matrices	38.4±6.7	48.2±7.5	-	t(43)=4.06, **p<0.001**	-
Rey Auditory Verbal Learning delayed recall	6.7±2.5	9.6±2.6	-	t(43)=3.36, **p=0.002**	-
Rey-Osterrieth complex figure delayed recall	9.5±3.6	16.4±5.9	-	t(43)=3.88, p<0.001	-
Stroop time interference effect	25.6 [19.5-42]	13.3 [10-19]	-	U=72.5, **p=0.002**	-
Stroop error interference effect	5.2 [2.4-6.1]	0 [0-0.4]	-	U=20, **p<0.001**	-
Verbal fluency on phonemic cue	24.7±8.8	36.2±9.1	-	t(43)=3.88, **p<0.001**	-
Naming (figures)	45.9 [44.7-47]	47.8 [46.6-48]	-	U=99.5, **p= 0.005**	-
Naming (verbs)	46 [43.9-48.5]	49.1 [47.4-50]	-	U=85.5, **p= 0.005**	-
Line orientation judgment test	20.5±6.1	25.1±3.5	-	t(43)=3.15, **p=0.003**	-
Unknown face recognition task	41.9±5.0	46.6±4.2	-	t(42)=3.09, **p=0.004**	-

Note. Descriptive data are given as Mean ± Standard Deviation (SD) for parametric statistics; Median [25th- 75th percentile] for non-parametric statistics.
p-value: * p<0.05, ** p< 0.01, *** p< 0.001.
Bold font – Significant p values.
CU - Cognitively unimpaired; MCI - Mild cognitive impairment; HC – Healthy controls; LEDD - L-dopa equivalent daily dose; MoCA - Montreal Cognitive Assessment.

3.3.2. Socio-cognitive deficits in PD classified according to cognitive status

The analysis of social performance between PD-MCI, PD-CU and HC showed significant differences in both emotion recognition and attribution tasks (Table 3). Global emotion recognition abilities were reduced in PD-MCI (p<0.001) compared to PD-CU (p=0.009) and HC (p=0.003). In particular, PD-MCI patients showed lower scores than HC in the recognition of fear (p=0.02), surprise (p=0.002) and sadness (p<0.001). Anger (p=0.04) and sadness (p<0.001) recognition was reduced in PD-MCI compared to PD-CU patients. Together with emotion recognition deficits, PD-MCI showed worse performance than HC in SET scores of emotion (SET-EA, p<0.001) and intention (SET-IA, p<0.001) attribution, as well as in the control condition of causal inference (SET-CI, p=0.03). Notably, SET-EA (p=0.002) and SET-IA (p=0.02) were also reduced in PD-CU compared to HC, while only a trend emerged in SET-CI (p=0.05).

Partial correlation (Spearman, r_s) results are reported in Table 4. These analyses showed a significant association between Ek60 and SET-EA scores (r_s=0.48, p<0.004), while no significant correlations emerged with SET-IA or SET-CI sub-scores. Executive functions (i.e., Stroop task) were significantly associated to the performance at both SET (SET-EA: r_s=-0.43, p=0.01, SET-IA: r_s=-0.45, p=0.01, SET-CI: r_s=-0.41, p=0.02) and Ek60 (r_s=-0.37, p=0.02) tasks. SET-EA performance was also associated to language functions (naming of coloured photographs: r_s=0.52, p=0.001; naming of verbs: rs=0.38, p=0.03). Finally, scores at the Ek60 test were positively associated with the performance at the unknown face recognition task (r_s=0.50, p<0.001).

No significant correlations emerged between social cognitive performance and mood disturbances evaluated through GDS and PAS scales. Moreover, no significant correlations were found between

LEDD, disease duration, Hoehn and Yahr stage and performances at social tasks in either the total group of PD patients or the CU and MCI subgroups.

Table 3. *Performance at social tasks between PD patients characterised according to cognitive status and HC*

	HC	***PD-CU***	***PD-MCI***	***Statistics***	***Post-hoc***
Ek60 global score	50.7±4.6	49.6±5.7	42.4±6.8	$F_{2, 86}$=12.21, **p<0.001**	MCI<CU**; MCI<HC**
Surprise	10 [9-10]	9 [8-10]	8 [7-9]	H_2=11.91, **p=0.003**	MCI<HC**
Happiness	10 [10-10]	10 [10-10]	10 [9-10]	H_2=2.96, p=0.228	-
Fear	4 [2-7]	4 [2-5.5]	2 [0-3]	H_2=7.3, **p=0.03**	MCI<HC*
Disgust	9 [7-10]	8 [7-9.5]	7 [6-9]	H_2=5.12, p=0.08	-
Anger	7 [7-8]	7 [7-9]	6 [4-8]	H_2=6.66, **p=0.04**	MCI<CU*
Sadness	8 [7-9]	8 [8-9]	5 [4-6]	H_2=18.65, **p<0.001**	MCI<HC***; MCI<CU***
SET Global score	17.1 [15.2-17.3]	15.3 [11.3-16.2]	11.2 [7.7-13.3]	H_2=29.33, **p<0.001**	MCI<CU*; CU<HC***; MCI<HC***
SET Emotion attribution	6 [5.05-6]	4.9 [3.6-5.6]	3.1 [2.1-3.3]	H_2=25.62, **p<0.001**	MCI<CU*; CU<HC**; MCI<HC***
SET Intention attribution	6 [5.2-6]	5.2 [4.05-6]	4 [3.1-4.2]	H_2=24.86, **p< 0.001**	MCI<CU*; CU<HC*; MCI<HC***
SET Causal Inference	6 [5.1-6]	5.05 [3.9-6]	4.3 [3.4-5.2]	H_2=9.43, **p=0.01**	MCI<HC*

Note. Descriptive data are given as Mean ± Standard Deviation (SD) for parametric statistics; Median [25th- 75th percentile] for non-parametric statistics.
p-value: * p<0.05, ** p<0.01, *** p<0.001.
Bold font – Significant p values.
CU - Cognitively unimpaired; MCI - Mild cognitive impairment; HC – Healthy controls; Ek60 - Ekman 60-faces test; SET - Story-based Empathy Task.

Table 4. *Partial correlations between social tasks, cognitive and behavioural variables*

	SET Emotion attribution	***SET Intention attribution***	***SET Causal Inference***	***Ek60 Global score***
Ek60 global score	**r_s=0.48**	r_s=0.32	r_s=0.14	—
	p=0.004	p=0.06	p=0.41	
Digit Backward	r_s=0.26	r_s=0.13	r_s=0.09	r_s=0.02
	p=0.13	p=0.48	p=0.59	p=0.90
Attentive matrices	r_s=0.32	r_s=0.30	r_s=-0.09	**r_s=0.40**
	p=0.05	p=0.08	p=0.62	**p=0.007**
Rey Auditory Verbal Learning delayed recall	r_s=0.08	r_s=0.31	r_s=-0.08	r_s=0.18
	p=0.66	p=0.07	p=0.64	p=0.24
Rey-Osterrieth complex figure recall	r_s=0.28	**r_s=0.40**	**r_s=0.41**	**r_s=0.47**
	p=0.10	**p=0.02**	**p=0.01**	**p=0.002**
Verbal fluency on phonemic cue	r_s=0.33	r_s=0.34	r_s=0.30	**r_s=0.60**
	p=0.05	p=0.05	p=0.08	**p<0.001**
Stroop time interference effect	**r_s=-0.43**	**r_s=-0.45**	**r_s=-0.41**	**r_s=-0.37**
	p=0.01	**p=0.01**	**p=0.02**	**p=0.02**
Unknown face recognition task	r_s=0.22	r_s=0.22	r_s=0.08	**r_s=0.50**
	p=0.20	p=0.20	p=0.64	**p<0.001**
Line orientation judgment task	r_s=0.30	r_s=0.10	r_s=0.16	r_s=0.12
	p=0.07	p=0.55	p=0.34	p=0.44
Naming of colored photographs	**r_s=0.52**	r_s=0.26	r_s=0.24	**r_s=0.51**
	p=0.001	p=0.13	p=0.16	**p<0.001**
Naming of verbs	**r_s=0.38**	r_s=0.08	r_s=-0.08	r_s=0.28
	p=0.03	p=0.62	p=0.65	p=0.07
Parkinson Anxiety Scale	r_s=0.07	r_s=-0.03	r_s=-0.17	r_s=-0.06
	p=0.69	p=0.85	p=0.33	p=0.71
Geriatric Depression Scale	r_s=-0.10	r_s=-0.26	**r_s=**-0.19	r_s=-0.22
	p=0.59	p=0.12	p=0.28	p=0.15

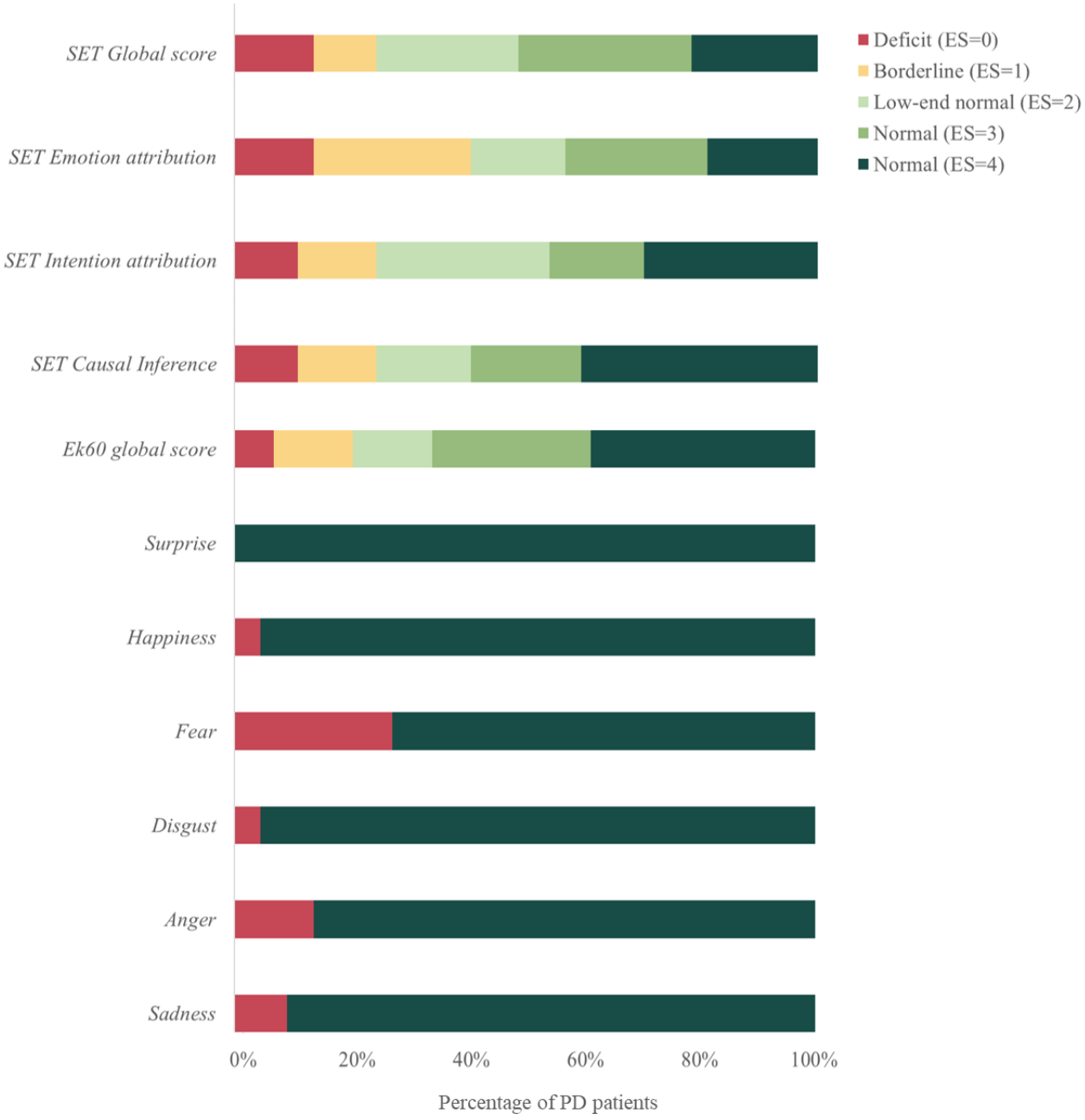
Note. r_s - Spearman's Rank Correlation Coefficient.
p-value: * p<0.05, ** p<0.01, *** p<0.001.
Bold font – Significant p values.
Ek60 - Ekman 60-faces test; SET - Story-based Empathy Task.

3.3.3. Socio-cognitive deficits in PD according to normative data

PD patients' performance at socio-cognitive tasks (i.e., SET and Ek60 test) was finally evaluated according to Italian normative data (Dodich et al., 2014, 2015) to define the prevalence of patients with socio-cognitive dysfunctions. In particular, 9 patients showed poor performance in social tasks, 5 of them were classified as PD-CU and 4 as MCI. Analysing the socio-cognitive profile of these patients in more detail, 2 PD-MCI patients showed a deficit in both Ek60 and SET tasks, while 7 patients (2 PD-MCI, 5 PD-CU) presented an isolated deficit at either the Ek60 (1 patient) or SET task (6 patients). Among patients showing a defective SET performance, 4 presented isolated deficits in mentalising sub-tasks (i.e., SET-IA and/or SET-EA), while the others were characterised by an overall deficit (i.e., mental states attribution and control condition). A borderline performance in SET-EA, IA and CI was found in 10, 5 and 5 patients, respectively, while 6 patients showed a borderline performance at the Ek60 test. Exploratively, we also evaluated the performance at single emotions recognition. Fear represented the most difficult emotion to be recognised (impaired in 12 patients) followed by anger (n=6) and sadness (n=4) (see Figure 2 for details on socio-cognitive deficits in PD according to normative data).

Finally, when considering social cognition among the cognitive domains for MCI criteria, 2 patients originally classified as PD-CU were re-classified as PD-MCI multiple domains, presenting a significant impairment in 2 neuropsychological tasks (i.e., socio-cognitive and executive functions task).

Figure 2. *Socio-cognitive dysfunctions in PD patients compared to HC*



Note. SET - Story-based Empathy Task; Ek60 - Ekman 60-faces test; ES: Equivalent scores according to Capitani and Laiacona method (Capitani & Laiacona 1997)

3.4. Discussion

Increasing evidence reports significant socio-cognitive dysfunctions in PD. However, the extent of these deficits according to the disease stage, as well as their clinical relevance, is still unclear. Thus, in this study, we adopted two social tasks clinically standardised for the Italian population in order to

assess emotion recognition and ToM in PD, with the final aim of investigating the prevalence of socio-cognitive deficits in a sample of non-demented patients classified according to MDS Level II criteria for MCI (Litvan et al., 2012).

Emotion recognition and ToM represent two core components of social cognition, driving social interaction through automatic and voluntary processes (Coricelli, 2005). Notably, these cognitive functions require the integrity of a set of specific and shared brain regions belonging to frontal and mesocorticolimbic circuits (Abu-Akel & Shamay-Tsoory, 2011; Mier et al., 2010), which can be significantly affected by PD neurodegenerative processes (Baggio et al., 2012; Diederich et al., 2016). In support of this evidence, we found significant deficits in both facial emotion recognition and mental states attribution in PD-MCI. Notably, despite previous authors suggested a progressive impairment in cognitive ToM and a later involvement of affective ToM with disease progression (e.g., Poletti & Bonuccelli, 2012), our results support the presence of early alterations in both cognitive and affective facets of mental states attribution (Coundouris et al., 2020; Enrici et al., 2015; Santangelo et al., 2012). This evidence is further supported by the results on PD-CU, which showed an isolated deficit in SET-IA and SET-EA.

Together with mentalising deficits, PD-MCI showed a significant impairment in negative emotion recognition in agreement with previous quantitative and qualitative literature reviews (Argaud et al., 2018; Gray & Tickle-Degnen, 2010). Notably, fear represented the most difficult emotion to recognise, confirming previous evidence (e.g., Mattavelli et al., 2021), followed by anger and sadness. On the other hand, no significant deficit has been found in disgust recognition. This result is inconsistent with earlier studies reporting a disproportionate deficit in disgust recognition in PD (e.g., Suzuki et al., 2006) ascribable to the disruption of the basal ganglia–insula system (Obeso, Marin, et al., 2008) involved in the recognition of this emotion (Fusar-Poli et al., 2009; Phan et al., 2002). However, more recent quantitative approaches showed heterogeneous results when considering single emotions, and a deficit in disgust recognition was found only in 47% of the studies taken into

consideration (Argaud et al., 2018). Many potential confounding factors, such as disease severity, medication, or mood disorders (Gray and Tickle-Degnen, 2010) could contribute to emotion recognition deficit in PD, causing high variability in study results. Despite we did not find a significant relationship in our sample with dopaminergic treatment or mood disorders, future studies should be devoted to fully elucidating the role of these factors in PD emotion recognition deficits.

Meta-analytical evidence concurs however in reporting a major impairment in the recognition of negative emotions rather than of positive ones, and this deficit has been previously associated with amygdalar (Diederich et al., 2016) and mesocorticolimbic alterations (Baggio et al., 2012; Ibarretxe-Bilbao et al., 2009) in PD. In this sense, it is interesting to underline that in the current study we found a specific correlation between emotion recognition abilities and affective ToM, evaluated through SET-EA. Considering that the low performance at this sub-task has been previously related to amygdalar structural damage in other neurological populations (Campanella et al., 2021; Cerami et al., 2014), these results suggest possible common underlying pathological mechanisms affecting both emotion recognition and attribution in these patients. This perspective opens new relevant research questions that should be further explored. Indeed, although recent models have underlined the role of these socio-cognitive facets in social interaction (e.g., Cassel et al., 2019), it is still to be fully elucidated the role of socio-cognitive deficits (in terms of emotion recognition or ToM) in altering social behaviour.

Despite the significant results at group level, when evaluating socio-cognitive performance in single subjects according to normative data we found a limited number of patients showing a deficitary performance. This possibly suggests in the PD group the presence of subtle alterations in socio-cognitive tasks, still below the threshold of clinical relevance. This hypothesis is further supported by the presence of patients showing a borderline performance in both emotion recognition and mental states attribution. When considering normative cut-off scores, 20% of patients showed a significant clinical deficit in global emotion recognition or mental state processing. This percentage is similar to

what has been previously reported (i.e., 30%) (Czernecki et al., 2021). The mismatch could be possibly explained in light of the different criteria adopted to define MCI (i.e., MDS Level II criteria in the current study and MDS Level I criteria in Czernecki et al., 2021). Indeed, MDS Level I criteria require an abbreviated evaluation compared to Level II criteria, with a foreseeable effect on diagnostic certainty, extent of clinical characterisation and MCI detectability (Litvan et al., 2012). In accordance with this consideration, we found a higher percentage of patients characterised by MCI (i.e., 29%) compared to Czernecki's study (i.e., 15.6%) (2021), and, consistently, a lower percentage of PD-CU (i.e., 11%) showing socio-cognitive deficits.

When we included social cognition among the cognitive domains for MCI criteria, 2 PD-CU patients were re-classified as PD-MCI multiple domains. Considering the contribution of MCI classification in predicting the hazard of PD dementia (Hoogland et al., 2017), this result indicates a possible benefit in considering social cognition among the MDS cognitive domains in order to improve MCI detectability. Consistently with previous literature findings (Barvas et al., 2021; Litvan et al., 2012), the classification of our PD sample according to MDS Level II criteria showed predominant executive functioning, memory, and visuospatial deficits, but none of the patients satisfied the criteria for PD-MCI single domain. This result is in line with previous evidence showing a prevalence of multiple domain impairments (Goldman et al., 2015), but suggests potential challenges in identifying domain-specific PD-MCI subtypes using MDS criteria.

The main limitations of this study are represented by the small sample size that might affect the statistical power of the analyses, and by the lack of detailed neuropsychological characterisation of healthy controls, which does not allow to exclude the presence in this sample of subtle deficits in single cognitive domains. Despite the MoCA cut-off score used to include healthy participants is lower than the one suggested by international meta-analytic results (e.g., Carson et al., 2018), this is in line with normative data provided by other Italian studies (Aiello, Gramegna, et al., 2022; Santangelo et al., 2015). Besides, due to the limited availability of validated socio-cognitive tests,

other sub-components of social cognition were not assessed. Finally, no motor scores including hypomimia were included in this study, thus preventing to evaluate the role of reduced facial mimicry in social tasks, particularly for emotion recognition (Künecke et al., 2014; Prenger & Macdonald, 2018).

In conclusion, the results of the present study support that alterations in affective recognition and attribution may occur in PD from the earliest stages of the disease. In agreement with previous evidence (Czernecki et al., 2021), we highlighted the presence of a PD subgroup with socio-cognitive dysfunctions, which in a small percentage of patients represented an isolated deficit. This strongly supports the importance of introducing socio-cognitive tasks in PD cognitive evaluation. The relevance of socio-cognitive evaluation in clinical practice has been recently underlined in different neurological populations (Cotter et al., 2018; Dodich et al., 2021; Henry et al., 2016), also in consideration of the significant consequences of these deficits in social integration, well-being and quality of life (Bodden, Mollenhauer, et al., 2010; Dodich, Papagno, et al., 2021; Martinez et al., 2018). The inclusion of social tasks in the cognitive assessment of PD, as well as in the evaluation of MCI due to other neurodegenerative diseases (e.g., Alzheimer's Disease) (Boccardi et al., 2021), will promote the full characterisation of these deficits, as well as their clinical role in the diagnostic and prognostic framework.

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Chapter 4 - The FAcial Complex Expressions (FACE) test: development and cross-cultural comparison of a new social cognitive task

This chapter introduces a novel task that has been developed, standardised and validated with the objective of enhancing the characterisation of social cognitive abilities in the clinical setting. In particular, the findings of two studies that investigated the task in greater detail are here presented. The first study (Study 2) was published as follows: "Terruzzi, S., Funghi, G., Meli, C., Barozzi, N., Zappini, F., Papagno, C., & Dodich, A. (2023). The FACE test: a new neuropsychological task to assess the recognition of complex mental states from faces. Neurological sciences: official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology, 44(7), 2339–2347. https://doi.org/10.1007/s10072-023-06697-w ", with open access under the Creative Commons CC-BY license, version 4.0 (http://creativecommons.org/licenses/by/4.0/). The author(s) retain the copyright for this work. All authors agreed on redistributing the following material for the purpose of this doctoral thesis. Terruzzi S. and Funghi G. are joint first authors of the study. The Journal Author Rights are reported in Appendix B.2. The objective of Study 2 is to present the *Facial Complex Expression (FACE) test*, which was recently developed in Italy for the purpose of assessing an individual's ability to recognise complex mental states from facial expressions. It is noteworthy that two abbreviated versions of the FACE test have been devised with the aim of facilitating multiple testing in both clinical and research settings, thereby avoiding learning effects. Study 2 provides both normative data for the Italian population (according to the method of equivalent scores) and an example of its clinical application to patients with PD.

The second section of this chapter (Study 3) presents the preliminary findings of a study aimed at adapting an English version of the FACE test for clinical and research purposes, and at cross-culturally validating it in English and Italian-speaking healthy older adults. Indeed, the assessment of neuropsychological performance in culturally, linguistically and educationally diverse older populations in Europe has become a relevant topic in recent years due to the increase of migration

and globalisation. However, the cross-cultural applicability of the few tools currently available to assess social cognitive deficits in clinical settings remains to be established.

The FACE test: A new neuropsychological task to assess the recognition of complex mental states from faces (Study 2)

4.1. Introduction

Social cognition refers to a broad range of cognitive abilities which allow humans to understand and interact with others by adopting appropriate, goal-directed, behaviours (Frith, 2008). As a multidimensional construct, it involves different subdomains, usually referred to as social perception, theory of mind (ToM), empathy and social behaviour (Henry et al., 2016). Social perception includes the ability to distinguish others by facial features, body postures, or voices, and to recognise their identity, as well as their emotions, from these features (Ferretti & Papaleo, 2019). ToM refers to the ability to infer others' complex mental states such as thoughts, intentions, beliefs, and motivations (cognitive ToM: "*I understand what you think*"), as well as feelings and emotional states (affective ToM: "*I understand what you feel*") (Abu-Akel, 2003). Together with empathy, identified as the ability to represent, share, and predict what another person is feeling (de Vignemont & Singer, 2006), these social cognitive skills are crucial to predict others' behaviour and to guide adaptive and homeostatic behavioural responses.

Social cognition has been recently included as a stand-alone cognitive domain in the American Psychiatric Association's Diagnostic and Statistical Manual for Mental Disorders – DSM-5, recognising that socially inappropriate behaviour can represent a clinical symptom in several neurodevelopmental, neuropsychiatric and neurodegenerative disorders. Social cognitive deficits represent a core cognitive feature since the early stages of the behavioural variant of frontotemporal dementia (bvFTD) (Rascovsky et al., 2011) and might characterise different clinical conditions (Cotter et al., 2018), among which other syndromes of the FTD spectrum, as well as amyotrophic lateral sclerosis, Alzheimer's Disease and atypical parkinsonisms (Christidi et al., 2018).

Among the different neurodegenerative conditions associated with cognitive decline, increasing evidence points to the presence of social cognitive dysfunctions in Parkinson's disease (PD). Indeed, a meta-analytic review has revealed significant and modest deficits of emotion recognition (Argaud et al., 2018), at least partially independent of patients' level of motor disability, depressive symptoms, executive and visual processing impairment, disease duration and severity (Argaud et al., 2018; Mattavelli et al., 2021). This disorder seems particularly pronounced for negative emotions, although contrasting results have been reported (Argaud et al., 2018). Together with emotion recognition dysfunctions, deficits of both ToM subcomponents have been described across the entire PD disease course (Santangelo et al., 2014; Xi et al., 2015). Initial evidence pointed towards a greater impairment of cognitive aspects of ToM (Péron et al., 2009), calling into question the spatiotemporal progression of striatal dopamine reduction in PD first involving regions associated with cognitive ToM (e.g., dorsolateral prefrontal cortex and striatum) (Abu-Akel & Shamay-Tsoory, 2011). However, recent evidence underlines an early alteration also in emotion attribution in these patients (Santangelo et al., 2014), and deficits in the representation of affective mental states have been now recursively reported (see Enrici et al. 2015 for a review of the main findings).

The clinical relevance of these deficits in PD has been recently emphasized by preliminary evidence suggesting socio-emotional impairments at the clinical neuropsychological assessment in 20% to 30% PD patients, even in the early stages of the disease (Czernecki et al., 2021; Dodich, Funghi, et al., 2022).

However, despite the extensive body of literature supporting the presence of socio-cognitive dysfunctions, its clinical assessment is still limited due to the paucity of clinical tools available (Dodich et al., 2020; Van den Stock, 2021), as shown in Table S1 of Supplementary Information, reporting the list of social cognition tests adapted in Italian for clinical use. There is thus an urgent need to develop and introduce new standardised tasks in the clinical practice to fully characterise socio-cognitive dysfunctions in neurodegenerative populations.

The aim of this study is to present a new test assessing complex mental states recognition through faces (FAcial Complex Expressions test; FACE test) and to provide normative data for the Italian population. In addition, the FACE test has been tested on a sample of 40 PD patients, as an example of its clinical application in a disorder possibly characterised by social cognition impairments. The prevalence of deficits in complex mental states recognition was computed in the PD sample, as well as the association with the performance in different cognitive domains (i.e., learning and memory, language, complex attention, executive functions and perceptual-motor abilities), including social cognition, under the hypothesis of a specific correlation between the FACE test and socio-cognitive tasks performance. Finally, to provide disease-specific cut-off scores, receiver operating characteristic (ROC) analyses were performed comparing PD patients characterised by difficulties in emotion recognition/attribution detected by other socio-cognitive tasks with unimpaired PD patients and healthy controls.

4.2. Materials and methods

4.2.1. Participants

A sample of 229 healthy adult Italian-native speakers [137 women; mean age=53.3±18.6 years; mean education=13.3±4.2 years; mean Montreal Cognitive Assessment (MoCA) raw score=26.2±2.8] was voluntarily recruited for the normative procedure. Exclusion criteria were a history or clinical evidence of neurological or neuropsychiatric diseases and a MoCA adjusted score below the national cut-off score (Aiello, Gramegna, et al., 2022). Sample stratification for age, education, and sex is reported in Table 5.

Table 5. *Stratification for age, education, and sex of the normative sample*

	Age in years								
Education in years	18-29	30-39	40-49	50-59	60-69	70-79	≥80	***Total (F/M)***	***Total***
≤5	NA	NA	NA	NA	1/0	3/1	6/1	**10/2**	**12**
6-8	NA	NA	2/1	8/4	6/5	7/3	1/1	**24/14**	**38**
9-16	14/6	7/9	11/7	15/8	13/9	6/6	3/3	**69/48**	**117**
≥17	7/7	6/6	6/4	6/2	4/5	4/3	1/1	**34/28**	**62**
Total (F/M)	**21/13**	**13/15**	**19/12**	**29/14**	**24/19**	**20/13**	**11/6**	**137/92**	**229**
Total	**34**	**28**	**31**	**43**	**43**	**33**	**17**	**229**	**-**

Note. In each cell, the number of participants as females/males is reported. F female, M male, NA not available.

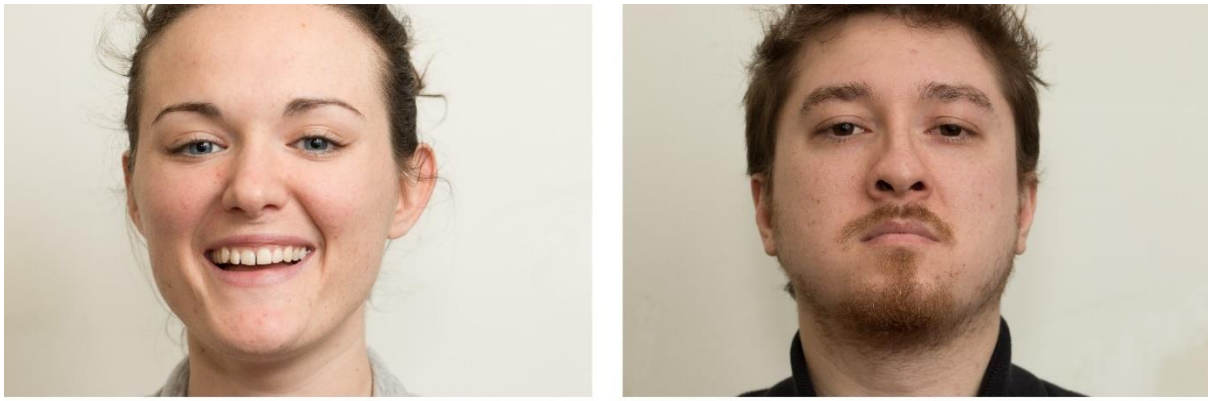
A group of 40 PD patients [15 women; mean age=70.4±5.3 years; mean education=11.4±4.0 years; mean Montreal Cognitive Assessment (MoCA) raw score=22.7±3.8], diagnosed according to the United Kingdom Parkinson's Disease Society brain bank criteria (Hughes et al., 1992), was recruited at the Center for Neurocognitive Rehabilitation of the Center for Mind/Brain Sciences (University of Trento). Inclusion criteria were: i) a diagnosis of idiopathic PD; ii) a Hoehn and Yahr score ≤3 (Hoehn & Yahr, 1967); iii) being under anti-parkinsonian medication; iv) age above 60 years old. Patients with dementia or other neuropsychiatric disorders were excluded. A baseline clinical and neuropsychological assessment, including socio-cognitive evaluation, was performed by experienced neurologists and neuropsychologists, and patients were tested while in their medication-on condition. All participants provided informed consent to the study, which was conducted following the ethical guidelines of the local ethics committee and the Declaration of Helsinki.

4.2.2. FACE test

The FACE test is a recognition task of complex mental states from facial expressions. It consists of 36 high-quality pictures derived from the McGill Face Database (Schmidtmann et al., 2020), which contains high-resolution validated pictures of 93 expressions of mental states interpreted by two professional actors (1 male and 1 female) in front and side view. Details on test construction are reported in Supplementary Information. Briefly, we performed a pilot study on 30 young healthy participants to select those images from the McGill Face Database judged to be the most representative of the different mental states. Participants were asked to judge the valence and arousal of the presented pictures through a Likert-point system, as well as to select the best definition of mental states based on three different options, defining in this way a glossary that could be used during the task administration.

Based on the results of the pilot study, the final version of the test consisted of 36 stimuli (see Supplementary Information, Table S2). Each stimulus was presented centrally on the screen, together with four complex mental state labels, of which one represented the target response and the other three wrong alternatives (see Figure 3). Participants were required to answer verbally, choosing the label that best described the actor's facial expression; no time limits were applied. Participants were also given the glossary and were encouraged to consult it for any label's meaning they were unsure of. A trial run preceded the task, consisting of an example of a stimulus that would not appear in the test, with associated response alternatives. The score range was 0-36, with a higher score corresponding to a better performance. For both clinical and research purposes requiring multiple task administrations, two 18-item versions of the FACE test (i.e., FACE - Version A and FACE Version B) were also derived from the 36-item version (see Supplementary Information for details on the construction of the short forms).

Figure 3. *Examples of images from the FACE test*



Note. Translation from Italian to English of examples of complex mental states labels: Desideroso = Desire; Rallegrato = Amused; Incuriosito = Intrigued; Minaccioso = Threatening; Demoralizzato = Dispirited; Divertito = Entertained; Dispiaciuto = Apologetic; Dominante = Dominant.

4.2.3. Statistical analyses

For the 36-item FACE test score, descriptive statistics were computed based on the performance of the 229 healthy control participants. Preliminary normality checks on raw scores were performed by both evaluating data distribution (Shapiro-Wilk test), and inspecting visually plots for outlier detection. Due to non-normal distribution (age: Shapiro-Wilk $W=0.965$, $p<0.001$; education: Shapiro-Wilk $W=0.965$, $p<0.001$; FACE test: Shapiro-Wilk $W=0.962$, $p<0.001$), between-variables associations (age, years of education, and FACE test raw score) were verified through non-parametric correlation analysis (Spearman's rank correlation coefficient, r_s). Sex differences were tested *via* the Mann-Whitney test (independent sample).

Regression-based norms, as well as the Equivalent Scores (ES), were derived according to the standardisation system proposed by Capitani & Laiacona (2017). In detail, different linear regression analyses were performed, to establish which demographic variables, enclosing age and years of education (including their quadratic, logarithmic, inverse, and square-root terms), had to be included in the final model, as the most effective in reducing the residual variance. Adjusted values were

computed by adding or subtracting the contribution of each demographic variable for each subject. The correction grid was then derived to adjust the performance of each newly tested subject for the effect of the demographic variables. Subsequently, the adjusted scores were classified into five categories, the equivalent scores (ES), ranging from 0 to 4. In particular, the ‘‘0’’ corresponds to the adjusted score equal to or lower than the outer unidirectional non-parametric tolerance limit, with a confidence of 95 % [the sixth observation for 229 subjects]. The ‘‘4’’ category corresponds to scores higher than the median value of adjusted scores. Equivalent scores ‘‘1’’, ‘‘2’’, and ‘‘3’’ are intermediate values on a quasi-interval scale calculated regarding the left half of the distribution.

Intraclass correlation coefficient (ICC) and Spearman’s rank correlation coefficient were used to evaluate, respectively, test-retest reliability and convergent validity between the FACE test performance and the Ekman 60-Faces Test (Dodich et al., 2014) in a subsample of 30 healthy participants.

Concerning the two 18-item short forms, their equivalence was preliminary assessed in healthy participants following previous studies (Aiello, Pucci, et al., 2022) and through a two one-sided test procedure (TOST) for dependent sample, performed via the R package TOSTER (https://cran.r-project.org/web/packages/TOSTER/TOSTER.pdf) (Lakens, 2017). The upper and lower equivalence bounds were defined as -0.5 and +0.5, respectively, and α level=0.05. The raw scores obtained in the short forms were then transformed into a 36-point raw score, on which adjustment based on normative data can be applied to derive the ES (see Supplementary Information for details on the conversion procedure).

To test the use of the FACE test in clinical practice we applied the normative procedure to the performance of a sample of 40 PD patients, computing the prevalence of socio-cognitive deficits in complex mental states representation. Besides, to explore the relationship between FACE test performance and cognitive functioning we computed Spearman’s rank partial correlation, controlling for MoCA raw score, between FACE test raw scores and variables representing cognitive functions

in different domains (working memory, long-term memory, executive functions, visuospatial abilities, semantic access), as well as in social cognition subdomains (i.e., emotion recognition - Ekman 60-Faces Test, Dodich et al., 2014), cognitive and affective TOM - Story-based Empathy Task, Dodich et al., 2015)). P-values resulting from correlation analyses were corrected for multiple comparisons using Bonferroni's method ($\alpha_{adjusted}$=0.05/k, with k equal to the number of correlations performed, i.e., k=16).

Finally, FACE test diagnostic accuracy was tested via ROC curve analysis, comparing PD patients (n=14) showing difficulties at social tasks of emotion recognition and/or attribution (ES equal to 0 or 1) with the normative sample (n=229) and with unimpaired PD patients (n=26). All statistical analyses were performed using Jamovi 2 (R Core Team, 2021).

4.3. Results

FACE test descriptive data of the 229 healthy controls are reported in Table 6. Correlation analyses revealed a negative association between FACE test raw scores and age (r_s=-0.502, p<0.001), and a positive correlation with years of education (r_s=0.441, p<0.001). Independent sample t-tests to verify the impact of sex on the FACE performance did not show significant differences (U=6244, p=0.921).

Table 6. *FACE test descriptive data of the 229 healthy controls*

	Education in years			***Age in years***			
	18-29	30-39	40-49	50-59	60-69	70-79	≥80
≤5	NA	NA	NA	NA	21.0	27.8 ± 6.4	23.6 ± 2.9
6-8	NA	NA	26.0 ± 1.0	27.8 ± 3.0	26.9 ± 2.9	26.7 ± 3.5	28.0 ± 0.0
9-16	30.6 ± 3.1	31.8 ± 2.2	30.1 ± 2.8	29.1 ± 2.9	28.1 ± 3.6	26.1 ± 3.5	25.8 ± 2.0
≥17	32.3 ± 2.8	31.7 ± 2.9	31.0 ± 2.6	30.4 ± 1.5	28.2 ± 3.0	29.4 ± 2.9	30.0 ± 4.2

Note. In each cell, mean ± standard deviation is reported.

The final model of multiple regression showed age and the square root of education in years as the best predictors of the FACE performance ($F_{(2,226)}$=53.0, p<0.001; adjusted R^2=0.313, Breusch-Pagan p=0.136), with higher scores for younger and more educated subjects. Table 7 reports the adjustment grid with the correction factors to be added or subtracted from the FACE test raw scores. ES and intervals for the FACE test global score are shown in Table 8.

Table 7. *Age and education adjustment grid for the FACE test score*

	Education				***Age***									
	20	**25**	**30**	**35**	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**	**85**
5						1.64	2.00	2.37	2.73	3.09	3.45	3.81	4.17	4.54
8					0.30	0.67	1.03	1.39	1.75	2.11	2.47	2.84	3.20	3.56
13	-2.42	-2.06	-1.70	-1.34	-0.98	-0.62	-0.25	0.11	0.47	0.83	1.19	1.55	1.91	2.28
17	-3.28	-2.92	-2.55	-2.19	-1.83	-1.47	-1.11	-0.75	-0.38	-0.02	0.34	0.70	1.06	1.42

Note. Adjusted FACE test score=raw score+0.0723*(Age–53.275)-1.6493*(Sqrt_Edu– 3.595).

Table 8. *Equivalent scores and intervals for the FACE test*

Equivalent Scores	*Adjusted scores intervals*
0	≤ 22.685
1	22.686 - 24.611
2	24.612 - 27.159
3	27.160 - 29.491
4	≥ 29.492

Note. Outer tolerance limit: 22.685, inner tolerance limit: 24.244

Spearman's rank correlation coefficient showed good convergent validity (r_s=0.578, p<0.001), test-retest reliability was moderate (ICC=0.66). When comparing the two 18-item short forms, no significant differences were found ($t_{(228)}$=1.2, p=0.21). Consistently, they also showed statistical equivalence at the TOST procedure (upper $t_{(228)}$=-2.3, p=0.011; Version A mean=14.6±2.2; Version B mean=14.4±2.0). See supplementary Table S3 for the conversion from the FACE - Version A and the FACE - Version B to the global FACE test raw score on which adjustment based on normative data can be applied (rounded integer values are reported together with the raw scores for sake of clarity).

We then applied the normative procedure to a sample of 40 PD patients to test the use of this test in clinical practice for the assessment of complex mental states recognition. Our results showed that 28% of PD patients (11 out of 40) had an impaired (n=4) or borderline (n=7) overall performance at the FACE test. Table S4 reports demographic data and FACE test scores with relative adjusted score and ES for each PD patient. The results of partial correlations controlling for MoCA raw score and for multiple comparisons (Table 9) showed significant correlations between the FACE test score and social-cognitive measures of emotion recognition (i.e., Ekman 60-Faces Test) and affective ToM (i.e.,

SET emotion attribution). Further significant correlations were found with attentive-executive functions and action naming.

Finally, ROC analyses showed that an adjusted cut-off score of 26.32 had 78.57% sensitivity and 79.91% specificity in distinguishing PD with socio-cognitive dysfunctions from the normative sample (AUC=0.821, accuracy=79.84%). The same cut-off score showed 78.57% sensitivity and 80.77% specificity in distinguishing PD with socio-cognitive dysfunctions from PD without emotion recognition/attribution impairments (AUC=0.78, accuracy=80%).

Table 9. *Partial correlations, controlling for MoCA raw score, between the FACE test and cognitive measures*

	FACE test		**FACE test**
Digit Backward	r_s=0.176	*SET Global score*	r_s=0.443
	p=0.303		p=0.005
Attentive matrices	**r_s=0.551**	*SET Emotion attribution*	**r_s=0.493**
	p=0.0005		**p=0.001**
Rey Auditory Verbal Learning	r_s=0.181	*SET Intention attribution*	r_s=0.417
delayed recall	p=0.290		p=0.008
Rey-Osterrieth complex figure	r_s=0.290	*SET Causal inference*	r_s=-0.021
recall	p=0.086		p=0.901
Verbal fluency on phonemic cue	**r_s=0.563**	*Ek60 Global score*	**r_s=0.464**
	p=0.0003		**p=0.0029**
Stroop time interference effect	r_s=-0.273		
	p=0.113		
Stroop error interference effect	r_s=-0.123		
	p=0.483		
Unknown face recognition task	r_s=0.310		
	p=0.065		
Line orientation judgment task	r_s=0.181		
	p=0.291		
Naming of colored photographs	r_s=0.164		
	p=0.340		
Action naming	**r_s=0.504**		
	p=0.001		

Note. Significant results after Bonferroni corrections ($\alpha_{adjusted}$=0.003) are depicted in bold. SET: Story-based Empathy Task, Ek60: Ekman 60-Faces Test; r_s=Spearman's rank correlation coefficient.

4.4. Discussion

Growing evidence supports the use of social cognitive tasks in the clinical assessment of socio-cognitive deficits in the diagnostic framework of neurodegenerative diseases (Boccardi et al., 2021; Czernecki et al., 2021; Dodich et al., 2020). However, the clinical availability of these tests is still strongly limited and there is thus an urgent need to develop new standardised tasks to cover the socio-cognitive sub-domains for which no tools are available. Therefore, this study aimed to provide standardisation and normative data for a new test of complex mental states recognition through faces (the FACE test). Psychometric properties, normative data, and cut-off scores for the FACE test were provided analysing the performances of a sample of 229 Italian healthy participants, taking into account the effect of socio-demographic variables (age, education, and sex). The raw score distribution at the FACE test correlated with age and years of education, resulting in a better performance for younger and more educated participants. This result is consistent with previous studies reporting increased difficulty for older adults in recognising basic emotions as well as complex mental states (Hayes et al., 2020), possibly due to age-related physiological modifications of the frontotemporal structures involved in social-cognitive processing (Ruffman et al., 2008), rather than to a decline of basic perceptual skills (Sullivan & Ruffman, 2004). Furthermore, previous normative studies supported the general role of education in predicting cognitive testing in social cognition tests (Dodich et al., 2014, 2015). On the other hand, no effect of sex was found on test performance. This result is in agreement with previous studies on healthy Italian participants (Maddaluno et al., 2022; Serafin & Surian, 2004), although contrasting results have been also reported (Dodich et al., 2014).

The usefulness of the FACE test has been then demonstrated by applying the correction grids and the equivalent scores to the performance of a sample of 40 PD patients. Difficulties in facial complex mental states recognition were found in 28% of our clinical sample, which is in line with recent preliminary evidence suggesting that this clinical population might present relevant socio-emotional

impairments at the neuropsychological assessment even in the early stages of the disease (Czernecki et al., 2021; Dodich, Funghi, et al., 2022). Besides, partial correlations showed a moderate to strong correlation between the FACE test performance and the results at other social-cognitive tasks of emotion recognition (i.e., Ekman 60-Faces Test) and attribution (i.e., emotion attribution subtask of the Story-based Empathy task), suggesting in these patients a possible broad alteration in affective processing. This hypothesis is further supported by the good accuracy (i.e., 80%) found for the FACE test in distinguishing PD patients with affective socio-cognitive dysfunctions (i.e., emotion recognition and attribution abilities) from PD patients without deficits and healthy controls. At the same time, FACE test performance also correlated with attentive/executive measures. A significant relationship between disorders of social and executive functioning has been previously described and attributed to the involvement of prefrontal cortical areas (Eslinger et al., 2011). Notably, these regions were also found to be involved in action naming in both healthy (Sörös et al., 2003) and pathological populations (Lubrano et al., 2014), suggesting a possible common role of frontal regions, affected by PD pathology, in causing such a constellation of cognitive impairments. On the other hand, no significant correlations were found with other cognitive domains, supporting overall in the early stages of the disease a lack of association of FACE test performance with deficits in semantic or perceptual domains that could affect mental states discrimination or basic facial processing.

Concerning the test construction, the FACE test shares different aspects with another famous test of attribution of complex mental states, the "*Reading the Mind in the Eyes Test*" (RMET) (Baron-Cohen et al., 2003). Both tasks require participants to choose the term best characterising the mental states of an actor picture, even though in the RMET only a portion of the face is shown (i.e., eyes region). While the RMET has proved to be of considerable value in detecting deficits of mental states representation in neurodevelopmental (e.g., Baron-Cohen et al., 2003) and neurological disorders, previous studies in PD reported some inconsistencies in the results (Enrici et al., 2015). This might be at least partially related to the low quality of the stimuli used in the original version concerning

image resolution, luminance, and perspective, as well as to the absence of preliminary validation, with the images taken from popular magazine photos. This might significantly affect test validity (Olderbak et al., 2015), with possible relevant clinical implications. One example is the cut-off score derived from Italian normative data (Maddaluno et al., 2022; Serafin & Surian, 2004) (cut-off range among studies: 8-16), which, in the best-case scenario, is slightly higher than the score of 13, representing the minimum score out of 36 to be performing significantly above chance (Baron-Cohen et al., 2003). A strength of the FACE test is the inclusion of high-quality pictures as stimuli extracted from the McGill Face Database (Schmidtmann et al., 2020), which contains validated pictures representing complex mental states. The 36 final stimuli were selected according to the results of a pilot study investigating the agreement among participants between the facial expression and the complex mental state terms, taking into consideration only those items showing a high image and label clarity (see Supplementary Information or details). This procedure allowed covering also possible cultural differences between our sample and the original one in the interpretation of facial expressions. Furthermore, the strong correlation with the performance at the Ekman 60-Faces Test (Dodich et al., 2014), another social cognition test assessing emotion recognition from facial expression, supports the potential of the test to measure the underlying construct.

The FACE test is however not exempt from limitations. Concerning sample stratification, some co-occurrences of age and education levels happened to be poorly represented (i.e., poorly educated individuals aged <40 years). This should lead to exercising attention when adjusting the raw scores of individuals with these socio-demographic features. Another limitation is the unbalance between the number of FACE stimuli with female and male actors. However, as specified in the method section, images were preliminary selected based on the results from Schmidtmann et al.'s (Schmidtmann et al., 2020) validation study, showing higher performance for images of the female actor. Finally, the results on the clinical sample and the derived cut-off score should be interpreted taking into consideration that no patients in the more advanced disease stages were included, thus

caution should be used when applying the here-proposed cut-off scores on these individuals. On the other hand, the absence of time limits for a response after stimuli presentation may allow better detection of a deficit in the ability to recognise complex mental states, rather than incorrect or null responses due to a general ideomotor slowdown, which is typical of several neurological conditions among which Parkinson's disease.

In conclusion, growing evidence underlines the importance of introducing social cognitive tests in the neuropsychological assessment of neurodegenerative diseases (Boccardi et al., 2021; Czernecki et al., 2021; Dodich et al., 2020). The FACE test investigates complex mental state recognition and thus responds to the need for new standardised tasks to cover the socio-cognitive sub-domains for which no validated tools are available. In the spirit of Open Science, test materials, instructions, and cut-off scores are freely available on the web under a Creative Common license (https://osf.io/dfjcu/?view_only=8e10518adff342c59e77ffe2d7da1903). Therefore, interested neuropsychologists can use them in both clinical and research settings. Moreover, the accessibility of the material may allow authors to replicate results as well as to translate and adapt the FACE test to specific cultures and languages and then proceed with the collection of normative data for population others than the Italian one. Finally, the introduction of two short versions of the test responds to clinical and research needs of longitudinal repeated assessments and multiple administrations for monitoring purposing, avoiding the test-retest learning effect. This represents the first test of social cognition in which alternative versions are available, that can be used for both clinical (e.g., monitoring of cognitive profile) and research purposes (e.g., pre-post assessment in clinical trials).

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4.5. Supplementary information

Table S 1. *Summary of the social cognition tasks with available normative data for clinical practice in Italy*

Authors	***Test***	***Social cognitive facet***
Social Perception		
Albonico et al., 2017	Benton Facial Recognition Test and Cambridge Face Memory Test	Face recognition
Dodich et al., 2014	Ekman 60-Faces Test	Basic emotion recognition
Theory of Mind (ToM)		
Dodich et al., 2015	Story-based Empathy Task (SET)	Cognitive and affective ToM
Maddaluno et al., 2022 and Serafin & Surian, 2004	Reading the Mind in the Eyes Test (RMET)	Affective ToM
Siciliano et al., 2017	Yoni test from the Edinburgh Cognitive and Beahvioural ALS Screen (ECAS)	Cognitive and affective ToM
Empathy		
Liotti et al., 2021	Brief-Mentalized Affectivity Scale (B-MAS)	Affective empathy
Maddaluno et al., 2022	Interpersonal Reactivity Index (IRI)	Cognitive and affective empathy
Decision making		
Maddaluno et al., 2022	Iowa Gambling Test (IGT)	Decision-making
Batteries		
Prior et al., 2003	i) ToM; ii) emotion attribution; iii) interpretation of social situation; iv) moral judgment	ToM; emotion attribution; interpretation of social situation; moral judgment

Pilot study

A pilot study involving 30 young healthy controls has been performed with the aim to select the most representative stimuli of mental states from the McGill Database (Schmidtmann et al., 2020).

Stimuli. Stimuli were extracted from the McGill Face Database (Schmidtmann et al., 2020). This database consists of high-quality pictures (.jpeg image files with a resolution of 5472 x 3648 pixels; colour space profile: sRGB IEC61966-2.1; size of each image: 7.3 MB), taken under controlled conditions in front and side view while two professional English-speaker actors (one male, age 29, and one female, age 23), interpreted 93 expressions of the mental states previously defined in Appendix B of Baron-Cohen et al. (Baron-Cohen et al., 2003). The McGill Face Database is then composed of a total of 372 pictures. For our purpose, only frontal-view pictures were considered. In particular, for each of the 93 mental states, we selected the image of the male/female actor showing the highest expression clarity ratings based on Schmidtmann et al. (Schmidtmann et al., 2020). All the mental states' labels were then translated from English to Italian and the obtained labels were re-translated from Italian to English to verify the accuracy of the translation. The process was carried out by an Italian-native professional English translator.

Pilot study. 30 healthy young participants (mean age:25.4±4.32) have been enrolled. For each of the 93 mental states, participants were asked to judge on a 5-point Likert scale (1" corresponds to "*for nothing*"; "*5*" to "*very much*") the clarity of the image *(CL):* (e.g., the selected picture for <<*TERRIFIED*>> was presented and participants were asked: "How much <<*TERRIFIED*>> does this person seems to you?"). Besides, they were asked to judge the *valence* of the presented pictures by choosing between "*positive*", "*neutral*" or "*negative*" (i.e., "What is the valence of the image? Remember that we are interested in whether, in your opinion, the emotional state is positive, negative or neutral") and the *level of arousal* of the presented pictures choosing between "*high*", "*medium*" or "*low*" (i.e., "What is the level of arousal that the image evokes to you? We are interested in knowing

the level of arousal that the person's expression transmits to you. Keep in mind that the level of arousal can be high in both positive and negative emotional states").

Data on valence and arousal were used in a later stage to define the two short versions. Besides, to define a glossary that could help participants in case of difficulties with mental state labels, participants were also asked to choose, among 3 definitions, the one that best defines each complex mental state. The survey was administered through Qualtrics software (Qualtrics, Provo, UT, USA. https://www.qualtrics.com)

Test construction. Among the 93 pictures, only those receiving *a CL* rating ≥3.5/5 were taken into consideration for test construction. The final set of 36 stimuli was then copied in the center of a slide in a presentation program. Immediately under the picture, four labels representing the target expression and three non-correct alternatives are presented in a row (*Font*: Calibri (Corpo), 18 points, capital letters).

Short versions. Two 18-item short versions (i.e., FACE test – Version A and FACE test – Version B) were derived from the 36-item FACE (Table S2). The two sets were matched for CL (Mann-Whitney U=126, p=0.26), valence (negative: Mann-Whitney U=150, p=0.71, neutral: Mann-Whitney U=160, p=0.97 and positive: Mann-Whitney U=137, p=0.40) and level of arousal (low: Mann-Whitney U=161, p=0.98, neutral: Mann-Whitney U=153, p=0.77 and high: Mann-Whitney U=149, p=0.69). To facilitate the use of the short versions, R package *Equate* (Albano, 2016a, 2016b) has been used for observed-score linking and equating under single-group using circle-arc functions. Converted scores from short- to long-version are reported in Table S3 for both FACE test – Version A and FACE test – Version B.

Table S 2. *List of the stimuli for Version A and B of the FACE test*

FACE test – Version A			
Target	***Alternative 1***	***Alternative 2***	***Alternative 3***
RALLEGRATO (*Amused*)	DESIDEROSO (*Eager*)	INCURIOSITO (*Intrigued*)	MINACCIOSO (*Threatening*)
TERRORIZZATO (*Terrified*)	SPREZZANTE (*Hateful*)	IMBARAZZATO (*Embarrassed*)	SOLLEVATO (*Relieved*)
CONTEMPLATIVO (*Contemplative*)	AFFASCINATO (*Fascinated*)	SPIRITOSO (*Joking*)	COLPEVOLE (*Guilty*)
SUPPLICHEVOLE (*Imploring*)	MINACCIOSO (*Threatening*)	SCETTICO (*Skeptical*)	AFFETTUOSO (*Affectionate*)
AFFABILE (*Friendly*)	CONVINTO (*Convinced*)	ENTUSIASTA (*Enthused*)	PENSIEROSO (*Thoughtful*)
PERPLESSO (*Perplexed*)	IMBARAZZATO (*Embarrassed*)	ATTERRITO (*Panicked*)	RASSICURANTE (*Reassuring*)
INORRIDITO (*Horrified*)	ACCUSATORIO (*Accusing*)	ESITANTE (*Tentative*)	SCHERZOSO (*Playful*)
SODDISFATTO (*Satisfied*)	SPIRITOSO (*Joking*)	ASSORTO (*Preoccupied*)	ACCUSATORIO (*Accusing*)
SPAVENTATO (*Fearful*)	IRRITATO (*Irritated*)	SCETTICO (*Skeptical*)	DESIDEROSO (*Eager*)
SARCASTICO (*Sarcastic*)	INDIGNATO (*Resentful*)	INDIFFERENTE (*Indifferent*)	INCORAGGIANTE (*Encouraging*)
SPIRITOSO (*Joking*)	RICONOSCENTE (*Grateful*)	AFFASCINATO (*Fascinated*)	RAMMARICATO (*Regretful*)
INTERDETTO (*Puzzled*)	INSISTENTE (*Insisting*)	TERRORIZZATO (*Terrified*)	RILASSATO (*Relaxed*)
ESITANTE (*Tentative*)	CURIOSO (*Curious*)	INORRIDITO (*Horrified*)	AFFABILE (*Friendly*)
SBALORDITO (*Bewildered*)	SUPPLICHEVOLE (*Imploring*)	DIFFIDENTE (*Distrustful*)	SODDISFATTO (*Satisfied*)
DOMINANTE (*Dominant*)	DISPIACIUTO (*Apologetic*)	DEMORALIZZATO (*Dispirited*)	DIVERTITO (*Entertained*)
SCHERZOSO (*Playful*)	SICURO (*Confident*)	ASSORTO (*Preoccupied*)	SHOCKATO (*Aghast*)
RILASSATO (*Relaxed*)	FERMO (*Assertive*)	SPIRITOSO (*Joking*)	INCREDULO (*Incredulous*)
INFELICE (*Depressed*)	TESO (*Nervous*)	INSOLENTE (*Defiant*)	CONFORTANTE (*Comforting*)

Note. For each stimulus, the target and alternative responses are shown.

FACE test – Version B			
Target	***Alternative 1***	***Alternative 2***	***Alternative 3***
SHOCKATO (*Aghast*)	SPREZZANTE (*Hateful*)	DUBBIOSO (*Doubtful*)	SODDISFATTO (*Satisfied*)
DIVERTITO (*Entertained*)	AFFETTUOSO (*Affectionate*)	RIFLESSIVO (*Reflective*)	SOSPETTOSO (*Suspicious*)
INDECISO (*Indecisive*)	COLPEVOLE (*Guilty*)	SPAVENTATO (*Fearful*)	AFFABILE (*Friendly*)
SOSPETTOSO (*Suspicious*)	TURBATO (*Uneasy*)	SCONCERTATO (*Flustered*)	DESIDEROSO (*Eager*)
APPAGATO (*Contented*)	DIVERTITO (*Entertained*)	ASSORTO (*Preoccupied*)	CONFUSO (*Confused*)
SCETTICO (*Skeptical*)	INSISTENTE (*Insisting*)	DISORIENTATO (*Baffled*)	SOGNANTE (*Fantasizing*)
MINACCIOSO (*Threatening*)	INDIGNATO (*Resentful*)	INDIFFERENTE (*Indifferent*)	SCHERZOSO (*Playful*)
SOGNANTE (*Fantasizing*)	RILASSATO (*Relaxed*)	ENTUSIASTA (*Enthused*)	IMBARAZZATO (*Embarrassed*)
CONFUSO (*Confused*)	INSOLENTE (*Defiant*)	SERIO (*Earnest*)	INCORAGGIANTE (*Encouraging*)
RIFLESSIVO (*Reflective*)	INCURIOSITO (*Intrigued*)	APPAGATO (*Contented*)	SECCATO (*Annoyed*)
ENTUSIASTA (*Enthused*)	DESIDEROSO (*Eager*)	ASSORTO (*Preoccupied*)	PREOCCUPATO (*Worried*)
SCONTENTO (*Disappointed*)	INCREDULO (*Incredulous*)	SPREZZANTE (*Hateful*)	CONVINTO (*Convinced*)
SERIO (*Earnest*)	INVIDIOSO (*Jealous*)	SUPPLICHEVOLE (*Imploring*)	AFFASCINATO (*Fascinated*)
PENSIEROSO (*Thoughtful*)	INCREDULO (*Incredulous*)	SBALORDITO (*Bewildered*)	AFFABILE (*Friendly*)
ALLARMATO (*Alarmed*)	DISPIACIUTO (*Apologetic*)	INVIDIOSO (*Jealous*)	SICURO (*Confident*)
SICURO (*Confident*)	ENTUSIASTA (*Enthused*)	RILASSATO (*Relaxed*)	DISPIACIUTO (*Apologetic*)
SOLLEVATO (*Relieved*)	SICURO (*Confident*)	AFFASCINATO (*Fascinated*)	AGITATO (*Anxious*)
DIFFIDENTE *(Distrustful)*	INDECISO (*Indecisive*)	SARCASTICO (*Sarcastic*)	INCURIOSITO (*Intrigued*)

Note. For each stimulus, the target and alternative responses are shown.

Table S 3. *Score conversion from FACE test – Version A and FACE test – Version B to global FACE test score*

FACE test Version A	***Global FACE test raw score***	***Global FACE test Score (rounded integer values)***	***FACE test Version B***	***Global FACE test raw score***	***Global FACE test score (rounded integer values)***
1	1.9	2	1	2.1	2
2	3.9	4	2	4.1	4
3	5.8	6	3	6.2	6
4	7.8	8	4	8.2	8
5	9.8	10	5	10.2	10
6	11.7	12	6	12.2	12
7	13.7	14	7	14.3	14
8	15.7	16	8	16.3	16
9	17.7	18	9	18.3	18
10	19.7	20	10	20.3	20
11	21.7	22	11	22.2	22
12	23.7	24	12	24.2	24
13	25.8	26	13	26.2	26
14	27.8	28	14	28.2	28
15	29.8	30	15	30.2	30
16	31.9	32	16	32.1	32
17	33.9	34	17	34.1	34
18	36.0	36	18	36.0	36

Table S 4. *PD demographic data and FACE test scores with relative adjusted and equivalent score*

Patient	***Demographic data***			***FACE test scores***		
	Age	***Education***	***Sex***	***Raw Score***	***Adjusted Score***	***Equivalent Score***
1	64.93	13	M	30	30.83	4
2	65.61	8	F	25	27.16	2
3	60.84	13	F	33	33.53	4
4	77.06	12	F	28	29.94	4
5	*80.46*	*12*	*F*	*21*	*23.18*	*1*
6	65.98	17	M	31	31.05	4
7	68.19	17	M	28	28.21	3
8	69.30	10	M	24	25.87	2
9	76.10	5	M	26	29.89	4
10	78.11	13	M	28	29.78	4
11	68.82	11	M	30	31.58	4
12	73.67	13	M	30	31.46	4
13	62.84	8	F	29	30.96	4
14	**71.39**	**5**	**M**	**17**	**20.55**	**0**
15	71.47	17	M	29	29.44	3
16	70.48	8	M	29	31.51	4
17	61.14	18	F	30	29.50	4
18	73.95	17	M	31	31.62	4
19	78.46	13	M	23	24.80	2
20	**75.01**	**23**	**M**	**15**	**14.59**	**0**
21	73.93	13	M	25	26.48	2
22	67.31	8	F	31	33.28	4
23	**70.47**	**10**	**M**	**16**	**17.96**	**0**
24	73.75	8	F	26	28.74	3
25	71.91	17	M	25	25.48	2
26	71.72	8	F	27	29.60	4
27	66.49	11	F	30	31.41	4
28	60.77	13	M	29	29.52	4
29	*65.66*	*13*	*F*	*22*	*22.88*	*1*
30	72.19	8	F	27	29.63	4
31	*82.17*	*8*	*F*	*21*	*24.35*	*1*
32	*71.05*	*12*	*M*	*23*	*24.50*	*1*
33	64.39	8	F	25	27.07	2
34	**68.44**	**13**	**M**	**21**	**22.08**	**0**
35	73.96	8	M	23	25.76	2
36	67.91	8	F	24	26.32	2
37	*72.31*	*10*	*M*	*22*	*24.09*	*1*
38	*66.44*	*5*	*M*	*20*	*23.19*	*1*
39	65.79	10	M	26	27.62	3
40	*73.81*	*13*	*M*	*22*	*23.47*	*1*

Note. Pathological (ES=0) and borderline (ES=1) are depicted in bold and italics, respectively.

Cross-Cultural Validation of the FACE Test: A Study in English and Italian-Speaking Older Adults (Study 3)

4.6. Introduction

Although ethnic diversity has historically existed in Europe to a certain extent, the increase in migration and globalisation patterns has led to a notable growth in diversity over recent decades (Nielsen, 2022). In light of these changes and considering the progressive ageing of the population (Prince et al., 2013), the assessment of neuropsychological performance in culturally, linguistically and educationally diverse older populations has become a matter of increasing importance in recent years (Nielsen, 2022). Indeed, the linguistic, educational and cultural heterogeneity that characterises European populations introduces variability that can impact both the administration and interpretation of neuropsychological tests (Franzen et al., 2022; Franzen, Mukadam, et al., 2021). In order to address this issue, the recent European Consortium for Cross-Cultural Neuropsychology (ECCroN) proposes that cognitive assessment should be adapted to account for factors such as culture and acculturation, language barriers, level and quality of education, and literacy (Franzen, Mukadam, et al., 2021). The ECCroN Consortium additionally advocates for collaboration in the implementation and validation of cross-cultural neuropsychological tests, particularly in the areas of social cognition and language. Moreover, it is recommended that initiatives be undertaken to enhance the utilisation of interpreters and to train neuropsychologists in order to ensure accurate assessments across diverse populations are strongly encouraged (Franzen et al., 2022; Franzen, Papma, et al., 2021).

The use of cross-culturally validated cognitive tests represents an efficacious strategy for the overcoming of the aforementioned challenges in the assessment of cognitive functioning (Nielsen, 2022). A number of cognitive tests have been adapted, validated and normed for cognitive examination in *specific* languages, cultures and educational groups on an international scale (see Nielsen, 2022 for a review). However, on the other hand, recent studies have sought to develop and validate instruments that may be applicable *across* diverse sociocultural groups (Nielsen et al., 2019;

Storey et al., 2004). Nevertheless, there is still a debate among experts as to the feasibility of developing tests of social cognition and language that are applicable across cultures and languages, or whether tests should be tailored to each specific minority ethnic group (Franzen, Papma, et al., 2021).

With regard to social cognition, the limited availability of tools for the assessment of these deficits in clinical settings, in addition to their narrow focus on only a few subdomains, is further compounded by a lack of information on their cross-cultural applicability.

Against this background, the present study aims to address this issue by adapting an English version of the FACE test, thereby expanding its applicability beyond its original Italian context. Furthermore, the study assesses the cross-cultural applicability of the FACE test (Terruzzi et al., 2023), along with two other social-cognitive measures (Ekman 60 Faces test – Ek-60F, Ekman & Friesen, 1976); Story based empathy task – SET, Dodich et al., 2015), by comparing performance across Italian and English-speaking cohorts and evaluating the equivalence in these groups' performance. Finally, the study aims to explore the associations between demographic, cognitive and social variables and FACE test performance in the ENG group, with a view to comparing the resulting data with that provided for the Italian population in Study 3.

4.7. Methods

4.7.1. Participants

The present study involved the voluntary participation of two cohorts of healthy older adults, aged between 64 to 85 years, who were native speakers of either Italian or English. The participants were recruited from the University of Trento (Italy) and the University of Edinburgh (United Kingdom) through a process of opportunity sampling, using word-of-mouth, social media, and the volunteer panel. To be eligible for inclusion in the study, participants were screened using the Montreal

Cognitive Assessment (MoCA) test (Nasreddine et al., 2005) with the aim of ascertaining the absence of dementia or MCI, as defined by national criteria. In particular, Italian participants were required to achieve a MoCA equivalent score ≥2 (Conti et al., 2015), while English-speaking participants were required to achieve a MoCA score ≥26 for inclusion (Nasreddine et al., 2005). Moreover, to ensure cultural homogeneity, only participants who identified as Caucasian were included in the study. Individuals with a self-reported history of neurological, psychiatric, or neurodevelopmental disorders were excluded from participation in the study. All participants provided written informed consent in accordance with the ethical guidelines established by the local ethics committees and the principles outlined in the Declaration of Helsinki (World Medical Association, 2013).

4.7.2. Neuropsychological Assessment

A comprehensive battery of social cognition tests was administered via computer to the participants in their native language by experienced psychologists. The battery of tests included the Ekman-60 Faces (Ek-60F) test (Ekman & Friesen, 1976) to assess the recognition of basic emotions conveyed by facial expressions, the Story-Based Empathy Task (SET) (Dodich et al., 2015) to evaluate the capacity to attribute intentions and emotions to others, and the Facial Complex Expressions (FACE) test (Version A, 18-items) (Terruzzi et al., 2023) to assess the ability to recognise complex mental states from facial expressions. Furthermore, cognitive reserve was evaluated using the Cognitive Reserve Index Questionnaire (CRIq) (Nucci et al., 2012), which assessed the participants' educational background, professional activities, and engagement in leisure pursuits. Finally, as a control for the phenomenon of the "*Other Race Effect*" (ORE), whereby participants demonstrate greater accuracy in recognising faces of their own race than faces of other races (Malpass & Kravitz, 1969), participants were asked to indicate their ethnicity.

4.7.3. Adaptation of the FACE Test

As detailed in the supplementary information for Study 3, the FACE test was originally developed in Italy using images and mental state descriptors in English extracted from the McGill database (Schmidtmann et al., 2020). Therefore, the original stimuli were employed to develop the English version of the FACE test.

4.7.4. Statistical Analysis

First, preliminary statistical analyses were performed to assess the distribution of the data (Shapiro-Wilk test) in the Italian (ITA) and English (ENG) groups. A combination of frequentist and Bayesian statistical methods was then used to analyse the data. The classical independent samples T-test was used to compare the means of demographic variables and neuropsychological measures between the ITA and ENG groups, with parametric (t-Student) or non-parametric (Mann-Whitney U test) statistics based on the data distribution. The Bayesian Mann-Whitney test was used to compare the data distributions between the two groups. The Two One-Sided Tests (TOST) procedure https://cran.r-project.org/web/packages/TOSTER/TOSTER.pdf (Lakens, 2017) was then used to assess the equivalence of performance between the two groups on social-cognitive measures (Ek-60F test, SET, and FACE test). The equivalence limits were set at 5% of the maximum possible score for each test.

Given that the Italian MoCA cut-off score employed to include healthy participants in the study (Conti et al., 2015) is lower than that recommended by the UK national criteria (Nasreddine et al., 2005), further exploratory analyses were performed matching the ITA and ENG groups on general cognitive ability using the MoCA score. In addition, these exploratory analyses included a visual inspection of the social tests box plots to identify any potential outliers that could be excluded from the subsequent analysis.

Finally, correlation analysis (Spearman) was used to examine the relationship between performance on the FACE test and other neuropsychological measures in the ENG group.

Statistical analyses were performed using Jamovi 2.0.0 (Jamovi, 2021) and JASP 0.18.03 (JASP Team, 2023) with a significance level <0.05.

4.8. Results

According to the established inclusion and exclusion criteria, forty-seven participants were included in both the ENG and ITA groups (Table 10). The two groups showed a balanced sex distribution and no statistically significant difference in age, as confirmed by the results of the Bayesian analysis. Conversely, a significant difference was observed in the level of education, with the ENG group having a higher level. Bayesian analysis strongly supported the evidence of a significant difference in educational attainment between the two groups. In terms of general cognitive functioning, the ENG group scored significantly higher on the MoCA test than the ITA participants, and the Bayesian analysis provided extreme evidence of a strong difference in cognitive performance between the groups. Similarly, the Cognitive Reserve Index (total score, education, leisure activities) was significantly higher in the ENG group, with Bayesian analysis providing extreme evidence of a difference. No significant difference was identified with regard to work-related cognitive reserve, indicating that the two groups exhibited comparable levels in this area. A modest yet notable difference was observed between the groups on the Ek-60F test, with the ENG group showing a slightly better performance in recognising basic emotions, while the equivalence test indicated the means of two groups were sufficiently similar. The most apparent difference on social cognitive measures was on the SET, where ENG participants outperformed their ITA counterparts, again with strong evidence from the Bayesian approach. Equivalence tests indicated non-equivalence between the groups. For the FACE test, no significant difference was observed using either the frequentist or Bayesian approach to analysis; the TOST procedure confirmed that the groups were equivalent,

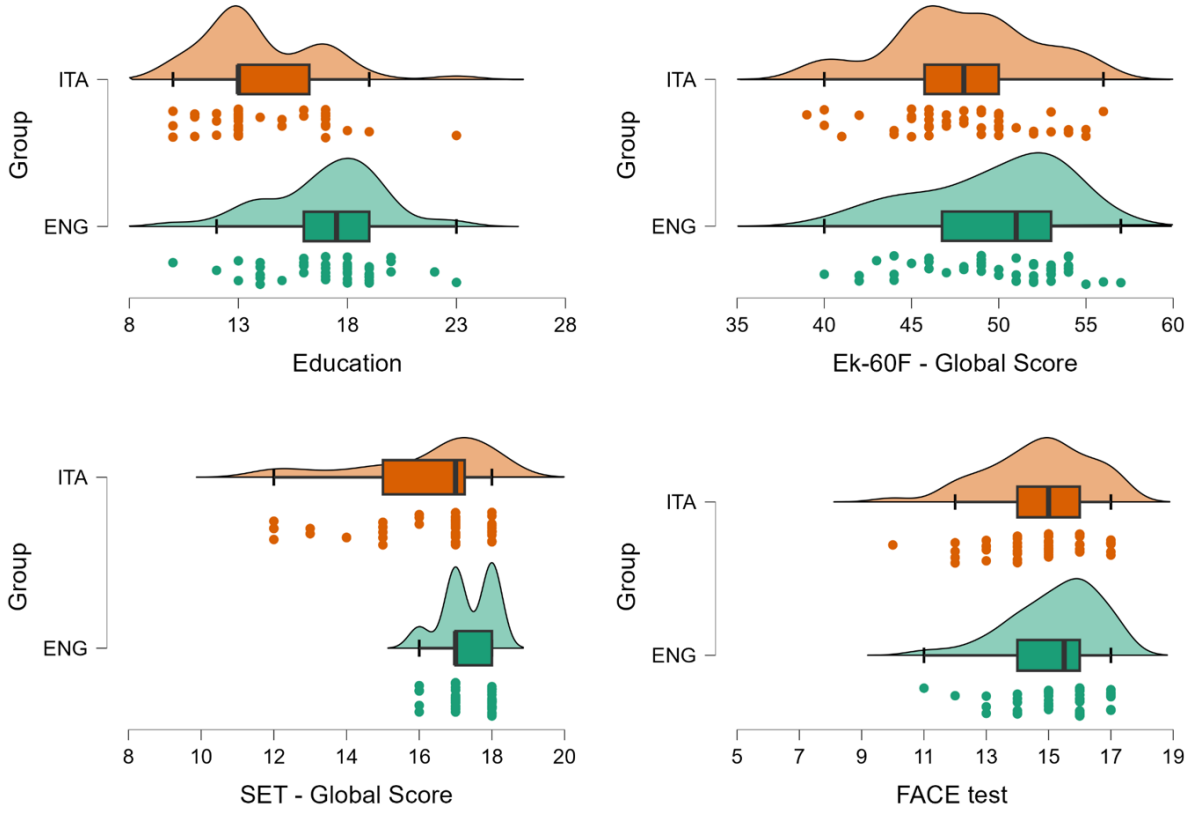
suggesting that the FACE test performs similarly in these two linguistically diverse groups. Table 10 reports the results of the comparison and equivalence tests between the two groups (ENG n=47; ITA n=47) on demographic and neuropsychological measures. Figure 4 shows raincloud plots illustrating the distribution of education, Ek-60F global scores, SET global scores, and FACE test performance in both groups.

Table 10. *Comparison of neuropsychological performance between groups (n=47; n=47)*

	ENG (n=47)	***ITA (n=47)***			***ENG (n=47)***	***ITA (n=47)***			
	Mean±St.Dev.		***Independent Samples T-Test***	***p-value***	***Median***		***Bayes Factor*** (BF^{10})	***Qualitative BF Interpretation***	***Equivalence***
Sex (M/F)	20/27	21/26	X2(1)=0.04	0.835					
Age	70.4±4.7	71.7±5.2	U=946	0.230	70	71	0.25	Moderate evidence for H0	
Education	17.2±2.6	14.0±2.7	t(92)=5.85	**<0.001**	18	13	731.24	Extreme evidence for H1	
MoCA test	28.0±1.2	26.2±2.0	U=482	**<0.001**	28	26	306.17	Extreme evidence for H1	
CRIq – Total	135.3±13.1	120.0±14.5	t(92)= 5.38	**<0.001**	135	121	224.22	Extreme evidence for H1	
CRIq – Education	129.1±11.3	115.4±8.1	t(92)= 6.73	**<0.001**	129	114	2454.73	Extreme evidence for H1	
CRIq – Work	115.1±15.3	111.5±18.5	t(92)= 1.04	0.299	115	115	0.33	Anecdotal evidence for H0	
CRIq – Leisure	135.6±18.8	117.9±18.1	t(92)= 4.66	**<0.001**	137	119	139.97	Extreme evidence for H1	
Ek-60F	49.5±4.5	47.7±4.3	U=801	**0.045**	51	48	1.10	Anecdotal evidence for H1	YES [-3;3]
SET	17.3±0.7	16.0±2.0	U=648	**<0.001**	17	17	14.62	Strong evidence for H1	NO [-1;1]
FACE test	15.2±1.4	14.5±1.8	U=860	0.053	15.5	15	0.96	Anecdotal evidence for H0	YES [-1;1]

Note. Parametric or non-parametric T-tests according to data distribution, Bayesian Mann-Whitney test, and Two One-Sided Tests (TOST).
Descriptive data are given as Mean ± Standard Deviation (St.Dev.) for parametric statistics; Median for non-parametric statistics.

Figure 4. *Bayesian Independent Samples T-Test raincloud plots (n=47; n=47)*



Note. Ek-60F - Ekman 60-faces test; SET - Story-based Empathy Task; FACE - Facial Complex Expression FACE test

When the ITA (n=27) and ENG (n=47) groups were matched on MoCA scores, a significant difference in educational attainment remained, with the ENG group having a higher level of education, as confirmed by the Bayes factor. The MoCA scores were still slightly higher for the ENG participants, although the difference did not reach statistical significance. Significant differences were confirmed on the Cognitive Reserve Index, with ENG participants achieving higher scores, particularly in education and leisure activities. With regard to social-cognitive measures, following the exclusion of outliers in single tests based on visual inspection of the box plots, no significant differences were observed between ITA and ENG participants on the Ek-60F, SET and FACE scores, using either the frequentist or Bayesian approach. However, the results of the TOST procedure indicated that the means of the ITA and ENG groups, matched for MoCA score, were statistically equivalent for the FACE and the Ek-60F tests, but not for the SET. These findings provide further

evidence that the FACE test is likely to perform similarly across these culturally and linguistically diverse groups, supporting its cross-cultural validity. Table 11 presents the results of the comparison and equivalence tests between the two groups (ENG n=47; ITA n=27) on demographic and neuropsychological measures. Figure 5 shows raincloud plots illustrating the distribution of education, Ek-60F global scores, SET global scores, and FACE test performance in both groups.

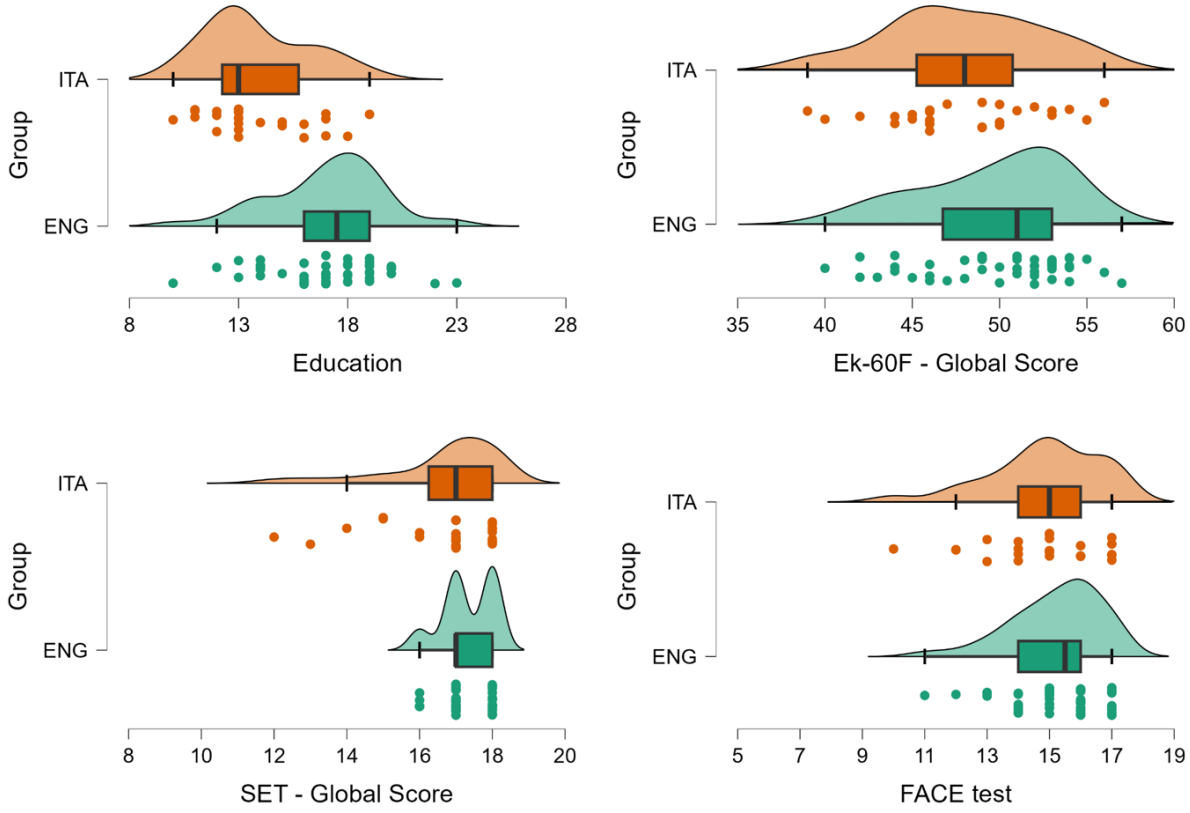
Finally, a significant correlation was observed between FACE test scores and Ek-60F test scores (r_s=0.30, p=0.04) in the ENG sample (n=47), which aligns with the Italian normative data (Terruzzi et al., 2023). This finding lends support to the reliability of the FACE test in different cultural and linguistic contexts. No significant correlation was found between FACE test scores and any of the other demographic, cognitive and social variables (Table 12).

Table 11. *Comparison of neuropsychological performance between groups matched for the MoCA score (n=47; n=27)*

	ENG (n=47)	***ITA (n=27)***			***ENG (n=47)***	***ITA (n=27)***			
	Mean± St.Dev.		***Independent Samples T-Test***	***p-value***	***Median***		***Bayes Factor (BF10)***	***Qualitative BF Interpretation***	***Equivalence***
Sex (M/F)	20/27	9/18	X2(1)=0.61	0.434					
Age	70.4±4.7	70.6±5.0	U=623	0.901	70	70	3.57	Moderate evidence for H0	
Education	17.2±2.6	13.8±2.3	t(72)=5.5	**<0.001**	18	13	0.02	Extreme evidence for H1	
MoCA test	28.0±1.2	27.5±1.3	U=482	0.08	28	27	1.52	Anecdotal evidence for H0	
CRIq – Total	135.3±13.1	118.8±14.9	t(72)= 4.94	**<0.001**	135	118	0.01	Extreme evidence for H1	
CRIq – Education	129.1±11.3	114.4±7.2	t(72)= 6.07	**<0.001**	129	114	0.00	Extreme evidence for H1	
CRIq – Work	115.1±15.3	111.7±19.1	t(72)= 0.83	0.409	115	115	3.44	Moderate evidence for H0	
CRIq – Leisure	135.6±18.8	115.6±17.9	t(72)= 4.49	**<0.001**	137	118	0.02	Extreme evidence for H1	
Ek-60F	49.5±4.5	48.0±4.4	t(71)= 1.45	0.153	51	48	2.20	Anecdotal evidence for H0	YES [-3;3]
SET	17.3±0.7	16.6±1.7	U=470	0.086	17	17	1.15	Anecdotal evidence for H0	NO [-1;1]
FACE test	15.2±1.4	14.7±1.9	U=530	0.288	15.5	15	2.55	Anecdotal evidence for H0	YES [-1;1]

Note. Parametric or non-parametric T-tests according to data distribution, Bayesian Mann-Whitney test, and Two One-Sided Tests (TOST).
Descriptive data are given as Mean ± Standard Deviation (St.Dev.) for parametric statistics; Median for non-parametric statistics.

Figure 5. *Bayesian Independent Samples T-Test raincloud plots (n=47; n=27)*



Note. Ek-60F - Ekman 60-faces test; SET - Story-based Empathy Task; FACE - Facial Complex Expression FACE test

Table 12*. Correlation analyses in the ENG group*

	Facial Complex Expression (FACE) test – Version A
Age	$r_{s=}$ 0.21, p=0.16
Education	$r_{s=}$-0.08, p=0.61
MoCA	$r_{s=}$0.06, p=0.68
CRIq – Total	$r_{s=}$-0.05, p=0.75
CRIq – Education	$r_{s=}$ 0.09, p=0.56
CRIq – Work	$r_{s=}$ -0.1, p=0.49
CRIq –Leisure time	$r_{s=}$-0.01, p= 0.94
Ek-60F	**$r_{s=}$0.3, p=0.04**
SET	$r_{s=}$-0.05, p= 0.74

4.9. Discussion

The objective of the present study was twofold: firstly, to adapt an English version of the FACE test and secondly, to assess the cross-cultural validity of this test, along with two other social cognitive measures, in Italian and English-speaking healthy older adults. The initial analyses revealed significant discrepancies in educational background, cognitive reserve, and overall cognitive performance between the English- and Italian-speaking groups. The ENG participants consistently demonstrated superior performance compared to their Italian counterparts. However, the discrepancy in performance on social cognition tasks (Ek-60F test and SET) was less pronounced, though still statistically significant. In contrast, the FACE test demonstrated no significant difference and statistical equivalence between the groups, indicating its potential suitability as a tool for cross-cultural applications. Once the groups had been matched on MoCA scores, significant differences in education and cognitive reserve remained, but no significant differences were observed in MoCA, Ek-60F, SET, or FACE test performances. Nevertheless, statistical equivalence between groups was demonstrated solely in basic and complex emotion recognition, whereas differences were still detectable in emotion and intention attribution. With regards to the relationship between the FACE and other social cognitive measures, the significant correlation observed with the Ek-60F test, consistent with the results of Study 3 on the Italian population, supports the reliability of the FACE test in different cultural and linguistic contexts. Conversely, the lack of significant correlation with SET score may be due to a ceiling effect observed in the ENG sample, as over 40% of participants achieved a score of 18/18 in this task.

Although the results are only preliminary, this study successfully adapted an English version of the FACE test, thereby extending its applicability for use in both clinical and research contexts. Moreover, the findings provide encouraging preliminary evidence for the cross-cultural validity of the FACE test in Italian and English-speaking healthy older adults. To achieve this, it is essential that equivalence testing be incorporated into the validation process for neuropsychological tools (Lakens

et al., 2018). Indeed, traditional difference testing may lead to the conclusion that a test performs similarly across groups if no significant differences are identified. On the other hand, equivalence testing goes beyond this by assessing whether the two tests are statistically equivalent, meaning that the difference between them is practically negligible or within a predefined margin. In the present study, the equivalence of performance between the two language groups suggests that the FACE test may be a reliable tool for assessing the recognition of complex mental states from facial expressions across different cultural contexts, as well as the Ek-60F for basic emotion recognition. Conversely, the observed discrepancies in SET performance suggest that cultural variations and/or educational attainment may exert an influence on this task. This is consistent with the results of the standardisation in the Italian population, which have demonstrated the role of education in performance on this specific task (Dodich et al., 2015).

Collectively these findings suggest that socio-cultural differences between countries may play an important role in studies comparing socio-cognitive performance using the same inclusion criteria. Consistent with the existing literature on this topic (Nielsen, 2022), this study emphasises the importance of accounting for socio-cultural and linguistic differences, as well as education and literacy, in cross-cultural cognitive assessment. This is crucial for multicentric studies at an international level, which should carefully consider the appropriateness of the “cognitive” inclusion criteria chosen for both healthy controls and patients enrolment (Ilardi et al., 2023). Further research is required to increase the sample size in order to achieve greater statistical power, to gain a deeper understanding of the influence of language and culture on social test performance, and to investigate the potential influence of additional factors on the test outcomes. This will facilitate the optimisation of the test for use in diverse culturally, linguistically and educationally diverse populations and it could enhance both the test's applicability and accuracy in detecting socio-cognitive dysfunction in a broader range of cultural settings.

Chapter 5 - Mental state recognition deficits linked to brain changes in Parkinson's disease without dementia (Study 4)

This chapter presents the findings of a neuroimaging study which aimed to investigate the association between the recognition of complex mental states, as assessed by the *Facial Complex Expressions (FACE) test*, and structural and functional brain changes in individuals with PD. The study examined resting-state functional connectivity and grey matter volume in a cohort of 24 PD patients, focusing on a specific group of brain areas known as the *emotion understanding network* (Spunt & Adolphs, 2019), as well as conducting whole-brain analyses. Furthermore, the patients were classified as either clinically impaired (n=8) or unimpaired (n=16) based on their performance on the FACE test, and imaging metrics were compared between these two groups. This study contributes to elucidate the neural correlates underlying socio-cognitive dysfunction in PD. Moreover, from a clinical perspective, a detailed characterisation of early emotional deficits in PD may have significant implications for the characterisation of the cognitive phenotype, with possible benefit for tailored non-pharmacological intervention.

5.1. Introduction

Parkinson's disease (PD) is a progressive multi-system neurodegenerative disorder characterised by progressive dopamine depletion in the basal ganglia, frontoparietal regions, and limbic system (Obeso, Marin, et al., 2008). These brain systems, responsible for motor, cognitive, and affective functions, also play a relevant role in social cognition, a complex and multifaceted cognitive domain involving multiple processes that collectively underlie everyday social interactions (Happé et al., 2017).

Although initially under-reported, in recent years numerous reviews and meta-analyses have consistently provided evidence of social-cognitive dysfunctions in PD patients, particularly in emotional processing (Argaud et al., 2018; Gray & Tickle-Degnen, 2010; Palmeri et al., 2017; Péron et al., 2012), ToM (Bodden, Dodel, et al., 2010; Bora et al., 2015b; Coundouris et al., 2020; Palmeri et al., 2017), and empathy (Coundouris et al., 2020), with significant difficulties in both emotion recognition and representation (Enrici et al., 2015). Such deficits can drastically reduce the quality of life of PD patients and families (Schwartz et al., 2020), possibly increasing demands on the health system.

Recently, our research group demonstrated the presence, detectable at clinical assessment, of significant deficits in the recognition of complex mental states from faces in a relevant proportion of PD patients (28%) (Terruzzi et al., 2023); however, despite extensive theoretical and behavioural research, the characterisation of these affective deficits in terms of underlying neural correlates remains still strongly limited (Baggio et al., 2012; Diederich et al., 2016; Lewis & Ricciardi, 2021; Rabini et al., 2023; Trompeta et al., 2021; Wabnegger et al., 2015).

A model of emotion understanding recently proposed by Spunt and Adolphs (2019) outlines the cognitive processes involved and synthetizes the available, mainly functional, neuroimaging data on brain regions associated with emotion understanding. According to this model, the first step is represented by all the subprocesses required for the *detection and orientation of attention* to emotion-

relevant sensory cues in the environment, which are associated with amygdalar function. The recruitment of temporal regions (i.e., the anterior temporal cortex and the posterior superior temporal sulcus) enables the *categorization* of these cues in emotional terms. Regions such as the primary and secondary somatosensory cortex as well as the insula contribute to this process via the *embodied simulation* of specific emotions. Finally, regions belonging to the frontal lobe (i.e., the dorsomedial prefrontal cortex and the ventrolateral prefrontal cortex) are recruited for the *causal attribution* of the affective signals.

Overall, preliminary evidence in PD patients indicates the presence of functional and structural alterations in these regions, which have been related to reduced performance in emotion recognition (Baggio et al., 2012; Benzagmout et al., 2019; Diederich et al., 2016; Ibarretxe-Bilbao et al., 2009; Tessitore et al., 2002; Wabnegger et al., 2015), emotion attribution (Orso et al., 2020), and valence processing (Bell et al., 2019). In particular, available studies investigating the neural correlates of emotion recognition impairment in PD identified an association between reduced abilities and structural neurodegeneration in limbic regions, including the orbitofrontal cortex, the amygdala, the anterior cingulate cortex, the insula and the ventral striatum (Baggio et al., 2012; Diederich et al., 2016; Ibarretxe-Bilbao et al., 2009; Suzuki et al., 2006). Evidence for functional changes in PD associated with deficits in emotion understanding is more limited, but supports the involvement of limbic (Banwinkler et al., 2022; Bell et al., 2019) and parietal regions (Wabnegger et al., 2015). The collective findings suggests that the potential for deficits in emotion processing may be associated with alterations in regions belonging to the "social brain" (Frith, 2007) in PD patients. The aim of the current study is therefore to extend the characterisation of these deficits in non-demented PD patients, by investigating the association between altered recognition of complex mental states from faces and brain changes using a multi-level neuroimaging approach (i.e., functional and structural).

Specifically, the first aim of this study is to investigate the relationship between performance on a test of complex mental state recognition, the *FAcial Complex Expressions* (FACE) test (Terruzzi et

al., 2023), and both resting-state functional connectivity (FC) and grey matter (GM) volume, taking into account the brain areas involved in the emotion understanding networks via region of interest (ROI) analysis (Spunt & Adolphs, 2019). A second exploratory aim is to investigate the association between FACE performance and functional/structural brain metrics at the whole-brain level, as this may potentially extend the network of regions involved in emotion understanding in these patients.

5.2. Methods

5.2.1. Participants

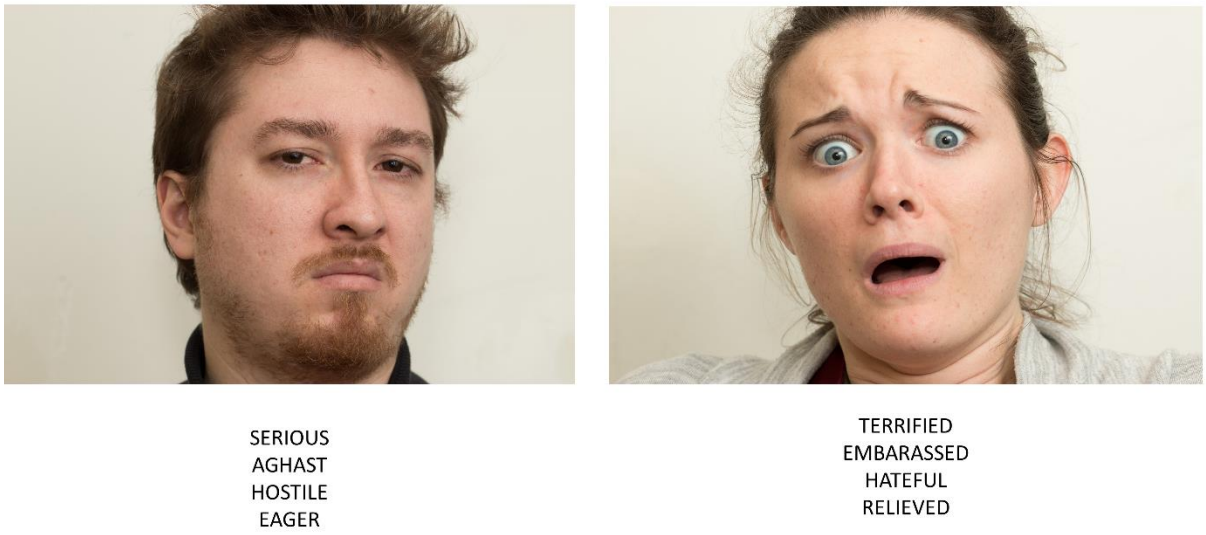
Twenty-four non-demented patients with PD according to the United Kingdom Parkinson's Disease Society brain bank criteria (Hughes et al., 1992) (13 male; mean age: 67.1±7.0 years; mean education: 10.8±3.8 years; mean MOCA score: 22.4±3.9) were recruited at the Centre for Neurocognitive Rehabilitation of the Centre for Mind/Brain Sciences - CIMeC (University of Trento). All patients underwent a comprehensive clinical neurological assessment and a neuropsychological evaluation, including the Montreal Cognitive Assessment (MoCA test) as a screening test (Conti et al., 2015). Inclusion criteria were as follows: (I) a diagnosis of idiopathic PD; (II) a Hoehn and Yahr score ≤3 (Hoehn & Yahr, 1967); (III) being under antiparkinsonian medication; and (IV) age over 50 years. Patients with a history of dementia or neuropsychiatric disorders were excluded from the study. No participants exhibited contraindications to magnetic resonance imaging (MRI) scanning based on medical history and physical examination. The study was conducted with patients taking their usual L-dopa medication (ON state), which was quantified by conversion to Levodopa Equivalent Daily Dose (LEDD) (not available for 4 patients).

All participants provided informed consent for the study, which adhered to the ethical guidelines of the local ethics committee (University of Trento Research Ethics Committee, protocol 2019-033) and the Declaration of Helsinki (World Medical Association, 2013).

5.2.2. Mental states recognition task

The ability to recognise complex mental states was assessed using the FACE test (Terruzzi et al., 2023), a novel task developed in Italy and validated in both healthy controls and patients with Parkinson's disease, showing satisfactory psychometric properties (Terruzzi et al., 2023). The test consists of 36 pictures of facial expressions representing different mental states and interpreted by professional actors. For each picture, participants were required to provide a verbal response by selecting from four adjectives the one that most accurately described the actor's facial expression. Illustrative examples of FACE pictures are presented in Figure 6.

Figure 6*. Examples of pictures from the FACE test*



Note. The figure shows two actors (male and female) displaying the facial expression corresponding to "Hostile" and "Terrified".

5.2.3. MRI data acquisition and processing

5.2.3.1. MRI acquisition protocol

The MRI data were collected at the Centre for Mind/Brain Sciences - CIMeC (University of Trento) using a 3.0 T MRI scanner (Prisma, Siemens) with a 64-channel head receive coil. The procedure

was adequately described to all PD subjects, who were instructed to keep their eyes closed and not to sleep during the MRI scan. Soft pads were placed around the patient's head to minimise head movement during the MRI scan. The MRI scan was performed within 3 months of the behavioural data collection. For each participant, T1-weighted MEMPRAGE structural images were acquired using the following parameters: MPRAGE_GRAPPA: 176 volumes, isotropic voxel resolution of 1 mm, sagittal plane orientation, flip angle of 7 degrees, matrix = 256x256, TR of 2.53 seconds, TE of 2.9 ms, TI of 1100 ms, slice thickness of 1 mm. Additionally, resting-state functional magnetic resonance images (rs-fMRI) were acquired using echo planar (EPI) T2*-weighted scans. The following acquisition parameters were used: TE of 28 ms, TR of 1.0 seconds, flip angle of 58 degrees, axial slice thickness of 2 mm. A total of 400 whole brain volumes were acquired in a resting state run of 6 min 40 s, isotropic voxel size 2 mm, AC/PC aligned.

5.2.3.2. Functional connectivity pre-processing

rs-fMRI analyses were performed using CONN functional connectivity toolbox (release 21.a - RRID: SCR_009550; https://web.conn-toolbox.org; Nieto-Castanon, 2021; Whitfield-Gabrieli & Nieto-Castanon, 2012), and Statistical Parametric Mapping (SPM12 - v7487 - RRID: SCR_007037; https://www.fil.ion.ucl.ac.uk/spm; Penny et al., 2011), based on MATLAB R2020b.

Functional and anatomical data were pre-processed using a flexible pre-processing pipeline including (a) realignment with correction of susceptibility-distortion interactions, (b) slice timing correction, (c) outlier detection, (d) direct segmentation and Montreal Neurological Institute (MNI) space normalization, and (e) smoothing (only for voxel-level analyses, not for ROI-level analyses). Functional data were realigned using the SPM realign & unwarp procedure, where all scans were co-registered to a reference image (first scan of the first session) using a least squares approach and a 6-parameter (rigid body) transformation, and resampled using b-spline interpolation to correct for motion and magnetic susceptibility interactions. Temporal misalignment between different slices of

the functional data (acquired in interleaved Siemens order) was corrected according to the SPM slice-timing correction (STC) procedure, using sinc temporal interpolation to resample each slice BOLD (Blood Oxygenation Level Dependent) time-series to a common mid-acquisition time. Potential outlier scans were identified using ART as acquisitions with framewise displacement above 0.9 mm or global BOLD signal changes above 5 standard deviations, and a reference BOLD image was computed for each subject by averaging all scans excluding outliers. Functional and anatomical data were normalized into standard MNI space, segmented into grey matter, white matter, and cerebrospinal fluid tissue classes, and resampled to 2 mm isotropic voxels following a direct normalization procedure using SPM unified segmentation and normalization algorithm with the default IXI-549 tissue probability map template. Last, functional data (only for voxel-level analyses) were smoothed using spatial convolution with a Gaussian kernel of 8 mm full width half maximum (FWHM).

In addition, functional data were denoised using a standard denoising pipeline including the regression of potential confounding effects characterised by white matter timeseries (5 CompCor noise components), CSF timeseries (5 CompCor noise components), motion parameters and their first order derivatives (12 factors), outlier scans (below 123 factors), session effects and their first order derivatives (2 factors), and linear trends (2 factors) within each functional run, followed by bandpass frequency filtering of the BOLD timeseries between 0.008 Hz and 0.09 Hz. CompCor noise components within white matter and CSF were estimated by computing the average BOLD signal as well as the largest principal components orthogonal to the BOLD average, motion parameters, and outlier scans within each subject's eroded segmentation masks. From the number of noise terms included in this denoising strategy, the effective degrees of freedom of the BOLD signal after denoising were estimated to range from 41.2 to 61.3 (average 58.8) across all subjects.

5.2.3.3. Grey matter pre-processing

Anatomical images were analysed using the Computational Anatomy Toolbox (CAT12.8.2 - r2170; https://neuro-jena.github.io/cat; Gaser et al., 2022) for Statistical Parametric Mapping (SPM12 - v7771; https://www.fil.ion.ucl.ac.uk/spm; Penny et al., 2011) in MATLAB R2019a.

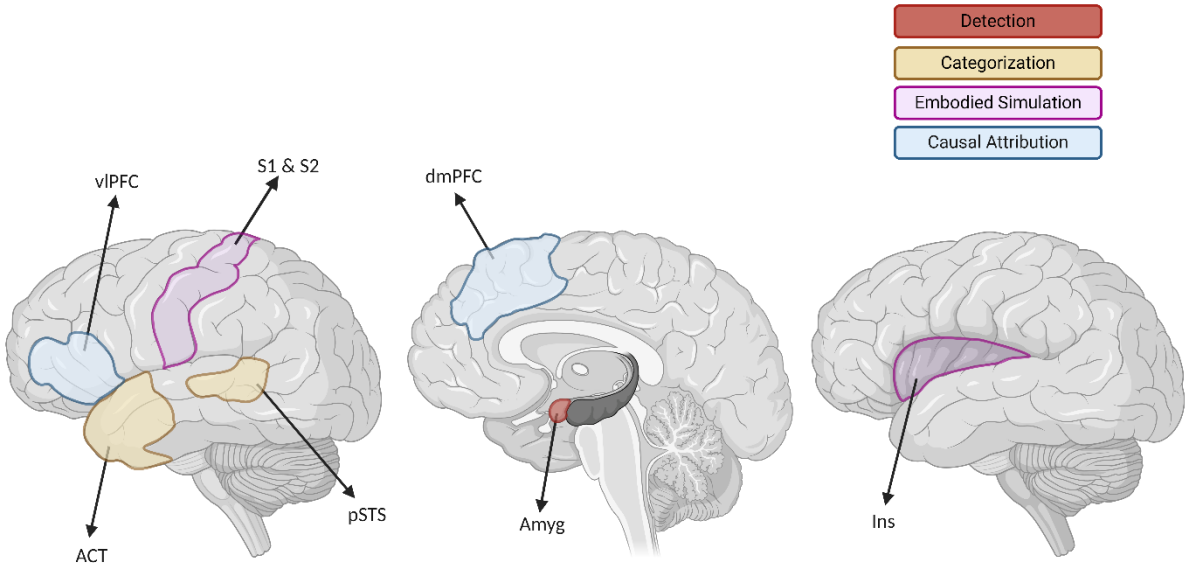
The T1-weighted anatomical images were pre-processed according to the standard VBM pre-processing pipeline of CAT 12, which includes: (a) tissue segmentation into grey matter, white matter and cerebrospinal fluid, (b) spatial normalization to the MNI space, (c) modulation, and (d) spatial smoothing with a Gaussian kernel of 8 mm full width at half maximum (FWHM) (Gaser et al., 2022).

In addition, to assess data quality, we visually inspected each segmented and modulated image and considered the Image Quality Ratings (IQR) index provided in the CAT12 reports. The IQR index is calculated based on measures of noise, bias, and image resolution, so we checked it to further ensure image quality. In this study, all images were above the satisfactory level of IQR (IQR index >70%), which is consistent with the description of quality ratings in the CAT12 guidelines.

5.2.4. Emotion understanding network

ROIs representing the emotion understanding network were selected based on the Spunt & Adolphs model (Spunt & Adolphs, 2019) and derived from the Brainnetome Atlas (https://atlas.brainnetome.org/) (Fan et al., 2016). The ROIs included were the anterior temporal cortex (ATC), the posterior part of the superior temporal sulcus (pSTS), the primary and secondary somatosensory cortex (S1/S2), the insula (Ins), the amygdala (Amyg), the dorsomedial prefrontal cortex (dmPFC) and the ventrolateral prefrontal cortex (vlPFC). A total of 14 ROIs were considered, comprising both left- and right-sided regions. See Figure 7 for a graphical representation.

Figure 7. *Brain regions associated with the different functional aspects of emotion understanding (adapted from Spunt & Adolph, 2019)*



Note. Image created with BioRender.com (https://www.biorender.com, agreement number: QC26XF9BAG).

5.2.5. Statistical analyses

5.2.5.1. Behavioural data

PD patients were classified as impaired (PD-IMP) or unimpaired (PD-UN) based on their performance on the FACE test according to Italian normative data (Terruzzi et al., 2023).

Group differences between PD-IMP and PD-UN patients in demographic, clinical, cognitive, and social characteristics were assessed using independent samples t-test or Mann-Whitney U-test based on data distribution. To account for possible differences in demographic variables between the two groups, the adjusted scores derived from the Italian normative data were used. The significance level was set at $p<0.05$. All statistical analyses were performed with Jamovi 2.0.0 (Jamovi, 2021; R Core Team, 2021).

5.2.5.2. MRI data

All twenty-four PD patients were included in the structural analyses, while two participants were excluded from the functional analyses due to excessive head movement during scanning (head movement >3 mm along any axis) or excessive mean framewise displacement [mean (FD); identified as an outlier with values greater than 3 scaled median absolute deviations from the median of the initial sample]. The results of the independent samples t-test indicated that there were no significant differences between the PD-UN and PD-IMP subgroups in either mean head movement (U=52, p=1.00) or mean FD (U=42, p=0.49).

To investigate the association between FACE test performance and functional and structural changes within the emotion understanding network (Spunt & Adolphs, 2019), ROI-based analyses were conducted. At the functional level, *ROI-to-ROI connectivity* (RRC) matrices were estimated to characterise the patterns of FC associated with FACE test performance within the 14 ROIs of the emotion understanding network (Spunt & Adolphs, 2019) (see "Regions of Interest" section). At the structural level, GM intensities were extracted from these 14 ROIs in subject-specific space during the pre-processing steps.

To investigate the potential involvement of other brain regions outside our network of interest, whole-brain exploratory analyses were also performed to complement the ROI results. Specifically, *seed-based connectivity* (SBC) maps were generated to characterise FC patterns at a whole-brain level, using the left and right amygdala separately as predefined seeds. This choice was based on previous evidence (Diederich et al., 2016) showing a relevant role of the amygdala in PD deficits, including dysfunction in emotion understanding. Instead, to examine the relationship between GM volume and the FACE test score, voxel-wise structural analyses were performed.

Two different approaches were used for both ROI-based and whole-brain analyses. First, multiple regression analyses were used to investigate the relationship between both structural and functional changes in the PD sample and FACE performance. Nuisance variables included the MoCA adjusted

score to control for patients' cognitive status and the Total Intracranial Volume (TIV) values (only in the structural analyses) to remove potential effects of brain size (Gaser et al., 2022). Furthermore, to assess potential possible differences between PD-IMP and PD-UN patients in terms of structural and functional characteristics, mean FC measures and GM values were contrasted between the two groups (two-sample T-test), controlling for MoCA adjusted score, sex and TIV (the latter only for the structural analyses).

The FC results were thresholded using a combination of a cluster-forming $p<0.001$ voxel-level threshold, and a familywise corrected False Discovery Rate (FDR) p-value<0.05 cluster-size threshold. For GM results, the statistical significance level was set at $p<0.05$ FDR-corrected for ROI-based analyses, while for whole-brain analyses, the significance level was set at $p<0.001$ (uncorrected) voxel-wise and $p<0.05$ FDR cluster-level.

5.3. Results

5.3.1. Behavioural data

The results of the statistical analyses revealed significant differences between the PD-UN and PD-IMP groups on the Unified Parkinson's Disease Rating Scale (UPDRS) – Part III ($t(22)=-2.17$; $p=0.04$) and MoCA ($t(22)=-2.74$; $p=0.01$). In particular, the PD-IMP group exhibited more severe motor symptoms and poorer cognitive function than the PD-UN group. Furthermore, the two groups were not balanced in terms of sex distribution (Fisher's exact test, $p=0.03$). Table 13 presents the demographic, clinical, cognitive, and social characteristics of the two groups (PD-UN vs. PD-IMP).

Table 13. *Between-group comparisons for demographic, clinical, cognitive, and social measures*

Variables	***PD-UN (n=16)***	***PD-IMP (n=8)***	***Statistics***
Sex (Female/Male)	10/6	1/7	Fisher's exact test, **p=0.03**
Age in years	65.2±7.6	70.9±3.4	t(22)=-2.00; p=0.06
Education in years	10.8±3.4	10.9±4.6	t(22)=-0.08; p=0.94
UPDRS – Part I	7.9±4.3	8.0±3.5	t(22)=-0.04; p=0.97
UPDRS – Part II	6.5±2.9	9.0±6.1	t(22)=-1.38; p=0.18
UPDRS – Part III	16.3±7.1	24.4±11.1	t(22)=-2.17; **p=0.04**
UPDRS – Part IV	1.8±3.2	1.0±1.4	U=62; p=0.88
Hoehn & Yahr Stage scale	1.6±0.7	2.1±0.6	t(22)=-1.87; p=0.08
LEDD	433.1±289.2	570.3±237.0	U=31; p=0.27
*MoCA**	23.7±3.4	19.7±3.6	t(22)=2.74; **p=0.01**
*FACE test**	31.0±2.1	21.0±2.2	t(22)=10.63; **p<0.001**

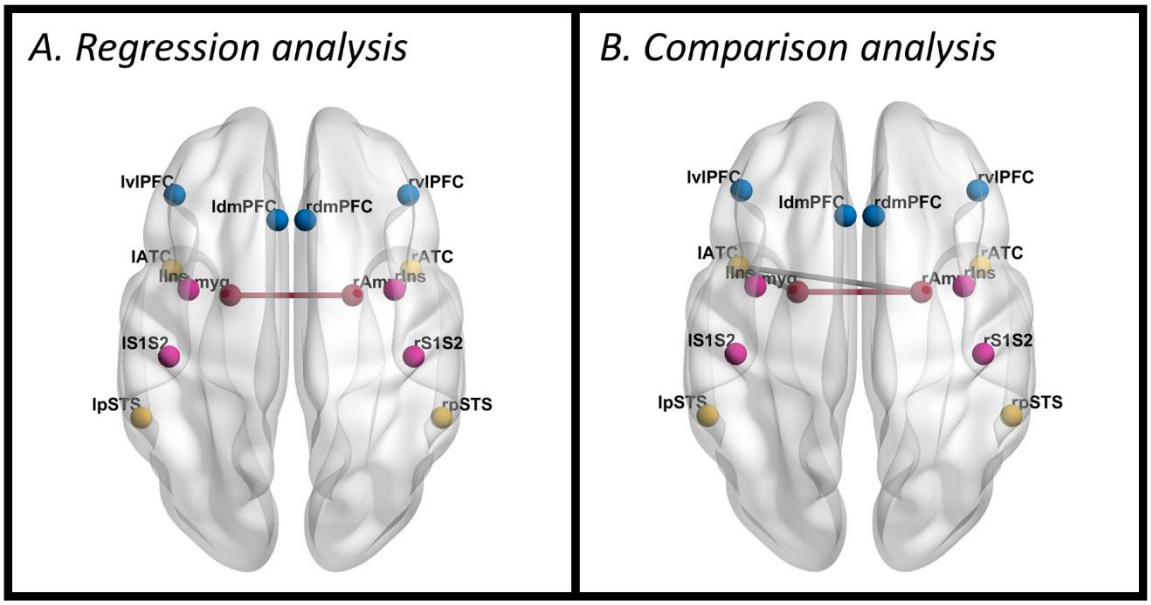
Note. *Adjusted scores based on Italian normative data.
Data represented as mean±standard deviation.
UPDRS: Unified Parkinson's Disease Rating Scale, LEDD: Levodopa equivalent daily dose; MoCA: Montreal Cognitive Assessment, FACE: FAcial Complex Expressions; PD-UN: classified as unimpaired based on their performance on the FACE test according to Italian normative data; PD-IMP: PD patients classified as impaired based on their performance on the FACE test according to Italian normative data.

5.3.2. Emotion processing according to Spunt & Adolphs model – ROI based analyses

At the functional level, the *RRC* matrix among 14 ROIs (91 connections sorted using hierarchical clustering) across the whole PD sample revealed a positive association between FACE test performance and BOLD co-activation of the right and left amygdala (t(19)=4.48, p-FDR=0.003) (Figure 8-A).

Besides, the results of the comparative RRC analysis between PD-UN and PD-IMP showed that PD patients impaired on the FACE test had lower FC than unimpaired PD patients between left and right amygdala (t(18)=-5.60, p-FDR=0.0003), left amygdala and left anterior temporal cortex (t(18)=-4.93, p-FDR=0.0007), and right amygdala and left anterior temporal cortex (t(18)=-4.27, p-FDR=0.0030) (Figure 8-B). No significant regions were identified with higher functional connectivity (FC).

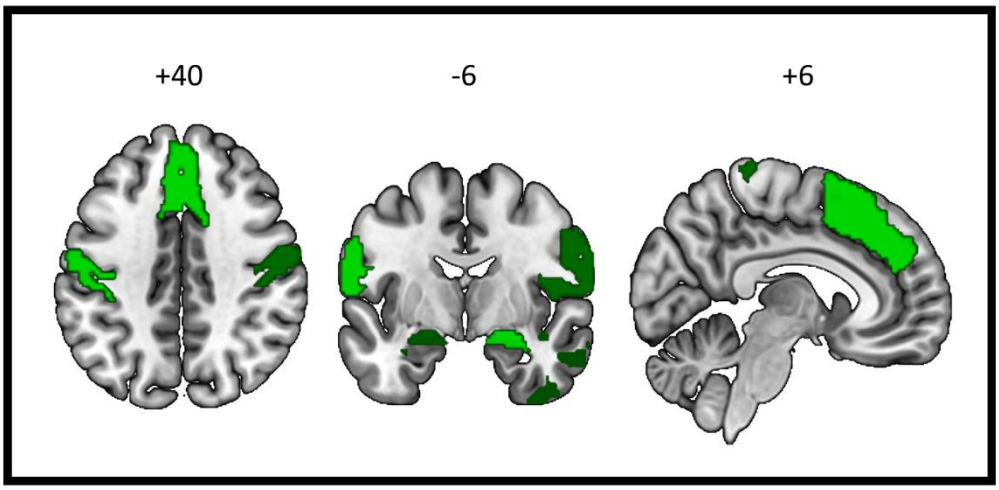
Figure 8. *ROI-based FC results*



Note. A) Significant positive association between ROI-to-ROI FC metrics and FACE test score in PD patients.
B) Difference in average connectivity between PD-UN and PD-IMP groups.
Images created with BrainNet Viewer (http://www.nitrc.org/projects/bnv/) (Xia et al., 2013).

At the structural level, ROI-based multiple regression analysis across the entire PD sample on 14 ROIs involved in emotion understanding showed a significant effect of FACE test score in bilateral dorsomedial prefrontal cortex, bilateral primary and secondary somatosensory cortex, bilateral amygdala, and right anterior temporal cortex (see Figure 9 and Table 14). A significant difference also emerged between the two groups (PD-IMP vs PD-UN) only in the right amygdala (p-value uncorrected=0.0057, t-value=2.82), where the PD-UN group had higher GM volume than the PD-IMP.

Figure 9. *ROI-based VBM results.*



Note. Significant positive association between GM volume and FACE test score in PD patients.
Colour scale indicates t-statistic: light green, t-value >3; dark green, t-value >2.
Significance: p<0.05 FDR-corrected.
Images displayed in neurological convention.

Table 14. *ROI-based VBM results - Significant positive association with GM volume in PD patients*

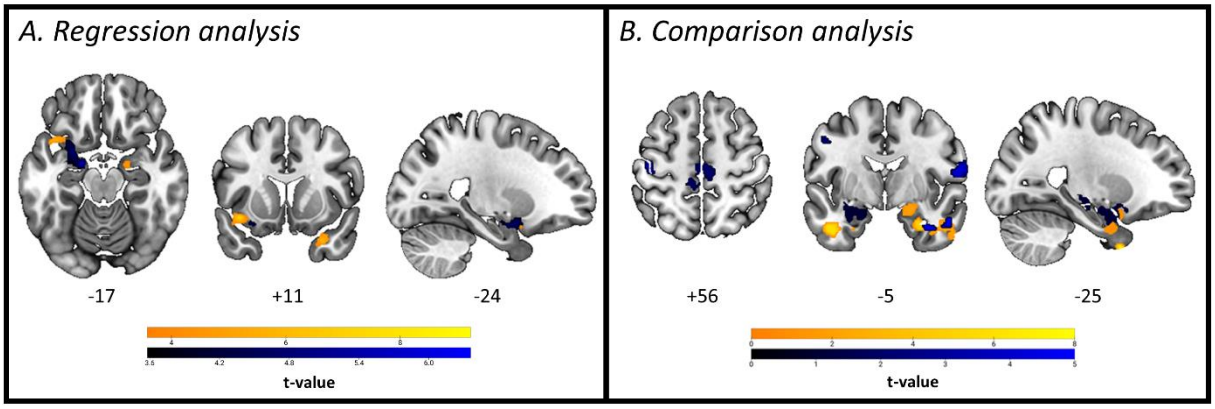
Regions of interest	***Uncorrected p-value***	***FDR-corrected p-value***	***t-value***
L dorsomedial prefrontal cortex	0.0025	0.0146	3.16
L ventrolateral prefrontal cortex	0.0326	-	1.95
L primary & secondary somatosensory cortex	0.0042	0.0146	2.93
L amygdala	0.0189	0.0440	2.23
L anterior temporal cortex	0.0336	-	1.94
R dorsomedial prefrontal cortex	0.0034	0.0146	3.01
R primary & secondary somatosensory cortex	0.0138	0.0386	2.38
R amygdala	0.0017	0.0146	3.33
R anterior temporal cortex	0.0242	0.0484	2.10

Note. Both FDR-corrected and uncorrected results are displayed. L: left; R: right.

5.3.3. Exploratory analyses at whole-brain level

At the functional level, further exploratory SBC regression analyses using the left and right amygdala separately as seeds revealed significant positive correlations between the FACE test performance and FC between the left amygdala and both the right temporal pole/right amygdala (x=30, y=10, z=-30; p-FDR=0.0258) and the left insular cortex (x=-40, y=14, z=-12; p-FDR=0.0258), as well as between the right-left amygdala (x=-18; y=-06;z=-18; p-FDR=0.0151) across the entire PD sample (Figure 10-A). On the other hand, results of comparative SBC analyses between PD-UN and PD-IMP showed a difference in mean FC between bilateral amygdala and bilateral temporal cluster (including inferior and middle temporal gyrus, temporal pole), as well as between right amygdala and bilateral pre/post-central gyrus, with PD-IMP group showing reduced FC (Figure 10- B, Table 15). No increased FC was found in the PD-IMP compared to the PD-UN subgroup.

Figure 10. *Whole-brain FC results.*



Note. A) SBC maps associated with FACE test score in PD patients.
B) SBC maps comparing PD-UN and PD-IMP.
Colours indicate connections from left (yellow) and right (blue) amygdala to the whole brain.
Images displayed in neurological convention.

At the structural level, VBM multiple regression analysis performed at the whole-brain level showed a significant cluster spanning the dorsomedial and the ventromedial prefrontal cortex (peak MNI coordinates: x=0; y=45; z=15; k=4109; p<0.05 FDR corrected at cluster level; t-value=6.72) across the entire PD sample. When comparing PD-IMP and PD-UN, no results survived FDR correction. Using an uncorrected threshold at voxel-level (p<0.001), the differences between impaired and unimpaired PD patients were located in the dorsomedial prefrontal cortex (paracingulate and cingulate gyrus, x=0,y=45, z=14; p-unc<0.001, t-value=5.83; middle frontal gyrus, x=-36, y=11, z=36, p-unc=0.001, t-value=3.65), left lateral occipital cortex (x=-32,y=-86, z=44; p-unc<0.001, t-value=4.38) and right temporal pole/amygdala (x=27,y=5, z=-29; p-unc=0.001, t-value=3.70).

Table 15. *Whole-brain FC results - SBC analysis of left/ right amygdala comparing PD-UN and PD-IMP*

Probabilistic anatomical label	***Cluster (x,y,z)***	***Uncorrected p-value***	***FDR-corrected p-value***	***t-value***
Seed - Left Amygdala				
L Temporal Pole	-40 +14 -12	0.000002	0.000077	9.81
R Hippocampus / Right Amygdala	+24 -26 -12	0.000088	0.001409	7.61
R Inferior Temporal Gyrus, posterior division	+50 -8 -28	0.000278	0.002433	6.22
L Middle Temporal Gyrus, posterior division	-64 -28 -8	0.000359	0.002433	5.89
R Temporal Pole	+28 -6 -30	0.000380	0.002433	5.78
L Inferior Temporal Gyrus, anterior division	-46 -8 -30	0.001479	0.007888	5.77
L Supramarginal Gyrus, posterior division	-42 -48 +10	0.004734	0.021641	5.54
L Temporal Pole	-40 +2 -44	0.005647	0.022589	5.12
Seed - Right Amygdala				
L Amygdala	-18 -06 -20	0.000001	0.000036	9.04
L/R Precentral Gyrus	+6 -22 +54	0.000004	0.000104	6.78
L Precentral & Postcentral Gyrus	-40 -18 +42	0.000007	0.000135	6.37
R Postcentral Gyrus	+66 -10 +14	0.001917	0.027314	5.80
R Inferior Temporal Gyrus, posterior division	+52 -8 -28	0.002688	0.030648	5.04

Note. Coordinates for each cluster that exceeds the thresholds specified in the text, showing a higher FC in the PD-UN vs PD-IMP group.

5.4. Discussion

A substantial body of evidence suggests that individuals diagnosed with PD exhibit a range of emotional processing deficits, from emotional experience to emotion production and recognition (Argaud et al., 2018; Péron et al., 2012). Nevertheless, despite mounting clinical evidence of socio-cognitive dysfunction in this population, the neural correlates underlying altered emotional processing in PD remain largely undefined. Overall, emotional processing deficits may arise from the dysfunction of the amygdala in PD (Diederich et al., 2016; Tessitore et al., 2002; Yoshimura et al., 2005) and the impairment of the cortico-striatal-thalamic-cortical loop, which is modulated by the mesolimbic dopamine system and is affected by PD pathology (Péron et al., 2012). However, the few neuroimaging studies currently available on PD patients have focused on the recognition of basic emotions (Baggio et al., 2012; Ibarretxe-Bilbao et al., 2009; Tessitore et al., 2002; Wabnegger et al., 2015), with no evidence for complex mental states. The present study aimed to address this gap by investigating the neural correlates of facial complex mental state recognition from faces in non-demented PD patients using a multi-level neuroimaging approach. Specifically, the association between FACE test performance and both resting-state FC and GM volumes in PD patients was tested within a defined network critical for emotion understanding (Spunt & Adolphs, 2019) and at the whole-brain level. Furthermore, we compared FC and GM values in PD patients with and without clinical deficits on the FACE test according to Italian normative data (Terruzzi et al., 2023).

The results of this study indicate that the bilateral amygdala plays a critical role in the recognition of complex mental states from facial expressions in PD patients at both the structural and functional levels. This is consistent with previous theoretical models proposing an early amygdala impairment in PD associated with altered processing of social signals (Argaud et al., 2018; Diederich et al., 2016; Wang et al., 2023). In particular, Diederich and colleagues (2016) emphasised the compromised recognition of emotional facial expressions as a prominent symptom of amygdala network dysfunction since the early stages of PD, along with impaired ToM and hypomimia.

While previous structural (Baggio et al., 2012; Ibarretxe-Bilbao et al., 2009) and functional (Tessitore et al., 2002) studies in PD have documented the impairment of the amygdala in basic emotion recognition, its involvement in complex emotion recognition remained unexplored. Consequently, our study offers novel insights by emphasizing the significance of this hub in the overall detection of emotion-relevant sensory stimuli.

Furthermore, the comparison of PD individuals with and without deficits in mental state recognition also revealed significant alterations in the patterns of FC between the bilateral amygdalae and the left anterior temporal cortex, which extended to the right anterior temporal cortex in the structural analyses. This result is consistent with the recent acknowledgment in the literature of the bilateral anterior temporal lobe as a crucial hub for social-semantic knowledge (Olson et al., 2007; Rouse et al., 2024; Thye et al., 2024), thanks to its structural connections with limbic structures (Olson et al., 2013).

The findings from functional whole-brain analyses confirmed the involvement of regions belonging to the emotion understanding network (Spunt & Adolphs, 2019) (the amygdala, the temporal cortex, and the insula) in the recognition of complex mental states. Interestingly, the insula did not emerge in the ROI-based analysis among the areas involved in FACE performance. However, it is worthy of attention that at the ROI level we did not distinguish between different sub-portions (i.e., anterior or posterior), while in the whole-brain analysis, we observed a specific involvement of the anterior portion. This is consistent with the well-known evidence supporting a prominent role of the anterior insula in emotional awareness, compared to the posterior part, dedicated to primary interoceptive representation (Craig, 2009; Kurth et al., 2010). Furthermore, the aforementioned analyses demonstrated the involvement of additional temporal areas not included in the Spunt and Adolphs model (Spunt & Adolphs, 2019), namely the inferior/middle temporal gyri bilaterally. The extensive engagement of temporal areas in the processing of both mental states in general (Abu-Akel &

Shamay-Tsoory, 2011), and specific features relevant to social cognitive processing, such as faces (Sellal, 2022), is required in FACE test performance and can justify these findings.

The structural imaging results confirmed the pivotal role of the amygdala in emotion processing and demonstrated a positive association between FACE performance and GM volumes in other brain areas included in the Spunt and Adolphs (2019) model, namely the dorsomedial prefrontal cortex and the primary/secondary somatosensory cortex bilaterally. Although neuroimaging studies in PD patients are still relatively limited in scope, preliminary evidence suggests that the medial prefrontal activation (Moonen et al., 2017) and the somatosensory recruitment (Wabnegger et al., 2015) may be involved in compensatory top-down cognitive control mechanisms, restoring striatal dysfunction related to the disease's pathology and modulating emotion regulation in PD patients. Collectively, these compensatory mechanisms could explain why we observed a positive association with the FACE test without GM reduction at the structural level in our PD sample, as previously suggested. However, the absence of a control group prevents us from ruling out the possibility of greater or lesser activation in these brain areas in relation to complex mental states recognition. Further research is required to more fully elucidate this aspect.

Despite the encouraging outcomes, it is essential to acknowledge the limitations of our study, which may influence our findings and suggest areas for future research. The principal methodological constraints of the present study are the relatively modest sample size and the absence of a healthy control group. Nevertheless, the inclusion of PD individuals without socio-cognitive dysfunctions as a comparison group, and the evidence of significant differences between this group and PD-IMP patients at the brain level, allowed us to partially overcome this limitation. Moreover, the test has been already clinically validated in PD patients, showing high diagnostic accuracy in discriminating PD individuals with and without socio-cognitive dysfunctions (Terruzzi et al., 2023).

In conclusion, the results of the current study indicate that complex mental state recognition from facial expressions in PD patients is associated with structural and functional changes in brain areas

involved in emotion understanding (Spunt & Adolphs, 2019), at both cortical and subcortical levels. In particular, the functional findings highlight the relevant role of the bilateral amygdala, in accordance with previous theoretical models (Diederich et al., 2016). Additionally, anatomical modifications are evident also in other brain areas involved in emotional cue detection (i.e., the amygdala), emotion categorization and maintenance of semantic knowledge about the social world (the anterior temporal lobes), embodied simulation (the primary and secondary somatosensory cortex) and causal attribution (the dorsomedial prefrontal cortex). Furthermore, the results of the whole-brain analyses extend the neural network associated with the recognition of complex mental states in PD patients to the medial prefrontal regions, which are known to be highly involved in the interaction between cognitive and emotional processes in the brain (Ray & Zald, 2012). Collectively, these findings contribute to providing valuable insights into the neural underpinnings of complex mental state recognition in PD. Besides, the characterisation of early socio-cognitive dysfunctions in a subsample of individuals may facilitate the definition of new cognitive phenotypes (Czernecki et al., 2021; Dodich, Funghi, et al., 2022; Pagonabarraga et al., 2015), and potentially the development of new non-pharmacological interventions tailored to the individual's specific needs.

Chapter 6 : General conclusion

For many years, social cognition impairment has been regarded as the core symptom of frontotemporal dementia (FTD), an umbrella term for diverse clinical syndromes characterised by the progressive, focal neurodegeneration of the frontal and/or temporal lobes, leading to changes in executive function, social behaviour, or language (Boeve et al., 2022; Borghesani et al., 2022). This has often resulted in the clinical community only assessing social cognition in suspected cases of FTD, with this domain not being included in the standard, or first-level, neuropsychological assessment (Harvey, 2012). However, recent research indicates that these deficits may also be present in other forms of neurodegenerative conditions, including amyotrophic lateral sclerosis, Alzheimer's or Huntington's disease, and atypical parkinsonisms (Arioli et al., 2018; Christidi et al., 2018; Elamin et al., 2012; Fortier et al., 2018; Ibañez et al., 2021; Maresca et al., 2020; Setién-Suero et al., 2022). This challenges the traditional view and highlights the need for a more nuanced understanding of the role that social cognition plays in different neurodegenerative diseases. Indeed, despite the fifth and final edition of the DSM (American Psychiatric Association, 2013) explicitly recognising social cognition as one of the core functional domains that may be affected in neurocognitive disorders (Van den Stock, 2021), social cognitive abilities are not systematically investigated in clinical settings.

Within this overall picture, PD has historically been diagnosed on the basis of its hallmark motor symptoms, including bradykinesia, tremor, rigidity, and postural instability (Poewe et al., 2017). However, an increasing body of research over the years has revealed that there is a significant period prior to the onset of cardinal motor symptoms during which the underlying pathophysiological process is already underway (Schaeffer et al., 2020). This indicates that non-motor symptoms, including cognitive deficits, may manifest at an early stage of the disease rather than many years later as previously suggested (Schapira et al., 2017).

In this context, the present thesis addresses three key issues in the field of clinical neuropsychology. The primary objective is to investigate the socio-cognitive dysfunctions associated with PD in the

clinical setting, with the aim of enhancing their characterisation and contributing to the elucidation of the underlying neural substrates. Furthermore, this thesis advocates the inclusion of social cognition in the diagnostic criteria for PD-MCI. In conclusion, this work emphasises necessity of incorporating social cognition into the routine clinical assessment of neurocognitive disorders.

In relation to the ***primary aim (i.e., the characterisation of socio-cognitive dysfunctions in PD in the clinical setting)***, despite some controversial findings, previous studies have consistently reported deficits in social cognition in PD patients in emotion processing (Enrici et al., 2015; Péron et al., 2012), ToM (Bora et al., 2015b; Poletti et al., 2011; Trompeta et al., 2021), empathy (Coundouris et al., 2020), decision-making (Colautti et al., 2021), moral decision-making (Ponsi et al., 2021), and apathy (Pagonabarraga et al., 2015). Nevertheless, a comprehensive characterisation of these impairments in PD patients, particularly in the earliest stages of the disease, remains to be undertaken. As outlined in Chapter 3, a limited number of studies have already investigated ***both emotion recognition and ToM in this clinical population*** (Alonso-Recio et al., 2021; Czernecki et al., 2021; Enrici et al., 2015; Fernández-Fernández et al., 2024; Foley et al., 2019), as well as the relationship between these two aspects. Moreover, the ***relationship between social cognitive abilities and the cognitive status of PD*** patients has only been examined in a limited number of recent studies (Alonso-Recio et al., 2021; Czernecki et al., 2021; Fernández-Fernández et al., 2024).

The results of Study 1 indicate a notable impairment in both emotion recognition and in cognitive and affective mental state attribution in ***PD-MCI patients***. These findings are consistent with those of Alonso-Recio and colleagues (2021), who observed deficits in social perception (emotion recognition) and ToM in PD individuals with cognitive decline. Similarly, Fernández-Fernández and colleagues (2024) reported that both cognitive and affective ToM were impaired in PD-MCI, although no significant results were found for facial emotion recognition. In contrast, in ***cognitively preserved PD*** patients, while Alonso-Recio and colleagues (2021) observed a decline in performance relative to healthy controls in the static facial expression recognition task, Study 1 revealed an isolated deficit

in intention and emotion attribution. The findings of Study 1 are consistent with those of Czernecki and colleagues (2021), who reported the presence of a subgroup of PD patients with a selective socio-cognitive dysfunction, in the absence of impairment in any other cognitive domain. However, the study of Fernández-Fernández and colleagues (2024) found that social cognition is normal in cognitively unimpaired PD patients, which is a contrasting result.

The discrepancies in these findings may be attributed to the heterogeneity of the social-cognitive assessment protocols and the varying criteria employed to define cognitive impairment. For illustrative purposes, the study by Czernecki and colleagues (Czernecki et al., 2021) characterised PD patients through an abbreviated evaluation in line with the MDS level I criteria (Litvan et al., 2012). In contrast, Study 1 classified PD patients as either cognitively normal or with MCI using a thorough neuropsychological assessment, following the MDS Level II criteria (Litvan et al., 2012). This approach led to the detection of a higher percentage of MCI patients (i.e., 29%) and, correspondingly, a lower percentage of cognitively unimpaired (i.e., 11%) showing socio-cognitive deficits, compared to the study by Czernecki and colleagues (i.e., 15,6%) (Czernecki et al., 2021). It is noteworthy that, although Fernández-Fernández and colleagues (2024) similarly applied the MDS Level II criteria to distinguish PD-MCI from PD cognitively preserved (Litvan et al., 2012), they did not find reduced socio-cognitive abilities compared to HC in the latter group. While these inconsistencies are worthy of further investigation in future studies, it is important to emphasise that in the study by Fernández-Fernández and colleagues (2024) an analysis at the individual subject level was not reported. Consequently, no information is available on the frequency of participants with social cognition deficits in the PD cognitively unimpaired group. Additionally, cultural aspects and the variability in the criteria used to define “normal” or “pathological” performance in the baseline neuropsychological assessment of PD may also contribute to the discrepancies observed across studies, as discussed in Study 3. In order to facilitate multicentre studies, it is essential to establish a consensus on the criteria

for including both control subjects and patients in cognitive assessments (e.g., use equivalent scores or z-scores, considering as cut-off 1.5 or 2 standard deviation from the mean) (Ilardi et al., 2023).

To better characterise affective processing in PD, Study 2 focused on the ***development and analysis of the clinical validity of a new test to assess the ability to recognise complex mental states*** through faces: the Facial Complex Expressions (FACE) test. This test shares certain characteristics with the "Reading the Mind in the Eyes" test (Baron-Cohen et al., 2001), a renowned and extensively utilized test for assessing mental state attribution. However, the FACE test differs in that it employs high-quality coloured stimuli, which may enhance the test's validity and have potential clinical implications. Study 2 not only introduced a new tool to enhance the characterisation of socio-cognitive dysfunction, but also provided normative data for the Italian population, thus allowing the clinical interpretation of test performance, for both the extended 36-item version and the two parallel 18-item versions. Nevertheless, the principal value of this work for the purposes of this discussion lies in its clinical validation on a sample of PD patients. This enabled the estimation of the prevalence of deficits in the recognition of complex mental states in this clinical population. The findings revealed that 28% of PD patients exhibited difficulties in recognising complex mental states from facial expressions. This is consistent with the results of Study 1, which collectively indicate that clinically significant socio-cognitive impairments may manifest even in patients with early-stage PD in emotion recognition, emotion attribution and complex mental state recognition. Besides, the observed correlation between emotion recognition and affective ToM in Study 1, as well as the robust correlation reported between the FACE test and both measures of emotion recognition and attribution (affective ToM) in Study 2, suggests the potential for a common underlying pathological mechanism affecting emotion understanding in PD patients. In this context, Study 4 aimed to ***investigate the relationship between performance on the FACE test and both structural and functional changes*** in a selected set of brain areas involved in emotion understanding (Spunt & Adolphs, 2019). Furthermore, given that amygdala network dysfunction has been previously linked to compromised

recognition of emotional facial expressions and impaired ToM since the early stages of PD (Diederich et al., 2016), Study 4 also explored the neural correlates of the FACE test at the whole-brain level, using bilateral amygdala as seeds, with the aim of potentially extending the network of regions involved in emotion understanding in PD. The results revealed that the recognition of complex mental states in PD was significantly associated with both defective and compensatory mechanisms at the functional and anatomical level within the emotion understanding network, particularly involving the amygdala, dorsomedial prefrontal cortex, primary/secondary somatosensory cortices, and right anterior temporal cortex. Furthermore, the whole-brain results broadened the network of emotion understanding to include temporal and medial frontal areas. The study also provided empirical evidence for theoretical models that posit a pivotal role of the amygdala in causing emotion recognition and in affecting the ability to attribute affective mental states in PD (Diederich et al., 2016). In support of this, significant differences in grey matter volume were observed in the right amygdala between individuals with PD who exhibited deficits in mental state recognition and those who did not. At the functional level, significant alterations in connectivity emerged between the bilateral amygdalae and the left anterior temporal cortex in the two groups.

Furthermore, these findings contribute to the ongoing debate in the literature regarding the differential impairment of the cognitive and affective dimensions of ToM in PD. Indeed, it is widely acknowledged in the literature that the cognitive and affective ToM components depend on distinct neural systems and circuits (Abu-Akel & Shamay-Tsoory, 2011), which are differentially affected in PD (Alonso-Recio et al., 2021; Poletti et al., 2011). In particular, the dlPFC and the nigrostriatal dopaminergic circuits have been related to the cognitive aspects, such as the ability to infer others' mental states. In contrast, the vmPFC and OFC, along with mesolimbic circuits, have been associated to the capacity to infer others' emotional states (Alonso-Recio et al., 2021). In the context of PD, some researchers propose that the nigrostriatal pathways, associated with cognitive processes, may undergo degeneration at an earlier stage than the mesolimbic pathways, which are involved in affective

processes (Bodden, Dodel, et al., 2010). However, recent studies examining frontal, limbic, and striatal networks in PD patients have identified alterations in structural and functional connectivity involving both nigrostriatal and mesolimbic circuits from the early stages of the disease (Koirala et al., 2019; Luo et al., 2014; Nigro et al., 2016). In this still open debate, the results from Study 4 lend support to the hypothesis of an early alteration of the affective component in PD patients.

The question of whether these alterations depend on specific neurodegenerative processes or on other ***confounding factors*** is still a matter of debate. In this regard, one of the main limitations of the studies presented in this thesis is the lack of control over the potential ***effect of drug medication on the performance at socio-cognitive tasks***. There is a paucity of consensus in the literature regarding the effect of dopamine replacement therapy (DRT) on facial emotion recognition in PD patients (Argaud et al., 2018; Gothwal et al., 2022). Some studies have reported a beneficial effect, whereas others have reported a detrimental effect (for a review see Argaud et al., 2018). This inconsistency may be attributed to the progression of the disease. Indeed, in the early stages of PD, the meso-cortico-limbic pathways would be relatively preserved in contrast to the motor pathway. Consequently, the dose of levodopa required to improve motor symptoms may simultaneously result in an overdose of mesolimbic projections to the amygdala. Conversely, in more advanced stages of the disease, the DRT compensates for the dopamine depletion in the brain, resulting in a beneficial effect (Argaud et al., 2018). However, DRT overdose effect on emotion recognition in early PD patients has only been marginally investigated by a limited number of studies (Delaveau et al., 2009; Péron et al., 2014). Additionally, only a few cross-over studies assessed PD patients under ON and OFF medication states (Sprengelmeyer et al., 2003). Hence further research is required to more clearly delineate this aspect, comparing medicated and unmedicated patients. The volumetric results of Study 4, reporting a significant decrease in grey matter volume especially in the amygdala (uncorrected whole brain results) in who were impaired on the FACE test compared to those who were unimpaired, support the hypothesis that deficits in emotion processing are at least partly due to neurodegenerative processes.

Although the findings presented in this collection of articles are encouraging, it is essential to recognise a few ***additional limitations*** that could potentially impact the results and suggest avenues for future research. The principal methodological limitation is the relatively limited number of PD patients who were enrolled in the studies, which may have affected the statistical power of the analyses (this is particularly the case for Study 4). Furthermore, the lack of a comprehensive neuropsychological assessment of the healthy controls involved in Studies 1 and 2 precludes the possibility of ruling out the presence of deficits in specific cognitive domains, despite the MoCA score falling within the normal range. The absence of a control group of healthy individuals in Study 4 precludes the possibility of excluding the influence of greater or lesser activation in brain areas in relation to complex mental state recognition. Nevertheless, insights of value can be gained from a comparison at the brain level between individuals with and without socio-cognitive deficits in complex mental state recognition, despite the limited number of patients in the two subgroups. Furthermore, the impact of reduced facial mimicry in social tasks, particularly in the context of emotion recognition (Künecke et al., 2014; Prenger & Macdonald, 2018), and the influence of laterality onset or motor subtype (akinetic-rigid, tremor-dominant, and mixed) have not been evaluated in any of the studies. Moreover, it would be beneficial to conduct longitudinal studies to examine the progression of social cognition deficits as the disease advances. Lastly, the results of the studies presented here demonstrate that, when accounting for the general cognitive state of the patients, alterations in social cognition persist, both behaviourally and neuroimaging-wise. This evidence supports the hypothesis that social cognitive abilities and global cognitive functioning are at least partially independent. However, the debate in the literature on the relationship between social cognitive abilities and performance in other cognitive domains remains open. In this regard, the results of Study 4 provide additional support for the hypothesis that the observed deficits in social cognition are not merely a consequence of general cognitive impairment. Specifically, the findings indicate that the areas that are impaired from the early stages of the disease are those that are specifically involved in social cognition processes.

Notwithstanding the aforementioned limitations, this doctoral thesis posits overall that deficits in socio-cognitive processes can be observed in patients with PD from the earliest stages of the disease and are associated with structural and functional changes in brain areas involved in emotion understanding.

Further avenues for investigation in future research could include an examination of the structural and functional brain alterations associated with other sub-components of social cognition, such as the theory of mind, empathy, and apathy, where the existing literature is less extensive. This may be achieved by using advanced MRI techniques and post-processed data analyses (including diffusion-weighted imaging, volumetric imaging, automated subcortical volume segmentation, and multimodal imaging).

Overall, the evidence presented in this doctoral dissertation provides support for the hypothesis that early socio-cognitive dysfunctions are present in PD, and that these are associated with functional and structural alterations in the brain. Nevertheless, despite substantial and increasing evidence documenting social cognitive impairments in PD (Christidi et al., 2018), social cognition remains excluded from the cognitive domains considered in the clinical diagnostic criteria for PD-MCI (Litvan et al., 2012).

In view of the pivotal role of MCI classification in predicting the risk of PD dementia (Hoogland et al., 2017), these findings suggest a potential advantage in incorporating social cognition into the MDS cognitive domains to enhance MCI detectability. Furthermore, the higher prevalence of multi-domain MCI patients (in comparison to no patients with PD-MCI single domain), which aligns with existing literature (Goldman et al., 2015; Pourzinal et al., 2022), suggests that improvements could be made to the MDS criteria to more accurately identify domain-specific PD-MCI subtypes. In accordance with this, a recent study employed machine learning to classify PD-MCI patients, incorporating a test of social cognition. The results demonstrated that this domain should be included in the standard neuropsychological assessment of PD patients to improve the detection of MCI (Longo et al., 2024).

This would be in line with an international initiative providing guidelines to harmonise the neuropsychological assessment for MCI in Europe, including social cognition among the domains to be evaluated (Boccardi et al., 2021). As a spin-off of this doctoral dissertation, the Signature Initiative is presented here as an international collaborative study group involving researchers, methodologists, physicians, psychologists and stakeholders. The ultimate goals of this initiative, in which I am delighted to be involved, are twofold: firstly, to promote the implementation of social cognition measures in the clinical practice of memory clinics and secondly, to facilitate a constructive dialogue between the clinical and research communities, with the objective of improving evidence-based clinical practice. In conclusion, the detection of social cognition deficits across a range of neurodegenerative diseases, particularly in the early stages, represents a crucial and innovative aspect that should be given due consideration for the diagnosis, management and care of affected individuals. The identification of these deficits at the earliest stages of the disease would facilitate the prompt implementation of targeted intervention strategies designed to address the specific affected domains. In this context, the development of intervention programmes, such as the SCOT project (see Appendix A- Study 5), and their adaptation to clinical populations represent a valuable resource for mitigating the impact of these changes on patients' social behaviour and relationships. This approach to patient care has the potential to markedly enhance the quality of life for those affected by neurodegenerative conditions and their caregivers.

Appendix A

The Social and Cognitive Online Training (SCOT) project: a digital randomized controlled trial to promote socio-cognitive wellbeing in older adults (Study 5)

This chapter was published as "Funghi, G., Meli, C., Cavagna, A., Bisoffi, L., Zappini, F., Papagno, C., & Dodich, A. (2024). The Social and Cognitive Online Training (SCOT) project: A digital randomized controlled trial to promote socio-cognitive well-being in older adults. Archives of gerontology and geriatrics, 122, 105405. https://doi.org/10.1016/j.archger.2024.105405" with open access under the Creative Commons Attribution-NonCommercial-NoDerivs (CC-BY-NC-ND) license (https://creativecommons.org/licenses/by-nc-nd/4.0/). The author(s) retains copyright alongside scholarly usage rights of this work. All authors agreed on redistributing the following material for the purpose of this doctoral thesis. The Journal Author Rights are reported in Appendix B.3. This study aims to assess the efficacy of the Social and Cognitive Online Training (SCOT) project, a randomised, controlled, parallel clinical trial designed to prevent the age-related decline in executive and social functions in 60 cognitively healthy older adults. Indeed, in light of the progressive ageing of the general population, the development of effective prevention programmes targeting risk factors for cognitive decline in the elderly is strongly recommended. The participants underwent a baseline clinical and neuropsychological assessment, after which they were assigned to either the experimental group (SCOT) or the non-specific cognitive training group (CON). Both interventions were conducted remotely via tablet and comprised two individual cognitive training sessions and one group meeting per week. The results provide preliminary evidence for the beneficial effects of SCOT training, particularly for those who performed best during the training. This suggests that individual motivation should be considered when designing new interventions for active ageing and dementia prevention. This research is presented as a pilot study paving the way for the potential future implementation of similar interventions in PD patients who present with early socio-cognitive impairments to mitigate them through individualized targeted training.

7.1. Introduction

Data reported by the United Nations in recent years clearly show that the world is undergoing profound demographic change, with a progressive ageing of the population affecting countries around the world, regardless of level of development. In particular, the World Health Organization (WHO) estimates that the global population of people aged 60 and over will double by 2050, reaching up to 2 billion people (Nichols et al., 2022). This significant increase has placed the prevention of cognitive decline and dementia at the top of global mental health priorities (World Health Organisation, 2017), as the impact of dementia extends beyond patients and their families to include high economic costs to society as a whole (Nichols et al., 2022).

7.1.1. Computerized cognitive training as a possible strategy to prevent dementia in healthy older adults

In response to this rapid expansion of the older population, effective policies and strategies are needed to manage the impact on economies and health systems and to develop comprehensive solutions that promote healthy and active ageing. Several modifiable risk factors have been identified to account for around 40% of the risk of developing dementia (Livingston et al., 2020), including cognitive inactivity and social isolation, and have become important targets for multi-modal prevention interventions (Andrieu et al., 2017; Kivipelto et al., 2020; Ngandu et al., 2015; van Charante et al., 2016). Indeed, a broader approach to dementia prevention includes strategies to promote and maintain cognitive reserve in old age by engaging in cognitively stimulating activities and social interactions, and a growing body of research supports the protective effects of cognitive stimulation and social contact on dementia incidence (Livingston et al., 2020; Sommerlad et al., 2023).

Recent systematic reviews and meta-analyses have reported positive effects of cognitive-oriented interventions in healthy older adults, particularly on general cognitive function, attention, working memory, processing speed and executive function (Chiu et al., 2017; Gates et al., 2019; Sanjuán et

al., 2020). As technology advances and the accessibility of digital tools continues to increase, several studies have addressed the question of the beneficial effects of computerized cognitive training (CCT) in cognitively healthy older adults (Bonnechère et al., 2020; Gates et al., 2019; Kueider et al., 2012; Lampit et al., 2014). Although efficacy varies by cognitive domain and intervention design (Lampit et al., 2014), and although current evidence is inconclusive due to the variability and low quality of meta-analyses and individual clinical trial results (Gates et al., 2019), the use of PCs, game consoles, smartphones and tablets has shown promising results, bringing significant improvements in executive function, processing speed, working memory and reasoning skills (Bonnechère et al., 2020; Rute-Pérez et al., 2023; Vaportzis et al., 2017; Wilson et al., 2022).

7.1.2. Socio-cognitive training in healthy older adults and their potential benefits

Interestingly, most of these interventions have focused on the main cognitive domains but have not included social cognition, despite the literature showing significant changes with advancing age. In particular, significant declines in mentalising and basic emotion recognition have been reported and attributed to structural and functional changes in the prefrontal cortex (PFC) (Fernandes et al., 2021; Gourlay et al., 2022), one of the areas most affected by age-related decline (Zanto & Gazzaley, 2019), which also contributes to executive dysfunction in this population (Circelli et al., 2013; Yıldırım et al., 2020).

Although the debate on the relationship between social cognition and executive functions remains open due to conflicting results and the multi-component nature of the domains themselves (Baksh et al., 2018), there is now substantial literature demonstrating that normal adult ageing is associated with changes in both social (specifically, declines in theory of mind [ToM] and social perception) (Grainger et al., 2023) and executive domains (Ferguson et al., 2021), which share, at least in part, the prefrontal brain areas as a neuroanatomical substrate. Emerging evidence suggests that socio-cognitive training interventions may have beneficial effects in healthy older people by improving

socio-cognitive skills and social functioning (Roheger et al., 2022). In particular, results from a small number of Italian studies investigating training focused on ToM tasks and conversations about mental states in adults aged over 60 years showed that interventions were highly effective in improving ToM in this age group (Cavallini et al., 2015; Rosi et al., 2016). Furthermore, a conversation-based ToM intervention conducted with cognitively healthy nursing home residents was found to be effective in improving socio-cognitive skills in both practised and non-practised tasks (Cavallini et al., 2021). However, it is worth noting that the use of online social cognitive interventions has been explored in other populations, such as individuals with schizophrenia (Nahum et al., 2014, 2021), autism (Golan & Baron-Cohen, 2006; Rosenblau et al., 2020) or traumatic brain injury (Westerhof-Evers et al., 2019), with encouraging results reported for social skills, social functioning and motivation. These findings across diverse populations provide a broader context for understanding the potential benefits and challenges associated with online interventions targeting cognitive and social cognitive skills.

7.1.3. Research gap and rationale for the SCOT project

To the best of our knowledge, no study has yet tested the effects of online computerized training on improving socio-executive functioning in healthy older people.

This kind of intervention might be of particular relevance, considering that age-related social cognition changes might significantly impact on everyday social functioning.

Against this backdrop, we conducted the Social and Cognitive Online Training (SCOT) project, a randomized, parallel, double-blind, controlled clinical trial (ClinicalTrials.gov identifier: NCT05023187), which aimed to evaluate the efficacy of a multidimensional online intervention, as compared to non-specific cognitive stimulation, in improving socio-executive functioning in healthy older people. Besides, considering that socio-cognitive alterations have been associated with increased loneliness (Cacioppo, 2009; Morese & Palermo, 2022), and that the latter represents a risk

factor for the development of dementia (Bransby et al., 2024; Livingston et al., 2020), we also assess the effect of the training on this psychological dimension.

This paper describes the methods and results of the SCOT project in accordance with the CONSORT (CONsolidated Standards Of Reporting Trials) guidelines (Moher et al., 2010) (see Supplementary data - Table S5 for CONSORT checklist for reporting a randomized trial).

7.2. Methods

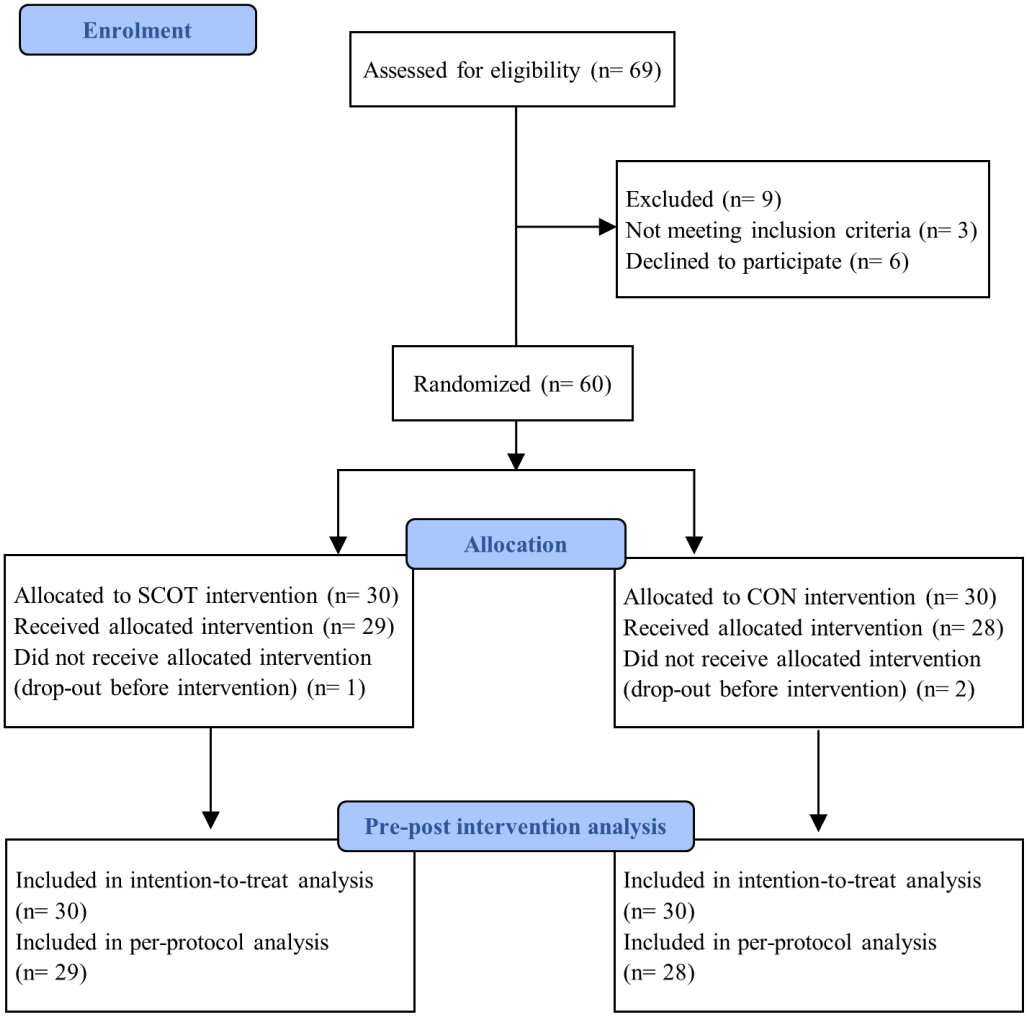
7.2.1. *Participants*

Between January 2021 and December 2021, 60 healthy older adult volunteers aged 64 to 85 years were enrolled at the Neurocognitive Rehabilitation Centre (CeRiN) of the Center for Mind/Brain Sciences (University of Trento). All participants underwent a medical history interview and cognitive screening to verify eligibility criteria.

To be included in the study, participants had to be aged ≥64 years (up to 90 years old) and have a Montreal Cognitive Assessment (MoCA) adjusted score ≥19.501, within normal limits according to Italian normative values (Conti et al., 2015). Exclusion criteria were a diagnosis of major or mild neurocognitive disorder according to the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition, DSM-V) and based on the results of a comprehensive neuropsychological assessment (see Supplementary data - Table S6), a history of current or past neuropsychiatric disorders, and/or substance abuse.

All participants provided informed consent for the study, which was conducted in accordance with the ethical guidelines of the local ethics committee (University of Trento Research Ethics Committee, protocol 2020-036) and the Declaration of Helsinki (World Medical Association, 2013). Participant inclusion and randomization is represented in Figure 11.

Figure 11. *Flow diagram of the SCOT project (adapted from CONSORT 2010 Flow Diagram, Moher et al., 2010)*

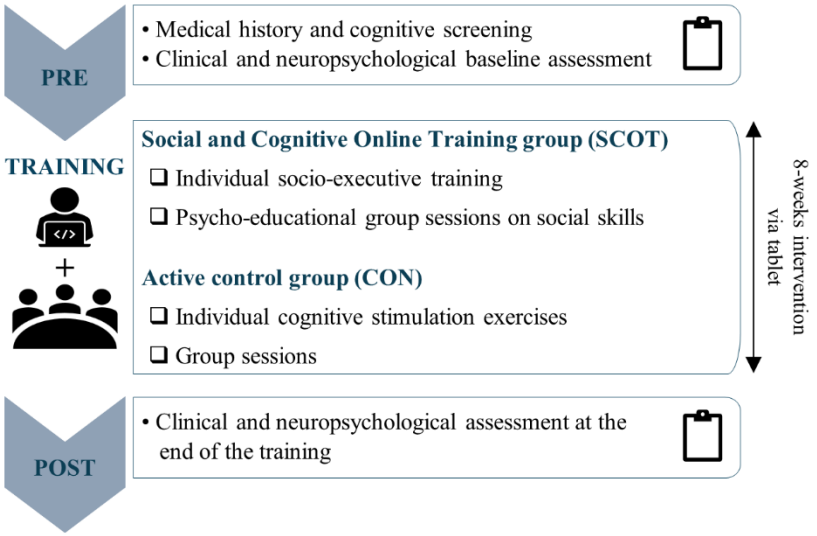


The sample size planning was conducted using G∗Power 3.1 (Erdfelder et al., 2009) based on an effect size for a 24-session intervention (effect size: 0.697) (Chiu et al., 2017) and power of 0.80. The results indicated that for a two-group design at least 27 participants per group were needed to detect a significant result. Considering a possible drop-out of 10%, 30 subjects per group were enrolled.

7.2.2. Randomization and Intervention

Participants were randomly allocated to either an experimental (Social and Cognitive Online Training - SCOT) or an active control group (CON) using a covariate adaptive randomization method (Colavincenzo, 2012) stratifying participants for age, education and sex. The cut-off assignment strategies for age and education were ≤ or >70 years old and ≤ or >13 years of education, respectively. Both participants and investigators were blinded to group allocation. Both interventions were delivered remotely via investigator-provided tablets and lasted eight weeks, during which, participants completed two individual sessions and one group meeting video call per week (24 sessions total, ~60 minutes each, in accordance with literature evidence (Chiu et al., 2017)). Details of the study design are shown in Figure 12.

Figure 12. *Study design*



The interventions were designed and delivered by qualified psychologists who provided all participants with detailed instructions before the intervention began. They also offered remote support to participants throughout the training period to help them complete the planned activities.

The SCOT group received an online social and executive intervention consisting of two individual sessions of adaptive online cognitive training and one psychoeducational group session per week. The individual training sessions consisted of six tasks selected from Posit Science's BrainHQ© Program 2020 (https://www.brainhq.com), which have previously been shown to be effective in randomized clinical trials (Smith et al., 2009; Tennstedt & Unverzagt, 2013) and chosen to improve attention-executive functions (i.e., "Double Decision" for visual processing speed, "Divided Attention", "Mind Bender" for cognitive flexibility and executive control and "Card Shark" for working memory) and social skills (i.e., "Face to Face" for emotion recognition and "Face Facts" for social memory).

Online psychoeducational group sessions led by psychologists included discussions and practical exercises focusing on social skills such as emotion recognition and attribution, ToM, empathy and social behaviour.

The active comparison group (CON), on the other hand, received a non-specific and non-adaptive online cognitive intervention consisting of two individual sessions of cognitive stimulation and one group session per week aimed at improving knowledge of cognitive functioning. Specifically, the individual sessions included digital exercises on memory, attention, language, executive function, perception, financial literacy, social skills and creativity/divergent thinking, which were reviewed, discussed and commented on during the group sessions with psychologists.

Throughout the intervention, the presence/absence of participants in the different components of the training was tracked in order to have a measure of adherence to the intervention.

Finally, to reduce the risk of dropping out, strategies according to Dziura and colleagues (2013) were implemented, including weekly reminders and/or assistance with the digital device.

7.2.3. *Outcome Measures*

The primary outcome measure was the Tower of London (ToL) test (Boccia, Marin, D'antuono, et al., 2017), which assess executive functioning. This test covers different aspects of executive functioning such as planning, problem-solving and processing-speed (Shallice, 1982; J. R. Sullivan et al., 2009) and it is frequently reported as outcome measure in clinical trials (Specht et al., 2023; Van Balkom et al., 2019). In clinical setting, performance is usually assessed separately in terms of accuracy, measured as the number of trials solved correctly in the minimum number of moves, as well as planning and execution times (Boccia, Marin, D'Antuono, et al., 2017). Although the use of all these parameters is recommended in the literature, no index exists that combine the information provided by each of them and optimise the assessment of each patient's performance. Then, we proposed a ToL index that simultaneously consider accuracy, planning time and execution time in participants' performance to further explore the efficacy of the intervention on executive functioning.

$$ToL-\ index = \left(\frac{ToL\ Accuracy_{sbj}}{ToL\ Accuracy_{Max\ score}}\right) \times \left(1 - \frac{\overline{ToL\ planning\ time}_{sbj}}{(\mu + 6\sigma)_{ToL\ planning\ time}}\right) \times \left(1 - \frac{\overline{ToL\ execution\ time}_{sbj}}{(\mu + 6\sigma)_{ToL\ execution\ time}}\right)$$

According to this formula, the higher the index, the better the subject's performance in terms of high accuracy, fast planning time and fast execution time. Overall, this index is therefore more representative of overall performance than individual scores. In addition, social cognition was assessed through the Ekman-60 Faces test (Ek-60F test, secondary outcome) (Dodich et al., 2014) as a basic emotion recognition task, and the Faux-Pas Recognition Test of the Mini-Social cognition & Emotional Assessment battery (Mini-SEA, explorative outcome) (Bertoux et al., 2013). Specifically, four scores were derived, representing the ability to detect inappropriate behaviour (faux pas detection), the cognitive and affective components of ToM, and a score representing the control condition. Finally, in order to assess a possible effect of the training on social functioning, the total score on the Italian Social and Emotional Loneliness Scale (ISELS) (Zammuner, 2008) was used, where higher scores indicate worse outcomes in terms of perceived loneliness (the higher the score,

the more loneliness the person reports). All outcome measures were assessed at baseline and at the end of the 8-week intervention.

7.2.4. Statistical Analyses

Statistical analyses were checked for underlying assumptions. The normal distribution of the data was assessed using the Shapiro-Wilk test, which allowed for the appropriate application of parametric or non-parametric statistical techniques. The efficacy of the randomization procedure was tested by comparing demographic, clinical and neuropsychological characteristics of the SCOT and CON groups at baseline using either the Student's t-test or the Mann-Whitney U test, depending on data distribution. Then, the efficacy of the experimental training in modifying executive and socio-cognitive functioning was tested using a mixed ANOVA comparing the performance of the SCOT and CON participants who completed the 8-week training (*per-protocol approach*), analysing the effect of time, group and interaction. Pre-post comparison analyses were performed on outcome measures, using Tukey's test as a post-hoc analysis. The efficacy of the intervention was also tested using the *intention-to-treat approach* with *'mean imputation'* per group.

Additionally, to account for the online nature of the intervention and participants' intrinsic motivation, which may have influenced the effects of the training, the SCOT group was further divided into "HIGH PERFORMANCE" and "LOW PERFORMANCE" subgroups, based on their performance in the individual training (according to the median number of levels achieved on the BrainHQ platform used for training). A mixed design ANOVA was then performed as a post-hoc analysis to compare the performance of the SCOT HIGH PERFORMANCE, SCOT LOW PERFORMANCE and CON groups before and after the intervention on the variables of interest. This analysis tested the hypothesis that those subjects who performed best during the intervention would achieve a greater improvement in the outcome measures.

Statistical analyses were performed using Jamovi 2 (Jamovi, 2021) with a significance level <0.05.

7.3. Results

Sixty-nine individuals were screened, and 60 were randomly assigned to either the experimental group (SCOT n=30) or the active control group (CON n=30). Of these, 57 (95%) completed the entire allocated training period and underwent the post-intervention evaluation, while 3 subjects (1 SCOT, 2 CON) dropped out of the study before the start of the intervention due to difficulties in participation.

7.3.1. Baseline assessment of SCOT and CON groups

Analysis of demographic and clinical characteristics, as well as performance on the social and cognitive tests at baseline, showed no significant differences between the SCOT and CON groups (Table 16). No harm or adverse events related to the intervention were reported by participants, and adherence to intervention was very high for both groups (CON mean 93.92%; SCOT mean 98.06%).

7.3.2. Pre – post comparison analyses in SCOT vs CON groups

The pre-post-comparison analyses showed a significant improvement after the intervention in both groups in the ToL Accuracy ($F_{1,55}$=7.19, p=0.010), in the ToL index ($F_{1,55}$=35.31, p<0.001) and in the Mini-SEA scores representing Faux Pas detection ($F_{1,55}$=8.50, p=0.005), cognitive ToM ($F_{1,55}$=25.38, p<0.001) and affective ToM ($F_{1,55}$=14.71, p<0.001). However, there were no significant *time*group* interactions for any outcome of interest (Table 17).

7.3.3. Pre – post exploratory post-hoc analyses based on training performance

The results of the exploratory analysis dividing the experimental group into the subgroups "SCOT HIGH PERFORMANCE" (n=15) and "SCOT LOW PERFORMANCE" (n=14) and comparing them with the CON group, confirmed a significant *time* effect on both ToL (Accuracy: $F_{1,54}$=4.38, p=0.041, Index: $F_{1,54}$=37.83, p<0.001) and Mini-SEA measures (Faux Pas detection: $F_{1,54}$=8.87, p=0.004;

cognitive ToM: $F_{1,54}$=28.67, p<0.001; affective ToM: $F_{1,54}$=15.82, p<0.001) (see Table S7 for baseline features of subgroups and Table 18 for results on the outcomes of interest).

Interestingly, the analyses also showed a significant *time*group* interaction for the EK-60F test ($F_{2,54}$=5.95, p=0.005) and for the ToL Index ($F_{2,54}$=6.61, p=0.003), as well as a trend for the Mini-SEA cognitive ToM ($F_{2,54}$=2.62, p=0.082) (Table 18). Specifically, post-hoc analysis with Tukey's test revealed in the "SCOT HIGH PERFORMANCE" group a significant difference between pre- and post-assessment for executive functioning (ToL – Index: p<0.001; Figure 13A), emotion recognition (EK-60F test: p=0.033; Figure 13B) and cognitive ToM (Mini-SEA – Cognitive ToM: p<0.001; Figure 13C). A significant improvement after the intervention was also found in performance in the ToL index in the CON group (p<0.001; Figure 13A).

No significant changes were found in the ISELS scale.

The results were confirmed when using the *intention-to-treat approach* with *"mean imputation"* per group.

Table 16. *Baseline assessment of SCOT and CON groups*

	SCOT (n=30)	***CON (n=30)***	***Statistics***
DEMOGRAPHIC DATA			
Sex (F/M)	18/12	20/10	$\chi(1)=0.3$, p= 0.6
Age	71.8(5.2)	71.7(5.5)	U=428, p=0.8
Education	12.2(4.2)	12.3(3.0)	U=444, p=0.9
CLINICAL & NEUROPSYCHOLOGICAL ASSESSMENT			
Montreal Cognitive Assessment (MoCA)	25.1(2.3)	25.1(2.5)	t(58)=0.1, p=0.9
CIRS – Severity index (SV)	0.4(0.3)	0.5(0.2)	U=416, p=0.6
CIRS – Comorbidity index (CM)	1.3(1.3)	1.7(1.4)	U=370, p=0.2
Digit span Forward	5.9(0.8)	5.8(0.6)	U=416, p=0.5
Digit span backward	4.3(0.8)	4.6(1.0)	U=340, p=0.2
Corsi block-tapping test	5.2(1.0)	5.2 (0.9)	U=445, p=0.9
Trail-making Test – A	42.8(14.0)	40.3(13.6)	U=401, p=0.5
Trail-making Test – B	97.1 (26.6)	106.7(35.4)	t(58)=1.2, p=0.2
Trail-making Test – B-A	54.3 (19.2)	66.4(30.8)	t(58)=1.8, p=0.1
Phonemic verbal fluency task	41.2(12.2)	42.7(11.0)	t(58)=0.5, p=0.6
Semantic verbal fluency task	46.0(8.0)	46.3(7.9)	t(58)=0.1, p=0.9
Rey auditory verbal list immediate recall	46.8(10.2)	46.5(9.7)	t(58)=-0.1, p=0.9
Rey auditory verbal list delayed recall	9.5(3.7)	9.4(2.6)	t(58)=-0.0, p=1.0
Rey-Osterrieth complex figure copy	32.1(2.6)	31.1(3.2)	U=361, p=0.2
Rey-Osterrieth complex figure delayed recall	16.4(4.9)	16.8(6.4)	U=427, p=0.7
Stroop task – Time	19.7(6.5)	23.6(9.7)	U=330, p=0.1
Stroop task – Errors	0.7(1.4)	1.0(1.3)	U=380, p=0.4

State-Trait Anxiety Inventory (STAI-Y)	37.5(8.5)	36.7(7.0)	t(58)=-0.4, p=0.7
Geriatric Depression Scale (GDS)	2.6(2.4)	2.6(1.9)	U=424, p=0.7
Mobile Device Proficiency in Older Adults (MDPQ-16)	61.8(15.4)	57.2(16.7)	U=371, p=0.2
Cognitive Reserve Index questionnaire (CRIq)	113.9(14.8)	115.4(15.5)	t(58)=0.4, p=0.7
OUTCOMES MEASURES			
Executive functions			
Tower of London (ToL)– Accuracy	36.6(3.9)	35.5(4.4)	t(58)=-1.0, p=0.3
Tower of London (ToL)– Index	0.3(0.1)	0.3(0.1)	t(58)=0.0, p=1.0
Social cognition			
Ekman-60 Faces test (Ek-60F test)	47.6(4.5)	46.2(6.0)	U=392, p=0.4
Mini-Social cognition & Emotional Assessment battery (Mini-SEA) – Faux pas Detection	13.5(1.2)	13.9(1.0)	U=376, p=0.2
Mini-Social cognition & Emotional Assessment battery (Mini-SEA) – Cognitive ToM	12.6(3.8)	13.7(3.4)	t(58)=1.3, p=0.2
Mini-Social cognition & Emotional Assessment battery (Mini-SEA) – Affective ToM	3.3(1.0)	3.5(1.1)	U=417, p=0.6
Mini-Social cognition & Emotional Assessment battery (Mini-SEA) – Control stories	19.7(0.7)	19.7(0.6)	U=438, p=0.8
Italian Social and Emotional Loneliness Scale (ISELS)	33.2(7.7)	34.5(8.0)	U=396, p=0.4

Note. Data are reported as mean (standard deviation).
Parametric or non-parametric statistical techniques were applied for each assessment based on the data distribution. The parametric Student's t-test (t) was used for variables with a normal distribution, while the non-parametric Mann-Whitney U test (U) was used for variables with a non-normal distribution.

Table 17. *Pre – post comparison analyses in SCOT vs CON groups*

		Pre-Intervention	***Post-Intervention***	***Statistics***		
OUTCOME MEASURES	***GROUP***	***Mean (St.Dev.)***	***Mean (St.Dev.)***	***p-value time***	***p-value group***	***p-value time*group***
Executive functions						
ToL– Accuracy Score range: 0–48	SCOT CON	36.6(3.9) 35.5(4.4)	37.4(4.4) 37.9(4.1)	F(1,55)=7.19, **p=0.010**** η^2_p=0.12	F(1,55)=0.10, p=0.756 η^2_p=0.00	F(1,55)=1.85, p=0.179 η^2_p=0.03
ToL – Index Score range: 0–1	SCOT CON	0.3(0.1) 0.3(0.1)	0.4(0.1) 0.4(0.1)	F(1,55)=35.31, **p<0.001****** η^2_p=0.39	F(1,55)=0.04, p=0.837 η^2_p=0.00	F(1,55)=0.00, p=0.999 η^2_p=0.00
Social cognition						
EK-60F Test Score range: 0–60	SCOT CON	47.6(4.5) 46.2(6.0)	48.4(5.9) 47.8(6.7)	F(1,55)=3.10, p=0.084 η^2_p=0.05	F(1,55)=0.39, p=0.537 η^2_p=0.01	F(1,55)=0.19, p=0.662 η^2_p=0.00
Mini-SEA – Faux pas Detection Score range: 0–15	SCOT CON	13.5(1.2) 13.9(1.0)	14.1(0.9) 14.2(1.1)	F(1,55)=8.50, **p=0.005***** η^2_p=0.13	F(1,55)=1.21, p=0.277 η^2_p=0.02	F(1,55)=0.53, p=0.469 η^2_p=0.01
Mini-SEA - Cognitive ToM Score range: 0–20	SCOT CON	12.6(3.8) 13.7(3.4)	15.3(3.1) 15.2(2.9)	F(1,55)=25.38, **p<0.001****** η^2_p=0.32	F(1,55)=0.52, p=0.476 η^2_p=0.01	F(1,55)=2.83, p=0.098 η^2_p=0.05
Mini-SEA – Affective ToM Score range: 0–5	SCOT CON	3.3(1.0) 3.5(1.1)	4.1(0.8) 3.9(0.8)	F(1,55)=14.71, **p<0.001****** η^2_p=0.21	F(1,55)=0.06, p=0.810 η^2_p=0.00	F(1,55)=1.29, p=0.260 η^2_p=0.02
Mini-SEA - Control Questions Score range: 0–20	SCOT CON	19.7(0.7) 19.7(0.6)	19.9(0.4) 19.9(0.3)	F(1,55)=3.22, p=0.078 η^2_p=0.06	F(1,55)=0.08, p=0.778 η^2_p=0.00	F(1,55)=0.15, p=0.669 η^2_p=0.00
ISELS Score range:0–57	SCOT CON	33.2(7.7) 34.5(8.0)	33.7(8.0) 33.8(8.8)	F(1,55)=0.62, p=0.434 η^2_p=0.01	F(1,55)=0.09, p=0.766 η^2_p=0.00	F(1,55)=0.99, p=0.325 η^2_p=0.02

Note. Data are reported as mean (standard deviation).
GROUP: Refers to the two groups in the study. SCOT (Social and Cognitive Online Training), n=29 participants; CON (Active Control), n=28 participants.
Significant p-values from a 2×2 ANOVA testing for between groups differences are shown in bold.
Effect sizes are reported as partial eta squared (η^2p).
*p<0.05; **p<0.01; ***p<0.005; ****p<0.0001.

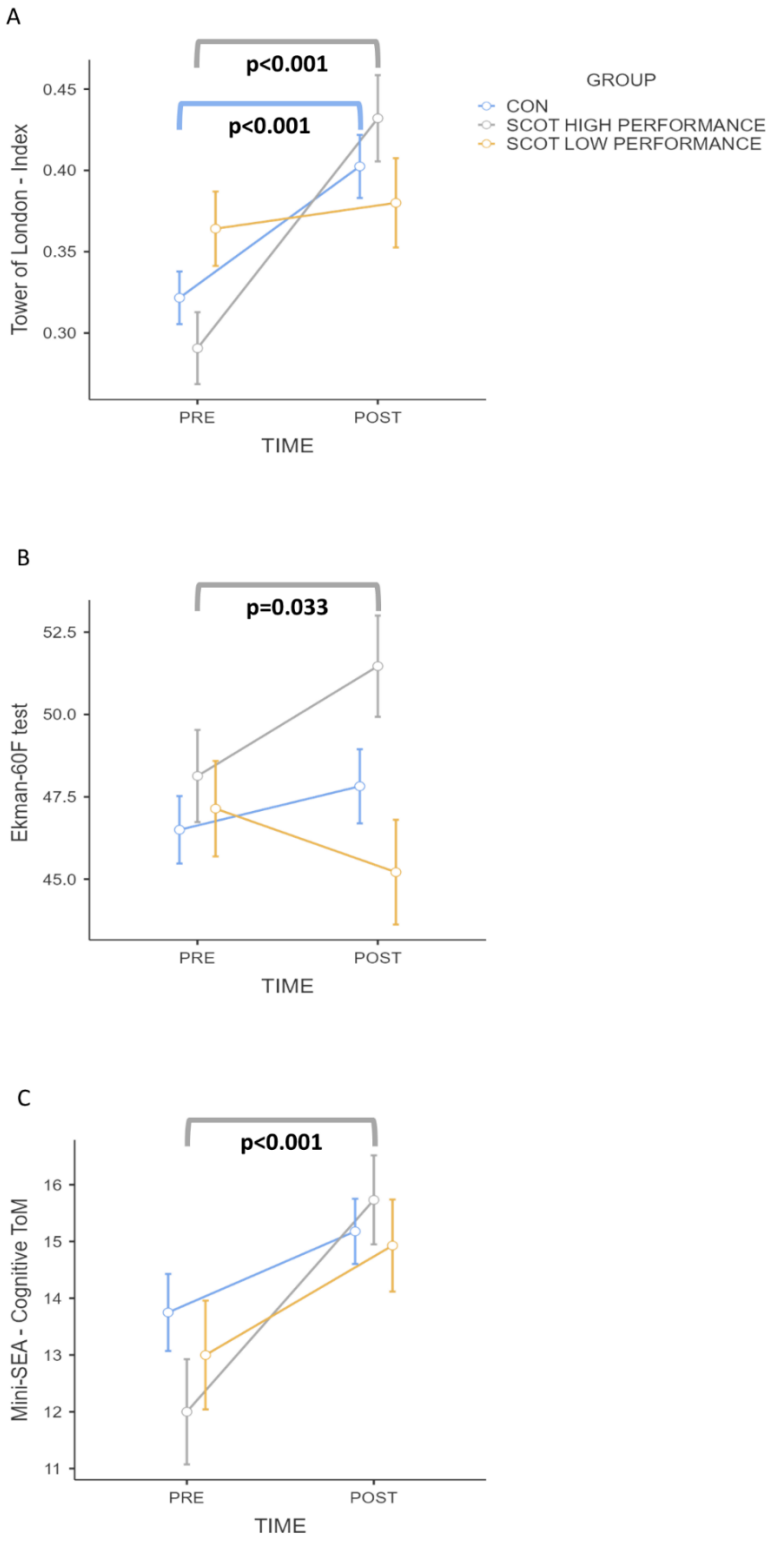
Table 18. *Pre – post comparison analyses in CON vs SCOT HIGH PERFORMANCE & SCOT LOW PERFORMANCE groups*

		Pre-Intervention	***Post-Intervention***	***Statistics***		
OUTCOME MEASURES	***GROUP***	***Mean (St.Dev.)***	***Mean (St.Dev.)***	***p-value time***	***p-value group***	***p-value time*group***
Executive functions						
ToL – Accuracy Score range: 0–48	SCOT HIGH	36.1(4.2)	37.6(4.1)	F(1,54)=4.38, **p=0.041*** η^2_p=0.08	F(2,54)=0.09, p=0.910 η^2_p=0.00	F(2,54)=1.42, p=0.250 η^2_p=0.05
	SCOT LOW	37.3(3.8)	37.2(4.8)			
	CON	35.6(4.6)	37.9(4.1)			
ToL – Index Score range: 0–1	SCOT HIGH	0.3(0.1)	0.4(0.1)	F(1,54)=37.83, **p<0.001****** η^2_p=0.41	F(2,54)=0.08, p=0.921 η^2_p=0.00	F(2,54)=6.61, **p=0.003*** η^2_p=0.20 □ **p<0.001****** ◊ **p<0.001******
	SCOT LOW	0.4(0.1)	0.4(0.1)			
	CON	0.3(0.1)	0.4(0.1)			
Social cognition						
EK-60F Test Score range: 0–60	SCOT HIGH	48.1(4.2)	51.5(4.8)	F(1,54)=2.49, p=0.121 η^2_p=0.04	F(2,54)=1.89, p=0.161 η^2_p=0.07	F(2,54)=5.95, **p=0.005*** η^2_p=0.18 ◊ **p=0.033***
	SCOT LOW	47.1(5.1)	45.2(5.3)			
	CON	46.5(6.1)	47.8(6.7)			
Mini-SEA – Faux Pas detection Score range: 0–15	SCOT HIGH	13.3(1.4)	14.2(1.0)	F(1,54)=8.87, **p=0.004*** η^2_p=0.14	F(2,54)=0.64, p=0.534 η^2_p=0.02	F(2,54)=0.64, p=0.531 η^2_p=0.02
	SCOT LOW	13.6(1.1)	14.1(0.7)			
	CON	13.9(1.0)	14.2(1.1)			
Mini-SEA – Cognitive ToM Score range: 0–20	SCOT HIGH	12.0(4.2)	15.7(3.1)	F(1,54)=28.67, **p<0.001****** η^2_p=0.35	F(2,54)=0.26, p=0.774 η^2_p=0.01	F(2,54)=2.62, *p=0.082* η^2_p=0.09 ◊ **p<0.001****
	SCOT LOW	13.0(3.4)	14.9(3.2)			
	CON	13.8(3.3)	15.2(2.9)			
Mini-SEA – Affective ToM Score range: 0–5	SCOT HIGH	3.2(1.2)	4.1(1.0)	F(1,54)=15.82, **p<0.001****** η^2_p=0.23	F(2,54)=0.19, p=0.830 η^2_p=0.01	F(2,54)=0.90, p=0.413 η^2_p=0.03
	SCOT LOW	3.5(0.8)	4.1(0.6)			
	CON	3.5(1.0)	3.9(0.8)			
Mini-SEA – Control Questions Score range: 0–20	SCOT HIGH	19.7(0.6)	19.8(0.4)	F(1,54)=2.48, p=0.121 η^2_p=0.04	F(2,54)=0.43, p=0.655 η^2_p=0.02	F(2,54)=0.07, p=0.928 η^2_p=0.00
	SCOT LOW	19.8(0.8)	19.9(0.3)			
	CON	19.7(0.7)	19.9(0.3)			

ISELS Score range:0–57	SCOT HIGH	32.6(8.3)	32.4(8.6)	F(1,54)=0.17, p=0.678	F(2,54)=0.34, p=0.712	F(2,54)=0.59, p=0.561
	SCOT LOW	34.6(6.8)	35.0(7.4)	η^2_p=0.00	η^2_p=0.01	η^2_p=0.02
	CON	34.7(8.2)	33.8(8.8)			

Note. Data are reported as mean (standard deviation).
GROUP: Represents the three groups in the study stratified by training performance. SCOT HIGH (SCOT HIGH PERFORMANCE), n=15 participants; SCOT LOW (SCOT LOW PERFORMANCE), n=14 participants; CON (Active Control), n=28 participants
Significant p-values from a 3×2 ANOVA testing for differences between groups are shown in bold; a trend towards a significant p-value is shown in italics.
Tukey HSD post-hoc results: □ PRE CON vs POST CON comparison; ◊ PRE SCOT HIGH PERFORMANCE vs POST SCOT HIGH PERFORMANCE comparison.
Effect sizes are reported as partial eta squared (η^2p).
*p<0.05; **p<0.01; ***p<0.005; ****p<0.0001.

Figure 13. *Pre-post comparison in cognitive and social outcome measures after the intervention*



Note. Estimated mean changes in (A) Tower of London, (B) Ekman 60-Faces test, (C) cognitive subtask of the mini-SEA between baseline and post-intervention assessments. Error bars represent standard errors. The p-values in the graphs represent the results of Tukey HSD post-hoc analyses.

7.4. Discussion

Older people who remain socially active and cognitively engaged tend to show higher cognitive function compared to those who are isolated and disengaged (Myhre et al., 2017). Furthermore, digital technologies have developed exponentially in recent years and have shown promise in promoting cognitive well-being in older adults (Lee et al., 2020). The use of online tools facilitates the delivery of preventive interventions remotely, making them accessible to a wide range of users who would not be able to participate in face-to-face activities due to the commitment these activities require (multiple sessions, availability of a caregiver to accompany the person). Within this framework, our study aimed to evaluate the positive effects of a multidimensional social and executive functioning intervention (SCOT) compared to non-specific cognitive stimulation (CON), both delivered via tablets, to promote socio-cognitive wellbeing in older adults.

Overall, the results comparing the performance of the SCOT and CON groups before and after the intervention showed a significant improvement in both groups in planning, evaluated via the accuracy and total index of the ToL as a comprehensive measure for executive functioning, as well as in faux-pas recognition (i.e., Mini-SEA).

Previous literature reports that attention, processing speed and executive function appear to benefit from cognitive stimulation in healthy older adults, regardless of whether these functions are specifically trained (Chiu et al., 2017). Thus, it is possible to hypothesize that, in our study, both interventions (SCOT and CON) may have had beneficial effects on these cognitive outcomes. In particular, since both groups included group sessions, this might have a beneficial effect on socio-cognitive functioning. Furthermore, given that the outcome measures differed from the training activities in terms of content and tasks, it is plausible that our results reflect training-related effects rather than consequences of mere practice. On the other hand, as the experimental design did not include a wait-list control group and parallel versions were not available for the outcome measures, we cannot rule out the possibility that the observed effects on planning and social skills are due to a

learning effect, rather than to a specific improvement in these capacities. The length of the intervention (8 weeks) could possibly increase the risk of observing a practice effect, however the training was built on previous meta-analytic evidence (Chiu et al., 2017) that found greater efficacy of 8-week interventions (total training of 24 sessions) in healthy older people.

The results of the exploratory analyses in which the SCOT group was divided according to training performance, revealed interesting results. In particular, the SCOT participants who achieved the highest levels of performance during training did indeed show significant improvements in executive functioning (ToL index) and basic emotion recognition (Ekman 60-Faces test), as well as a trend towards enhanced cognitive ToM, as evaluated by the Mini-SEA. By contrast, these improvements were not found in the SCOT LOW PERFORMANCE and CON groups. To the best of our knowledge, while previous evidence reports the possibility of training and improving executive functions and ToM in healthy older adults (Cavallini et al., 2015, 2021; Rosi et al., 2016; Rute-Pérez et al., 2023; Vaportzis et al., 2017), this is the first study that has directly tested emotion recognition training in older healthy adults (rather than in clinical populations). Our results showed an improvement in emotion recognition in SCOT HIGH PERFORMANCE, which could have positive consequences in real-life scenarios, such as the ability to accurately perceive, understand and interpret emotional states in others. Indeed, as mentioned above, these skills may decline in older adults, so maintaining them may have beneficial effects, potentially improving social interactions and emotional well-being (Döllinger et al., 2021). Furthermore, our results in emotion recognition are particularly relevant, considering that the training was conducted using an emotion-matching task, where participants had to match pictures with the same emotion expression, whereas we used a simple emotion-recognition task (Ek60 F; Dodich et al., 2014) as an outcome measure. Furthermore, it is important to emphasise the importance of adhering to treatment. The high adherence rates, averaging at 93.92% for CON and 98.06% for SCOT, indicate excellent participants involvement. This suggests that the training was

not only well-received but also deemed feasible for cognitively healthy older adults, reinforcing the overall success of the intervention.

Overall, these results are consistent with previous research suggesting that the efficacy of computerized cognitive training interventions is closely related to the intensity and quality of training (Butler et al., 2018). In essence, individuals who actively engage and excel in training activities are more likely to experience substantial cognitive gains. Moreover, these findings suggest that participants' intrinsic motivation to carry out the planned activities may have played a significant role in shaping the training outcomes. This highlights the importance of considering inter-individual differences when implementing cognitive training protocols (Tagliabue et al., 2022). Taken together, these observations highlight the complexity underlying the efficacy of cognitive training interventions, with engagement, performance, and intrinsic motivation all contributing to the ultimate success of such programs. Digital tools for cognitive training offer additional advantages, including widespread availability of the software, increased user enjoyment compared to traditional exercises, performance monitoring with immediate feedback (Bonnechère et al., 2020), low economic cost, avoidance of problems due to reduced mobility and/or limited access to health resources (Rute-Pérez et al., 2023), and equal or greater efficacy than traditional paper-and-pencil methods, while being less labor-intensive (Kueider et al., 2012). In addition, older adults do not necessarily need advanced technological skills, nor prior experience with the technologies (such as video games, computers, smartphones, or tablets) to benefit from training using these novel approaches (Kueider et al., 2012; Vaportzis et al., 2017). On the other hand, the benefits of such training may be limited if carried out unsupervised (absent close monitoring of participant activity during sessions).

Finally, we found no significant effect on loneliness, a complex construct influenced by a variety of sociodemographic, psychosocial, and health-related risk factors (Barjaková et al., 2023), which refers to the subjective feeling of being alone, separated or apart from others, regardless of the amount of social contact (Veazie et al., 2019). Although some efficacy of socio-cognitive interventions in

reducing loneliness in older people has been documented (Veronese et al., 2021), the lack of significant post-training effects observed in our study is in line with other research suggesting limited efficacy of video calls and/or electronic interventions in reducing social isolation and loneliness in older people (Noone et al., 2020). Given this heterogeneity in the available evidence and the complex nature of loneliness, future research should target older people who exhibit signs of loneliness and/or social isolation, using a more comprehensive approach. These efforts will provide a broader understanding of the efficacy of digital interventions in addressing loneliness and social isolation in older people, a matter of critical importance given its association with cognitive decline and dementia risk (Chipps et al., 2017).

Our study has limitations that must be acknowledged. First, no specific questionnaires were administered to evaluate the success of double-blind manipulation. Besides, the absence of a wait-list control group prevents us from drawing definitive conclusions about the specific effects of the CON and SCOT interventions. Although the observed improvements in executive functioning and social cognition are suggestive of positive outcomes, they could also be due to the mere passage of time or to the non-specific benefits of engaging in cognitive tasks, as mentioned above. Another limitation of this study is the relatively small sample size of the SCOT HIGH PERFORMANCE and SCOT LOW PERFORMANCE groups. Although our results suggest differential responses between these subgroups, a larger sample size would provide greater statistical power and confidence in the observed effects for both subgroups and general analyses of the main outcomes. Future research should aim to replicate these results with larger participant cohorts to further explore this relationship. In addition, it remains unclear whether the observed improvements in executive function and social cognition are long-lasting or instead represent short-term effects. Follow-up analyses of our study and other longitudinal studies that follow participants' progress over several months or years could shed light on the duration of these cognitive gains.

7.5. Conclusions

In conclusion, our study provides valuable insights into the positive effects of the multidimensional online SCOT intervention in improving executive functioning and social skills (emotion recognition and cognitive ToM) in healthy older adults, particularly in those subjects who were more engaged during the training phase and thus performed better. This suggests that subject motivation may influence the efficacy of interventions and should be considered when designing new online interventions in clinical and research settings. Future studies should consider individual motivation as a relevant variable in influencing training success. In addition, the choice of endpoints that represent the construct of interest on which the training intervention is targeted, with good psychometric properties (e.g., no ceiling effects in task performance) and possibly with parallel versions is a desirable aspect. Unfortunately, although there are now new measures of social cognition with parallel versions (Terruzzi et al., 2023), the availability of these tests is still very limited and thus represents a research priority.

Overall, efforts to improve socio-cognitive skills in healthy ageing are of paramount importance, as poor social skills can significantly influence social behaviour, potentially leading to social isolation, loneliness and reduced quality of life (Cavallini et al., 2021; Roheger et al., 2022). Given this, and the limited availability in the literature of socio-cognitive interventions for healthy older people, particularly in the domain of emotional recognition, SCOT training may represent an innovative program that could be implemented on a larger scale to promote socio-cognitive well-being in older people in the context of active ageing and dementia prevention.

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7.6. Supplementary materials

Table S 5. *Checklist of information to address in a randomised Clinical Trial Report from the CONSORT 2010 Statement (Moher et al., 2010)*

Section/Topic	*Item No*	*Checklist item*	*Reported on page No*
Title and abstract			
	1a	Identification as a randomised trial in the title	127
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	127
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	128-131
	2b	Specific objectives or hypotheses	130-131
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	131-132
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	131
	4b	Settings and locations where the data were collected	131
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	133-134
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	135
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	132
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	133-134
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	133-134
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	133-134

Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	133-134
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	133-134
	11b	If relevant, description of the similarity of interventions	133-134
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	136
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	136
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	132, Figure 11
	13b	For each group, losses and exclusions after randomisation, together with reasons	132, Figure 11
Recruitment	14a	Dates defining the periods of recruitment and follow-up	131
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	137, Table 16; 154, Table S7
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	137
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	137, Table 17
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	137-138, Table 18
Harms	19	All-important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	None
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	148
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	149
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	145-148

Other information			
Registration	23	Registration number and name of trial registry	130
Protocol	24	Where the full trial protocol can be accessed, if available	NA
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	149

Note: CONSORT, Consolidated Standards of Reporting Trials;
*It is strongly recommend reading this checklist in conjunction with the CONSORT 2010 statement guidelines (Schulz et al., 2010), as well as Explanation and Elaboration for important clarifications on all the items (Moher et al., 2010) and with the CONSORT extensions for non-pharmacological treatments (Boutron et al., 2017). The CONSORT 2010 statement checklist is distributed under the terms of the Creative Commons license.

Table S 6. *Clinical and neuropsychological assessment*

CLINICAL INTERVIEW
Modified Cumulative Illness Rating Scale (CIRS) – Severity index (SV) (Salvi et al., 2008)
CIRS – Comorbidity index (CM)
COGNITIVE SCREENING
Montreal Cognitive Assessment (MoCA) (Conti et al., 2015)
NEUROPSYCHOLOGICAL ASSESSMENT
Digit span Forward (Monaco et al., 2013)
Digit span Backward
Corsi block-tapping test (Monaco et al., 2013)
Trail-making Test – A (Giovagnoli et al., 1996)
Trail-making Test – B
Trail-making Test – B-A
Phonemic verbal fluency task (Carlesimo et al., 1995)
Semantic verbal fluency task (Zarino et al., 2014)
Rey auditory verbal list immediate recall (Carlesimo et al., 1995)
Rey auditory verbal list delayed recall
Rey-Osterrieth complex figure copy (Caffarra, Vezzadini, Dieci, et al., 2002)
Rey-Osterrieth complex figure delayed recall
Stroop task – Time (Caffarra, Vezzadini, F., et al., 2002)
Stroop task – Errors
State-Trait Anxiety Inventory (STAI-Y) (Spielberger et al., 1983)
Geriatric Depression Scale (GDS) (Sheikh & Yesavage, 1986)
Mobile Device Proficiency in Older Adults (MDPQ-16) (Roque & Boot, 2018)
Cognitive Reserve Index questionnaire (CRIq) (Nucci et al., 2012)
OUTCOME MEASURES
Tower of London (ToL) (Boccia, Marin, D'Antuono, et al., 2017)
ToL – Accuracy
ToL – Index
Ekman-60 Faces test (Ek-60F test) (Dodich et al., 2014)
Ek-60F test – Global score
Mini-Social cognition & Emotional Assessment battery (Mini-SEA) (Bertoux et al., 2013)
Mini-SEA – Faux pas Detection
Mini-SEA – Cognitive ToM
Mini-SEA – Affective ToM
Mini-SEA – Control stories
Italian Social and Emotional Loneliness Scale (ISELS) (Zammuner, 2008)

Table S 7. *Baseline assessment of subgroups based on exploratory analyses*

DEMOGRAPHIC DATA	***CON (n=28)***	***SCOT HIGH (n=15)***	***SCOT LOW (n=14)***	***Statistics***
Sex (F/M)	18/10	9/6	8/6	χ^2=0.2, p=0.9
Age	71.5(5.3)	71.6(5.1)	72.0(5.6)	F(2,28.8)=0.03, p=1.0
Education	12.5(3.0)	12.5(3.6)	12.4(4.7)	F(2,25.5)=0.01, p=1.0
CLINICAL & NEUROPSYCHOLOGICAL ASSESSMENT				
Montreal Cognitive Assessment (MoCA)	25.3(2.5)	25.7(2.7)	24.5(1.9)	F(2,30.1)=1.08, p=0.4
CIRS – Severity index (SV)	0.5(0.2)	0.4(0.3)	0.4(0.3)	F(2,26.3)=0.27, p=0.8
CIRS – Comorbidity index (CM)	1.8(1.4)	1.3(1.3)	1.3(1.3)	F(2,29.5)=1.17, p=0.3
Digit span Forward	5.8(0.6)	5.9(0.8)	5.9(0.8)	F(2,26.2)=0.08, p=0.9
Digit span backward	4.7(1.0)	4.5(0.9)	4.1(0.5)	F(2,31.6)=2.73, p=0.1
Corsi block-tapping test	5.3(0.9)	5.1(1.2)	5.3(0.8)	F(2,28.5)=0.18, p=0.8
Trail-making Test – A	40.9(13.8)	41.7(14.7)	44.8(13.6)	F(2,28.8)=0.38, p=0.7
Trail-making Test – B	106.5(36.2)	94.7(30.9)	98.9(23.0)	F(2,32.1)=0.66, p=0.5
Trail-making Test – B-A	65.6(31.4)	53.0(23.3)	54.1(14.1)	F(2,32.9)=1.51, p=0.2
Phonemic verbal fluency task	42.5(11.0)	40.9(13.3)	41.3(11.9)	F(2,27.4)=0.11, p=0.9
Semantic verbal fluency task	47.0(7.7)	48.1(9.3)	43.7(6.1)	F(2,29.4)=1.55, p=0.2
Rey auditory verbal list immediate recall	47.1(9.8)	50.8(11.1)	42.7(7.8)	F(2,29.7)=2.74, p=0.1
Rey auditory verbal list delayed recall	9.6(2.6)	10.8(3.5)	7.9(3.5)	F(2,25.5)=2.55, p=0.1
Rey-Osterrieth complex figure copy	31.1(3.3)	32.1(3.0)	31.9(2.3)	F(2,31.6)=0.67, p=0.5
Rey-Osterrieth complex figure delayed recall	17.0(6.7)	16.7(5.5)	16.4(4.4)	F(2,32.1)=0.07, p=0.9
Stroop task – Time	23.7(10.0)	18.9(6.9)	20.5(6.5)	F(2,31.9)=1.70, p=0.2
Stroop task – Errors	0.9(1.3)	1.0(1.7)	0.4(0.9)	F(2,28.3)=1.76, p=0.2
State-Trait Anxiety Inventory (STAI-Y)	36.9(7.1)	37.0(8.2)	38.7(9.0)	F(2,26.7)=0.22, p=0.8
Geriatric Depression Scale (GDS)	2.6(1.8)	2.5(2.1)	2.9(2.7)	F(2,25.7)=0.13, p=0.9

Mobile Device Proficiency in Older Adults (MDPQ-16)	56.6(17.1)	60.6(17.1)	63.0(14.6)	F(2,29.9)=0.82, p=0.5
Cognitive Reserve Index questionnaire (CRIq)	115.4(16.1)	112.6(16.2)	116.9(12.5)	F(2,30.4)=0.31, p=0.7
OUTCOMES MEASURES				
Executive functions				
Tower of London (ToL)– Accuracy	35.6(4.6)	36.1(4.2)	37.3(3.8)	F(2,30.4)=0.82, p=0.5
Tower of London (ToL)– Index	0.3(0.1)	0.3(0.1)	0.4(0.1)	F(2,29.2)=2.95, p=0.1
Social Cognition				
Ekman-60 Faces test (Ek-60F test)	46.5(6.1)	48.1(4.2)	47.1(5.1)	F(2,31.5)=0.53, p=0.6
Mini-Social cognition & Emotional Assessment battery (Mini-SEA) – Faux pas Detection	13.9(1.0)	13.3(1.4)	13.6(1.1)	F(2,27.1)=0.79, p=0.5
Mini-Social cognition & Emotional Assessment battery (Mini-SEA) – Cognitive ToM	13.8(3.3)	12.0(4.2)	13.0(3.4)	F(2,27.5)=1.00, p=0.4
Mini-Social cognition & Emotional Assessment battery (Mini-SEA) – Affective ToM	3.5(1.0)	3.2(1.1)	3.5(0.8)	F(2,30.2)=0.37, p=0.7
Mini-Social cognition & Emotional Assessment battery (Mini-SEA) – Control stories	19.7(0.7)	19.7(0.6)	19.8(0.8)	F(2,28.1)=0.10, p=0.9
Italian Social and Emotional Loneliness Scale (ISELS)	34.7(8.2)	32.6(8.3)	34.6(6.8)	F(2,30.1)=0.34, p=0.7

Note. Data are reported as mean (standard deviation).
A one-way ANOVA was conducted to compare the mean scores across the three groups in the study stratified by training performance. SCOT HIGH (SCOT HIGH PERFORMANCE), n=15 participants; SCOT LOW (SCOT LOW PERFORMANCE), n=14 participants; CON (Active Control), n=28 participants.

Appendix B

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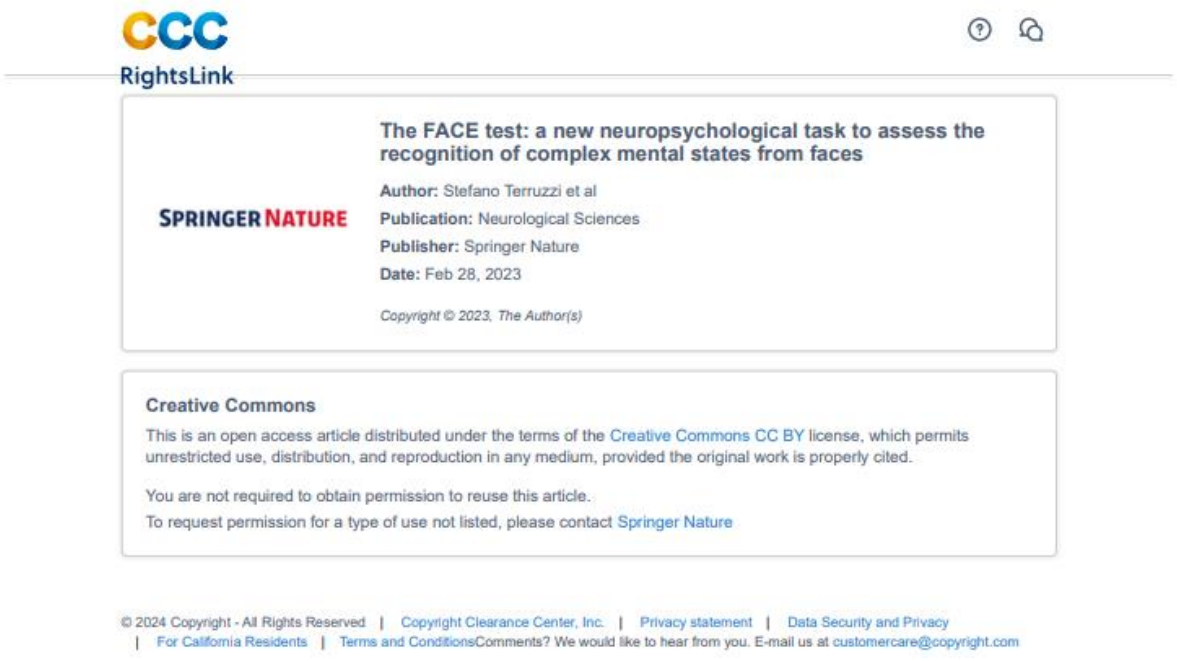
B.1 Study 1 - Deficits in emotion recognition and theory of mind in Parkinson's Disease patients with and without cognitive impairments

B.2 Study 2 - The FACE test: A new neuropsychological task to assess the recognition of complex mental states from faces



B.3 Study 5 - The Social and Cognitive Online Training (SCOT) project: a digital randomized controlled trial to promote socio-cognitive wellbeing in older adults

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The Social and Cognitive Online Training (SCOT) project: A digital randomized controlled trial to promote socio-cognitive well-being in older adults

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Study 1 - Deficits in emotion recognition and theory of mind in Parkinson's Disease patients with and without cognitive impairments

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Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this thesis the author used DeepL in order to improve to improve spelling, grammar, general readability and language of the work. After using this tool, the author reviewed and edited the content as needed and takes full responsibility for the content of the published article.

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