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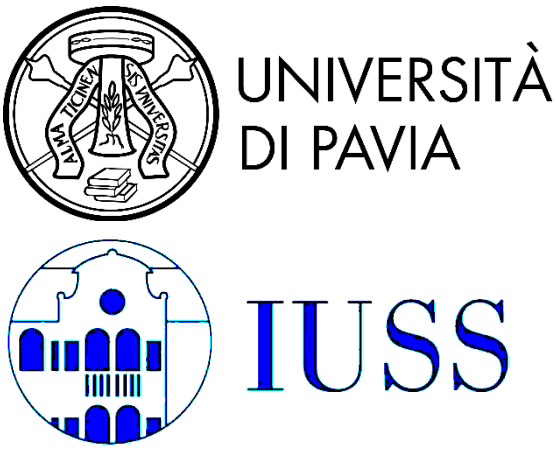

Diagnostic performance of Social Norms Questionnaire Italian version (SNQ-IT) for the early and differential diagnosis of dementia: the role of break and overadherence error patterns

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The art of love is largely the art of persistence
Albert Ellis

To my niece Emilia and nephew Uros

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Abstract

Social norm knowledge is one of the main socio-cognitive facets that can be affected in neurocognitive patients. It includes understanding of social boundaries and adapting behavior according to the social context. Overadherence or violation of social norms characterize the cognitive profile of behavioral variant of frontotemporal dementia (bvFTD) patients. In this study, we explored social knowledge impairment patterns in a sample of patients with bvFTD compared to Alzheimer's disease (AD) patients and healthy control subjects (HC), with the aim to define the diagnostic role of social norm deficits and the added value of the clinical error pattern analysis in the early and differential diagnosis of bvFTD. The Italian version of the Social norms questionnaire (SNQ-IT) was administered to 33 bvFTD, 20 AD and 20 HC. Global score (SNQgs), overadhere (SNQoes) and break (SNQbes) subscale scores were computed. Diagnostic performance of SNQgs, SNQoes and SNQbes scores were evaluated with the Receiver Operating Characteristic (ROC) curve analysis. A stepwise logistic regression model was applied to accurately classify bvFTD, including in the model only those variables found to be significant predictor variables. All scores significantly differed in bvFTD vs HC while SNQoes scores did not differ in bvFTD vs AD. SNQgs showed an excellent performance in differentiating bvFTD from AD (AUC 0.82). Logistic regression analysis identified SNQbes as the main variable, in combination with SNQgs, in accurately distinguishing bvFTD from HC and correctly classifying the 93% of patients. The combination of SNQbes and SNQgs was able to distinguish bvFTD from AD, correctly classifying the 90% of bvFTD patients. Knowledge of social norms is a crucial socio-cognitive subdomain early affected in bvFTD. SNQ-IT is a useful clinical tool for early

diagnosis of bvFTD. Error pattern analysis may add crucial information for differential diagnosis identifying violations of social norms which are core signatures of social cognition changes in bvFTD.

Chapter 1
Introduction to social cognition

1.1 The broad galaxy of social cognition

Social Cognition (SC) is a broad cognitive domain presenting with the capacity to interpret and predict others' behaviors based on their beliefs, intentions and emotions while decoding social stimuli from the environment and adapting one's behavior accordingly (Adolphs, 2009), ultimately encompassing mental processes such as attention, perception and memory by which individuals perceive, interpret and make sense of social interactions, form impressions and reasoning about people, relationships and finally enabling empathy, behavior prediction and appropriate social response (Fiske & Taylor, 2013; Baron & Branscombe, 2012).

Such a process is a matter of survival, and it depends on the exchange of signals. This type of cognition related to social situations in humans is closely linked to verbal cues and competences as speech is the most salient instrument of social communication in humans. Nonetheless, there are other non-verbal social cues extremely relevant for meaningful social interactions. Among these facial expressions and body postures are crucial to give significant inputs about mental states of others (Frith & Frith, 2008). These cues are particularly important in the early life phases, as demonstrated by social reference phenomena in infants (Emery et al., 2007).

In humans, the first early forms of social cognition, such as distinguishing between familiar and unfamiliar faces, responding to social cues like smiles, recognizing goal-directed actions, emotional mimicry as a subcomponent of empathy and affiliative

behavior appears at around 6 months old (Johnson, 2000; Tomasello, 2003). It develops further in subsequent years and remains essential throughout life (Slaughter et al., 2015). When it comes to social referencing, babies use their mothers' expressions to determine whether to approach a new object. One important part of this process is observational learning, which is the process by which people pick up knowledge only by watching other people (Klinnert et al., 1986). A large portion of this signaling happens instinctively for the sender as well as the receiver. However, this process is very useful because it makes it possible to learn without experiencing potentially disastrous errors.

These processes are enabling deliberate communication, teaching and cooperation (C. Frith & Frith, 2012). They are often referred to as *mentalizing or having theory of mind* which can be defined as implicit, or explicit (strictly related to human species) "attribution of mental states to others and self in order to explain and predict what they will do" (C. Frith & Frith, 2012). They enable individuals to understand each other's behaviors with a high degree of precision. Explicit mentalizing is related to meta-cognition which represents "reflection on mental states, including one's own mental states (introspection); others' mental states (popular psychologizing); mental states in general (philosophy of mind)" (C. Frith & Frith, 2012).

The importance of this broad cognitive domain is evident in various pathological conditions where social skills are compromised. Numerous neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and Frontotemporal Dementia (as will be discussed in detail in the second chapter), psychiatric disorders including schizophrenia, major depressive disorder, bipolar disorder, neurodevelopmental disorders such as autism spectrum disorders and ADHD, Attention-Deficit/Hyperactivity Disorder, traumatic brain injuries and strokes can exhibit different degrees of deficits in this cognitive domain (Kennedy & Adolphs, 2012). In all these cases, albeit with their

specificities, patients with social cognition deficits may also show concurrent deficits in other cognitive functions, psychological alterations (Jones et al., 2015), functional (Henry et al., 2015) and social disabilities (Jones et al., 2015), and generally a reduced quality of life (Phillips et al., 2010). These impairments inevitably negatively impact the formation and maintenance of interpersonal relationships (Henry et al., 2015).

1.2 Social cognition subcomponents and neural correlates

From a theoretical perspective, social neuroscience recognizes distinct but interrelated psychological processes that account for the different aspects of social cognition domains such as social perception and attention to social cues, social understanding and attribution of mental states, social decision-making, and finally social behavior (Adolphs, 2002; Kennedy & Adolphs, 2012; Arioli et al., 2018; Ruff & Fehr, 2014). Socio-cognitive subcomponents are in(ter)dependent by other non-social domains as memory, visuo-spatial skills or executive functions (M. H. Beauchamp & Anderson, 2010).

1.2.1 Social Perception

Social perception is the fundamental ability to distinguish between objects, whose behavior is predictable as it is solely determined by physical forces, and individuals, whose actions are not as easily predicted since they stem from personal experiences and internal states. These actions are therefore related to individual motivations, reasons, and intentions (Fiske & Taylor, 2013; Vogeley, 2017). The importance of social stimuli in human life is evident at various levels: in individual survival instincts, in couple communication, in the social coordination of groups, and within institutional cultures (Dolan, 2002). A prime example of this is the neural processing of human faces (McKone

et al., 2007), which provides information about both mutable characteristics, such as emotions and intentions, and immutable ones, like an individual's identity.

Among all visual stimuli, the human face holds a unique significance in cognitive processing (Kato & Konishi, 2013). This assertion is supported by numerous experiments showing that faces and objects are processed differently—faces holistically and objects through detailed part-by-part analysis (Maurer et al., 2002). Moreover, human faces elicit a greater neural activation when presented upright compared to inverted (Yovel & Kanwisher, 2004). Eyes are the most dynamic and informative social stimulus, capturing attention more effectively than head or body movements and posture (Adams & Nelson, 2016). Gaze direction clearly indicates shifts in attention, and eye movements convey mental states, serving as a prerequisite for understanding others' mental states (mentalization) (Baron-Cohen et al., 1997). Besides gaze, the emotions expressed through facial muscle contractions provide significant social information (Adolphs, 2002; Santana et al., 2014). Ekman and Friesen's well-known Facial Action Coding System (FACS) describes facial expressions as combinations of "action units" that characterize different emotions (Ekman et al., 1987). This model identifies six universal basic emotions (happiness, anger, sadness, fear, disgust, and surprise) that can be expressed and recognized by all humans regardless of socio-cultural influences (Ekman et al., 1987). However, a greater interplay between biological and socio-cultural factors in the processing of facial expressions and the interpretation of emotions has been suggested (Elfenbein & Ambady, 2002).

Body and voice also play significant roles in emotional communication (Dael et al., 2012). The voice, through both non-verbal vocalizations like laughter or crying and prosody in spontaneous speech, conveys mostly non-specific aspects of affective states, such as the physiological arousal of the nervous system, rather than specific emotions

(Scherer, 1995; Russell et al., 2003). According to the feedback hypothesis, face, body, and voice not only express emotions but can also influence them, as they produce sensory feedback that modulates the intensity of emotional experience (Aucouturier et al., 2016). This experience is increased by expressing a coherent emotion through face, body, and voice or, conversely, decreased by expressing an incoherent emotion or inhibiting a coherent one (Hyniewska & Sato, 2015). This concept is closely related to the notion of embodied simulation, a mirror-like mechanism underlying the connection between first-person and third-person experiences (Gallese et al., 1996; Rizzolatti & Sinigaglia, 2010). Through this mirror system, humans can grasp the meaning of others' actions and emotions (Gallese et al., 2004). Understanding the emotion expressed on another person's face involves activating the neural system responsible for the actual activation of the muscle groups responsible for that facial expression (i.e., the imitation of the movement in the observer) (Adolphs et al., 2000; Niedenthal & Brauer, 2012).

1.2.2 Social Understanding

Crucial component of social understanding is related to Theory of Mind (ToM). ToM is considered the cognitive ability to refer and attribute mental states that involve beliefs, desires, intentions, or emotions to oneself and others and also understand that these states may be different from one's own (Baron-Cohen, Leslie, & Frith, 1985). This cognitive ability allows individuals to anticipate and explain events within other persons' behaviors by means of their mental states (Baron-Cohen, Leslie, & Frith, 1985). Significant distinction exists between cognitive or cold ToM, which refers to the ability to attribute mental states, and affective or hot ToM, which pertains to understanding affective states (Molenberghs et al., 2016). Additionally, recognizing others' thoughts, desires, feelings,

and character traits differs from automatically grasping and sharing their affective states (Singer & Lamm, 2009). This latter aspect is part of the affective empathy, which is considered the ability to experience an affective state elicited by perceiving, imagining, or deducing the affective state of another individual. The other facet of empathy is cognitive empathy, the ability to understand others' feelings and affective experiences, and affective empathy (Decety & Jackson, 2004). As this classification suggests, there is some overlap between the subcomponents of social cognition: affective ToM and cognitive empathy (Stietz et al., 2019).

According to Shamay-Tsoori's model, cognitive ToM is hypothesized to be a prerequisite for affective ToM, and the latter interacts with affective (or emotional) empathy (Shamay-Tsoory et al., 2010). Lastly, in line with the well-known Mindreading model, social perception and mentalization are components of a broader system that contributes to perceiving and appropriately responding to others' emotions and intentions (Baron-Cohen et al., 2009; Decety, 2010). There is a bidirectional relationship between social perception and mentalization: social perception, particularly emotion decoding, precedes mentalization (Mitchell & Phillips, 2015), representing a low-level perceptual process that sends signals to a higher level where integration processes—ToM—occur (J. P. Mitchell, 2006). However, ToM also influences social perception through a top-down mechanism based on long-term knowledge acquired over time (Arioli et al., 2018).

1.2.3 Social Decision-Making

Social decision-making is a process influenced by the environment and involves understanding others' behavior, both in terms of choices already made and future actions (Arioli et al., 2018; Ruff & Fehr, 2014). From a purely utilitarian perspective, it is

expected that individuals will make the best choices for themselves among the possible options. However, neuroeconomic studies have shown that decision-making also depends on prosocial and affective considerations, laying the foundation for another subdomain of social cognition: emotional decision-making (Arioli et al., 2018). Using social decision-making tasks originally developed by economists, such as the Ultimatum Game, the Dictator Game, and Fehr and Fischbacher's 2006 Trust Game, researchers have observed that individuals tend to make less selfish and more fairness-oriented choices compared to what the Nash equilibrium model would predict (Arioli et al., 2018; Nash, 1950; Camerer, 2003). Thus, the process of social decision-making is complex, involving various nuances that have been extensively studied in the field of neuroeconomics. Among these nuances is the principle of "altruistic punishment," which involves choosing between self-enrichment and the possibility of punishing a wrongdoer in mutually exclusive options, with a tendency toward the latter (Camerer, 2003; Fehr & Gächter, 2002). Another principle is the "expectation of reciprocity," where individuals feel justified in engaging in altruistic punishment, believing that others in their social context would make the same choice in a given situation (Arioli et al., 2018). Altruistic punishment can also be driven by a desire for revenge, fueled not only by negative emotions related to perceived injustice or betrayal but also by the sense of satisfaction derived from seeing the wrongdoer penalized (Arioli et al., 2018; Fehr & Gächter, 2002). In light of this evidence, it has become clear that social decision-making is largely driven by a range of emotions and feelings. Individuals make certain choices to experience positive sensations, such as those associated with prosocial behavior and gain, and to avoid negative ones (Arioli et al., 2018; Fiske et al., 2010).

1.2.4 Social Behavior

Social behavior represents an extensive concept that encompasses the variety of actions and interactions that take place in the company of others, illustrating individual traits and situational factors (Aronson, Wilson, & Akert, 2019). This phenomenon includes observable behaviors like communication, collaboration, aggression, as well as the provision and reception of social support. For example, social behavior occurs in everyday communication wherein individuals use verbal and non-verbal cues to relay their message and emotions to each other. In relation to group settings, social behavior may be explored in the form of group dynamics wherein leadership, conformity, and group cohesion (Cialdini & Goldstein, 2004). Other behaviors more related to individuals' response to others' emotional states with understanding and support depict the role of social cognition and ToM (Baron-Cohen, Leslie, & Frith, 1985). Social behavior is influenced by cultural norms and societal expectations which determine appropriate responses and interactions in various contexts (Triandis, 1995). The research into such behaviors has important implications for understanding the nature of how people adjust their behaviors to different social circumstances and how social norms affect interpersonal relations and societal organizations (Triandis, 1995).

1.2.5 Neural Correlates

Thanks to various techniques, neuroscience has extensively explored the neural correlates activated during different social cognition tasks. In social perception, the occipitotemporal cortex is identified as the primary node involved in processing visual social stimuli. Distinct brain areas are associated with interpreting different parts of the social visual scene: the occipital face area (OFA), located in the inferior occipital gyrus,

is dedicated to facial processing, while the extrastriate body area (EBA), located in the lateral occipitotemporal cortex, focuses on bodies. Both areas are activated in processing information from various parts of the face and body. Additionally, the fusiform face area (FFA) and the fusiform body area (FBA), both located in the fusiform gyrus, are involved in decoding elements of the social scene (Arioli et al., 2018; Bernstein et al., 2018; Peelen & Downing, 2007; Taylor et al., 2007). The spatial proximity of these areas facilitates the functional integration of different visual stimuli for recognizing individuals as a single entity, especially when one element alone is not sufficient (Peelen & Downing, 2007). Another critical brain region for social perception is the posterior portion of the lateral temporal cortex. Specifically, the posterior superior temporal sulcus (pSTS) plays a crucial role in social perception by processing variable features of biological stimuli, such as gaze direction (Beauchamp et al., 2002; Rizzolatti et al., 2001; Allison et al., 2000). The pSTS serves as a vital hub for social cognition skills, sending sensory outputs to the fronto-parietal mirror system, which analyzes the meaning of sensory inputs from the pSTS to attribute social significance to others' actions (Arioli et al., 2017; Canessa et al., 2012). It is also closely connected with the amygdala and the orbitofrontal cortex, which are involved in assigning emotional value to perceived social stimuli (Winston et al., 2002).

The fronto-parietal mirror and the mentalizing systems are the two neural networks responsible for social understanding. The mirror system includes the inferior frontal gyrus, premotor cortex, and parietal cortex (Gallese et al., 1996), while the mentalizing network involves the medial prefrontal cortex (mPFC), the temporoparietal junction (TPJ), the medial precuneus/posterior cingulate cortex, and the temporal poles (Amodio & Frith, 2006; Bahnemann et al., 2009; Mar, 2011). These two systems play complementary roles in understanding others' behavior and decoding intentions and

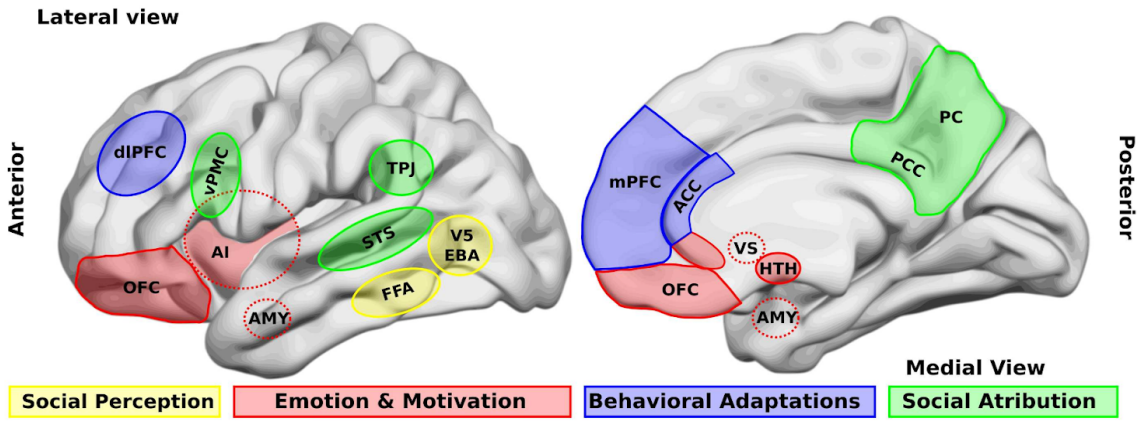
feelings. The mirror system, which is activated both when performing and observing an action, is engaged during active observation of real scenes involving biological actions, passive or implicit observation, and decoding how a movement is performed in relation to a behavioral state. In contrast, the mentalizing system is activated when inferring others' intentions from mental states, especially during abstract information processing (e.g., reading a story), explicit instructions (e.g., understanding others' intentions), and interpreting why an action is performed (Van Overwalle & Baetens, 2009; Spunt & Adolphs, 2014; Spunt & Lieberman, 2012a; Spunt & Lieberman, 2012b). The two systems are connected via the superior longitudinal fasciculus (Wang et al., 2018).

Regarding empathy, several limbic system regions, along with various subcortical structures and the hypothalamic-pituitary axis, constitute its primary neural correlates. Some researchers have demonstrated that a complex mirror neuron system also underpins proper empathic functioning, although it differs from the previously described fronto-parietal network (Arioli et al., 2018). Functional magnetic resonance imaging (fMRI) studies have widely shown that activation of limbic structures, particularly the anterior insula and the dorsal anterior cingulate cortex (ACC), is associated with autonomic and somatosensory responses, forming the basis for embodied simulation, which is essential for affective empathy (Lamm et al., 2011; Fan et al., 2011). In this context, the uncinate fasciculus linking the medial temporal and orbitofrontal cortices (Catani & Thiebaut De Schotten, 2008), and the anterior thalamic radiation, connecting the hypothalamus and limbic structures to the prefrontal cortex and ACC (Catani et al., 2013), play crucial roles in ensuring proper communication among the different components of the empathic circuit.

To conclude, as shown in Figure 1 modified from Billeke & Aboitiz (2013), social processing involves several key brain regions, each participating in distinct but

interconnected processes. Firstly, the perception of basic social stimuli, such as biological motion (V5), parts of the body (extra-striate body area, EBA), and faces (fusiform face area, FFA), sets the stage for social interaction. Secondly, emotional and motivational appraisal is facilitated by regions including the amygdala (AMY), anterior insula (AI), subgenual and perigenual anterior cingulate cortex (ACC), and the orbitofrontal cortex (OFC). These cortical structures interact with subcortical areas such as the ventral striatum (VS) and hypothalamus (HTH). Thirdly, goal-directed, adaptive behaviors, and categorization processes are supported by the dorsolateral and medial prefrontal cortex (dlPFC, mPFC) and the ACC. Lastly, social attribution involves both automatic, bottom-up inferences of others' mental states, processed by the ventral premotor cortex (vPMC), superior temporal sulcus (STS), AI, posterior cingulate cortex (PCC), and precuneus (PC), and more cognitive theory of mind skills, mediated by the mPFC and temporo-parietal junction (TPJ). These integrated neural processes underpin our ability to understand and navigate social norms, reflecting the complex interplay between perception, emotion, motivation, behavior, and social cognition.

Figure 1. *Neural correlates of different social cognition subcomponents*



Note. Modified from "Social cognition in schizophrenia: From social stimuli processing to social engagement", by Billeke, P., & Aboitiz, F., 2013, Frontiers *in Psychiatry*, 4, 4. (https://doi.org/10.3389/fpsyt.2013.00004)

1.3 Social norms knowledge, neural correlates and neuropsychological measures

1.3.1 Social norms knowledge

Social norms represent unwritten rules that govern behavior in society. They are generally accepted beliefs about what constitutes proper behavior, also known as the "grammar of social interaction", and are composed of a number of principles that are intended to promote social cohesion, social harmony and maintain cooperation (Ostrom, 1990).

Social norms knowledge refers to awareness and comprehension of these implicit rules that direct behavior that govern specific social contexts. They can be injunctive, suggesting what people should do, or descriptive, describing what the majority of people already do (Cialdini, Kallgren, & Reno, 1991). We learn about them through socialization processes, including observation, imitation and reinforcement (Bandura, 1977).

Descriptive norms describe what is a typical behavior within a society. People might observe that most individuals dress more formally and elegantly than usual for a theater in their community and therefore they perceive this as a normative behavior. Injunctive norms involve perceptions of what might be approved or disapproved by others, for example supporting a local football club in competition. From the combination of these two types of norms, often Personal Norms derive, and they represent internalized beliefs regarding how one should behave (Schwartz, 1977). These norms come in a range of forms, from highly culturally specific standards of behavior with little moral significance ("Thou shalt not wear white after Labor Day") to more universal norms with moral significance that differs depending on the culture ("Thou shalt not commit adultery"), to norms with such moral significance that they are so widely accepted as to be formalized and codified into laws ("Thou shalt not kill") (Buckholtz & Marois, 2012). When social demands are not fulfilled, deviating from social norms frequently leads to the punishment or removal of the norm violator from the group. However, the role and type of punishment varies depending on the severity of the norm violation and the specific socio-economic system of society (Garfield et al., 2023).

1.3.2 Neural Correlates of Social Norms Knowledge

Multiple neural correlates of social norms knowledge have been identified in several brain regions. Brain areas related to theory of mind and social cognition are commonly as well those being active when people are processing and representing social norms. These brain regions are frequently activated during mentalizing activities, which entail

understanding other people's intentions, viewpoints, and beliefs, but additionally, they are implicated in processing and adherence to social norms (Zinchenko & Arsalidou, 2017). Although there has been inconsistencies regarding social norm knowledge correlates (Zinchenko & Arsalidou, 2017), key brain regions identified so far include Prefrontal Cortex (PFC), Orbitofrontal cortex (OFC), Anterior Cingulate Cortex (ACC) and Temporal-Parietal Junction (TPJ) (Zinchenko & Arsalidou, 2017; Forbes & Grafman, 2010; Cavada & Schultz, 2000; Koban & Pourtois, 2014; Van Overwalle, 2009).

One of the crucial brain areas for social cognition in general is PFC. Apart from being involved in decision making, perspective taking and evaluating social information, medial prefrontal cortex (mPFC) particularly is crucial for social norms representation. On the other hand, lateral PFC plays a role in cognitive control and decision-making process, helping people align their behavior with social norms (Zinchenko & Arsalidou, 2017; Forbes & Grafman, 2010). ACC helps in processing norm violations and emotional consequences of such. It is associated with error detection, conflict monitoring and emotional regulation (Koban & Pourtois, 2014; Zinchenko & Arsalidou, 2017). According to Van Overwalle (2009), the TPJ is important for comprehending the intentions of others, which is necessary for compliance to norms and identifying when they are being violated, but it is no less critical for perspective taking and understanding others' beliefs and intentions (Zinchenko & Arsalidou, 2017). In reward processing, the OFC assesses social behavior outcomes, but also adherence to social norms (Cavada & Schultz, 2000). Apart from the previously mentioned, Zinchenko and Arsalidou (2017) synthesized findings from various fMRI studies to identify consistent patterns of brain activity associated with processing social norms studies and identified another 2 common and distinct brain areas involved in social norms processing: anterior insula and striatum. The anterior insula is associated with emotional responses to norms violations, such as

feeling of guilt, embarrassment and discomfort when social norms are violated. The striatum is related to reward processing, suggesting that compliance to social norms can be intrinsically rewarding and, in the opposite, deviations may trigger negative reinforcement. When people follow social norms that are considered advantageous or ethically correct, their brain activity may also be enhanced in regions linked to reward processing and positive affect (Zinchenko & Arsalidou, 2017). Brain areas linked to cognitive conflict, mistake detection, and emotional processing are frequently more active when people observe or participate in norm violations (Zinchenko & Arsalidou, 2017). Brain areas linked to processing negative emotions and social aversion, such as the insula and amygdala, may be activated in emotional reactions to norm violations (Zinchenko & Arsalidou, 2017).

1.3.3 Neuropsychological measures of Social Norms Knowledge

The large majority of experimental tasks developed to assess social cognition domain explore facets different from social norm knowledge. Some socio-cognitive measures indirectly explore social rules and norms understanding and knowledge. These tasks mainly focus on recognizing faux pas in social contexts, understanding socially appropriate behaviors and complex social situations. Among these, the Faux Pas Test (Baron-Cohen, Leslie, & Frith, 1999) is one of the most used tests for evaluating individual aptitude for identifying and understanding social faux pas in narratives. This measure assesses only indirectly social norm knowledge. In this test, participants must read or listen to short stories in which a main character unintentionally says or does something that is unacceptable in social situations (a faux pas). Then, participants are

asked to find out whether the story reports a gaffe or not, why there is a gaffe, and what the story characters think or feel. Another example is the Awkward Moments Test (Hezel & McNally, 2014), in which participants watch videos of awkward social situations and are asked to assess their comprehension of real-life scenarios, including social cues, social norms and characters' emotions. The Moral and Conventional Transgressions Task presents participants with scenarios which either represent conventional violations (e.g. breaking the dress code) or moral violations (e.g. stealing). Participants are asked to assess severity and appropriateness of behaviors, and to justify their decisions. In this task, understanding of social norm knowledge is indirectly evaluated by differentiating between actions that are socially inappropriate due to moral constraints and those which are inappropriate due to social conventions (Turiel, 1983).

Additionally, some emotion decision-making tasks may also provide useful information on social norm understanding. The Ultimatum Game (Güth et al., 1982) involves 2 players from which one proposes how to divide a sum of money, and the other one accepts or rejects the offer. If the offer is rejected, both players have nothing. This task can indirectly measure social norm knowledge by assessing one’s expectations (norms) of fair behavior and individual willingness to respect the norms they have by rejecting unfair offers. In the Public Goods Game (Ledyard, 1995), participants contribute to a common pole which is subsequently multiplied and divided. This game evaluates cooperation and the propensity to follow norms that are in the best interests of the group as a whole. Knowledge of social norms related to collaboration and the welfare of the group can be assessed using the Public Goods Game. Greater contributions to the common pool show that norms that advance the interests of the group as a whole have been understood and internalized. The Trust Game (Berg, Dickhaut, & McCabe, 1995) involves two participants from which one decides how much money to send to the other,

which is then tripled, and the recipient decides how much to return. This game evaluates reciprocity and trust, two essential elements of adhering to social norms. The quantity of money sent and received indicates an understanding of social rules related to reciprocity and trust (Berg, Dickhaut, & McCabe, 1995).

Apart from the previously reported tasks which assess only indirectly the understanding and knowledge of social norms and rules, there is a measure specifically developed to this socio-cognitive subcomponent. This is the Social Norms Questionnaire (SNQ-22) created by Katherine Rankin as part of the NIH EXAMINER battery. The SNQ assesses one's understanding and ability to accurately identify implicit yet widely accepted social boundaries (Kramer et al., 2013). It is a yes/no questionnaire of 22 items classified as socially appropriate (e.g. "laugh when you trip and fall", "blow the nose in public" or "eat ribs with fingers") or inappropriate (e.g. "laugh when someone else trips and falls", "pick the nose in public" or to "eat pasta with fingers"). Errors may thus present different patterns, either in the direction of breaking a social norm or of interpreting a social norm too rigidly. Error profile can be accounted for considering the "Break" and the "Overadhere" scores. This questionnaire has been proved to be particularly useful in clinics to assess neurocognitive patients. According to Panchal et al. (2015), patients affected by the behavioral variant of frontotemporal dementia (bvFTD) exhibited greater overadhere errors and significantly lower SNQ total scores compared to patients with early onset Alzheimer's disease (AD). Notably, global performance at the SNQ and overadhere score respectively correlate with semantic knowledge and executive functions.

Chapter 2
The behavioral variant of frontotemporal dementia

Clinical and scientific interest in frontotemporal dementia (FTD) is rapidly growing as it can be best seen by burgeoning literature in this field (Dickerson, 2016). The selective derangements of frontal and temporal lobe networks involved in social cognition, language, and semantic memory—which can be remarkably selective for a number of years—is a unique feature of FTD, making this clinical condition so fascinating from the standpoint of behavioral neuroscience research.

2.1 The frontotemporal dementia spectrum

An initial point of interest for the research in this field can be found in the landmark paper "On the symptomatology of left-sided temporal lobe atrophy," published by Arnold Pick twelve years after he reported, while working in Prague, that a 71-year-old man with progressive mental deterioration and unusually severe aphasia had marked atrophy of the left temporal lobe post-mortem (Dickerson, 2016). In the last twenty years, significant progress has been made in our comprehension of the primary neurodegenerative illnesses affecting frontal and temporal lobes and causing selective cognitive impairments. These conditions were for long time known as Pick's disease and, more recently, classified as

FTD. FTD is not a single nosological entity but rather an umbrella term that encompasses various clinical syndromes. These syndromes are characterized by selective atrophy of the frontal and temporal lobes (Rohrer & Rosen, 2013; Piguet et al., 2011) and progressive changes in one or more cognitive domains (e.g., executive functions, language, social cognition) and/or in behavioral profile (Bang et al., 2015; Boeve et al., 2022). From a epidemiological point of view, FTD is the third most common form of dementia across all age groups, following AD and dementia with Lewy bodies (DLB) (Vieira, 2013), and the second most common early-onset dementia (< 65 years of age) after early onset AD (Ratnavalli et al., 2002; Rosso et al., 2003). According to two independent studies conducted in the UK, the prevalence is around 15 cases per 100,000 people, with onset typically between 45 and 65 years of age (Ratnavalli et al., 2002). However, it is necessary to consider the potential underestimation of late-onset FTD cases, where symptoms appear at age 65 or older, due to fewer in vivo exams and autopsies generally performed in this population segment (Piguet et al., 2011).

FTD is a highly heritable clinical syndrome, almost uniquely within neurodegenerative diseases, as it is neither purely genetic, like Huntington's disease (HD), nor predominantly sporadic, like AD (Greaves & Rohrer, 2019). Approximately 30-40% of FTD patients have a positive family history of dementia (Greaves & Rohrer, 2019; Rosso et al., 2003). However, these data should be taken with caution as the high prevalence of non-FTD dementias in the general population suggests that older individuals with a known family history of FTD included in such estimates may have other causes of dementia (Piguet et al., 2011). The heritability of the condition seems to vary based on the phenotype. For example, in bvFTD, a strong family history is seen in about 50% of cases, while in PPA this percentage drops to 12% (Wood et al., 2013). The heritability of motor phenotypes

is less defined due to the paucity of studies (Greaves & Rohrer, 2019). For instance, in FTD-ALS a strong family history is evident in 10% to more than 40% of cases (Wood et al., 2013; Rohrer et al., 2009; Goldman et al., 2005). Only 10-15% (Rohrer et al., 2009; Ntymenou et al., 2021) of FTD patients have a family history consistent with autosomal dominant transmission, meaning two first-degree relatives affected across two subsequent generations (Rohrer et al., 2009).

Among the causative mutations, the open reading frame 72 mutation on chromosome 9 (*C9orf72*) is the most common cause of genetic FTD, followed by mutations in the progranulin (*GRN*) gene, and thirdly, mutations in the *MAPT* gene (Greaves & Rohrer, 2019; Mahoney et al., 2012; Snowden et al., 2012). These three mutations contribute to 5-10% of all FTD cases (Greaves & Rohrer, 2019; Rohrer et al., 2009). While *MAPT* mutations are mostly fully penetrant, *GRN* (Gass et al., 2006) and *C9orf72* (Murphy et al., 2017) mutations show age-dependent penetrance, with a low number of asymptomatic carriers even into the ninth or tenth decade of life (Greaves & Rohrer, 2019).

Classically, the FTD spectrum includes two main clinical presentations, each with a certain degree of phenotypic heterogeneity. The first is known as the behavioral variant or bvFTD and is primarily characterized by progressive deterioration in social behavior and personality. The second is primary progressive aphasia (PPA) and is marked by a progressive loss of language functions with relative preservation of other cognitive abilities (Grossman, 2010; Neary et al., 1998). PPA itself is further divided into three subtypes based on the characteristics of the language deficit: the nonfluent variant (nfvPPA), the semantic variant (svPPA), and the logopenic variant (lvPPA). The latter clinical syndrome is usually included among the atypical variants of AD since more than 90% of cases show *in vivo* evidence of AD pathology (Hodges & Patterson, 2007; Gorno-Tempini et al., 2011). To complicate the clinical classification of FTD syndromes is the

overlap with the clinical spectrum of the amyotrophic lateral sclerosis (ALS) (Boeve et al., 2022). This clinical, genetic, and pathological overlap between FTD and motor neuron diseases (MND) (Piguet et al., 2011) means that approximately 10% of patients with FTD show clinical and/or neurophysiological evidence of MND (Lillo et al., 2010; Lomen-Hoerth et al., 2002). Conversely, a portion of patients diagnosed with MND exhibit cognitive symptoms primarily involving language, executive functions, and behavior, severe enough to meet the criteria for FTD (Lillo, Mioshi, et al., 2010). More recently, the FTD spectrum has also included two forms of atypical parkinsonism: corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP), which fall under the corticobasal syndrome (CBS) spectrum (Armstrong et al., 2013). In this case, the overlap is not only clinical but also neuropathological, with Tau protein alterations observed in these syndromes being a common element with some forms of bvFTD and PPA (Kertesz et al., 2005). See Table 1 for the different abbreviations.

Table 1. *Currently used abbreviations for clinical syndromes of FTD*

Clinical syndromes	**Abbreviations**
Frontotemporal dementia (umbrella term)	FTD
Behavioral variant of FTD	bvFTD, fvFTD, FTD
Corticobasal degeneration syndrome	CBS, CBDS
Frontotemporal dementia with amyotrophic lateral sclerosis	FTD-ALS
Frontotemporal dementia with motor neuron disease	FTD-MND
Logopenic variant of PPA	LPA, lvPPA
Primary progressive aphasia	PPA
Non fluent variant of PPA	PNFA, nfvPPA
Progressive supranuclear palsy	PSP, PSPS
Semantic variant of PPA	SD, svPPA, tvFTD

2.2 The clinical-neuropsychological and instrumental profile of bvFTD

2.2.1 Clinical manifestation of bvFTD

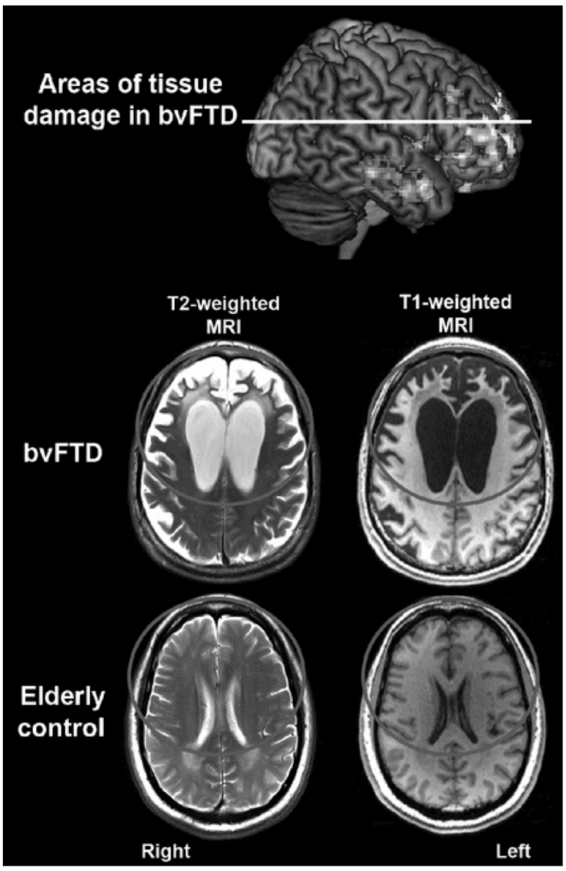
BvFTD is a clinical syndrome characterized by progressive deterioration of cognitive functioning and behavior alterations (Dickerson, 2016). Approximately 50-60% of FTD individuals present bvFTD presentation. The illness has a median age of onset of 58 years, is predominantly male, and often manifests in the mid- to late-fifties (Dickerson, 2016). When considering other dementias, bvFTD progresses more quickly than the others. Death usually occurs three to four years after the initial diagnosis and about eight years after the onset of symptoms. The syndrome is clinically characterized by disinhibition, apathy, loss of empathy, compulsive behavior, dietary changes and executive dysfunctions. Inappropriate social and moral judgments, changed decision-making, lack of empathy or sympathy and trouble interpreting emotions and mental states of others are other core symptoms of bvFTD. A gradual degradation of the frontal and anterior temporal lobes is linked to this pattern of impairment (see Figure 2).

Six main characteristics have been identified in 2011 by a group of 46 experts as core symptoms for the diagnosis of bvFTD (Rascovsky et al., 2011). These criteria provide a more flexible combination of clinical characteristics compared to previous classification by Neary et al. (Neary et al., 1998) and are categorized into three levels of diagnostic certainty for bvFTD: "possible," "probable," or "definite" bvFTD.

Similar to other neurodegenerative diseases, the symptoms appear slowly at first and get worse with time. Initial behavioral symptoms are frequently mistaken for other

conditions, like stress or mood disorders (Dickerson, 2016). Patients with bvFTD exhibit significant phenotypic variability in the manifestation of symptoms. While some individuals exhibit disinhibition and hyperactivity, others mostly struggle with apathy and low motivation. Because they often lack insight, patients with bvFTD rarely seek medical assistance for their symptoms. Typically, the patient's friends or relatives are in charge of arranging the problem addressed to medical treatment. In a small percentage of bvFTD cases, psychotic symptoms may be present in addition to other behavioral changes. Some patients experience hallucinations or delusional ideas. This is more frequent in patients with genetic FTD as *C9orf72* hexanucleotide repeat expansion carriers (Snowden et al., 2012).

Figure 2. *Pattern of grey matter density reduction in a sample of bvFTD vs. controls (upper panel) and example of atrophy pattern in a 63-year-old bvFTD patient compared to a 60-year-old healthy control subject (lower panel).*



Note. *Modified from Hodges' Frontotemporal Dementia, 2nd Edition, by Dickerson, 2016, p. 123*

2.2.2 Neuropsychological profile of bvFTD

According to Rascovsky et al. criteria the only neuropsychological tests accepted in support of the diagnosis of bvFTD are those capable of identifying the dysexecutive syndrome. However, research in this field has continually questioned the central role of executive functions in the diagnosis of bvFTD (Dodich et al., 2017), particularly in the early stages of the disease (Dodich et al., 2020). Evidence of executive deficits in patients with atypical presentations of AD (Dubois et al., 2014; Ossenkoppele et al., 2015) and relative preservation of executive functions in some early bvFTD patients (Dodich et al., 2017; Torralva et al., 2009) have supported a questioning of the crucial importance attributed to this cognitive domain in early bvFTD identification. Despite the fact that frontal lobe functions are frequently compromised, up to 25% of individuals with behavioral presentations perform well on typical "frontal" tests, particularly if they are diagnosed early (Dodich et al., 2017; Torralva et al., 2009). More recent research showed that tasks assessing social cognition domain could represent a valuable instrument for early and differential diagnosis of bvFTD (Panchal et al., 2015; Fong et al., 2016; Possin et al., 2013; Van Den Berg et al., 2021). This experimental work has opened the door to the use of socio-cognitive neuropsychological tasks in clinics to explore subdomains such as empathy, emotion recognition, and theory of mind.

Spared long-term memory functioning is considered a core neuropsychological criterion for the diagnosis of bvFTD (Rascovsky et al., 2011). Nonetheless, more recent literature proved that bvFTD patients may exhibit episodic memory deficits similar to those seen in patients with typical AD (Hornberger & Piguet, 2012; Irish et al., 2012; Irish et al.,

2013; Schubert et al., 2016; Ramanan et al., 2016; Fernández-Matarrubia et al., 2017). Deficits in attention, motivation, and/or language skills may affect performances at memory tasks and cause memory complaints in bvFTD patients (Dickerson, 2016). Moreover, even in cases that have been pathologically verified, memory preservation is by no means universal in FTD, despite the fact that it is not a memory dominating condition (Graham et al., 2005). A recent neuropathological study demonstrated that a third of patients with pure/mixed AD pathology are non-amnesic at presentation and ≈45% of patients without AD pathology are amnesic (Bertoux et al., 2020).

Visuospatial function is typically unaffected in bvFTD patients, despite the fact that drawings in these patients may be less accurate due to a motivational performance (Dickerson, 2016). During neuropsychological testing, impulsivity, disinhibition, perseverance, echopraxia, and utilization behavior are occasionally seen. Later on, the patient can become too agitated or have linguistic impairments to be tested.

One of the most helpful diagnostic instruments is the caregiver interview on patients' behavioral profile using questionnaires like the Frontal Behavioral Inventory (FBI) (Kertesz et al., 2003) including both negative and positive behavioral changes typical of FTD. Negative behaviors such apathy, aspontaneity, indifference, rigidity, concreteness, personal neglect, distractibility, inattention, loss of insight were included in the initial batch of items. In order to improve possible identification of speech and motor alteration related to FTD, logopenia, verbal apraxia and alien limb phenomenon were also added among the questionnaire items. Positive behaviors included perseveration, irritability, jocularity, irresponsibility, inappropriateness, impulsivity, restlessness, aggression, and hyperorality. Impulsivity, socially unacceptable behavior, and indifference were determined to be the most diagnostic using discriminant analysis (Dickerson, 2016).

Another recently constructed diagnostic instrument is a short FBI version (i.e., mini-FBI) (Cerami et al., 2022). It is made with the aim to provide clinicians with a brief tool for the identification of early behavioral changes in bvFTD, also facilitating the differential diagnosis with AD. The mini-FBI proved to be a valuable easily administrable questionnaire able to early identify symptoms effectively contributing to the bvFTD behavioral syndrome, differentiate between distinct behavioral phenotypes of bvFTD and making it easier to differentiate bvFTD from other neurodegenerative syndromes such as AD (Cerami et al., 2022).

2.2.3 Instrumental profile of bvFTD

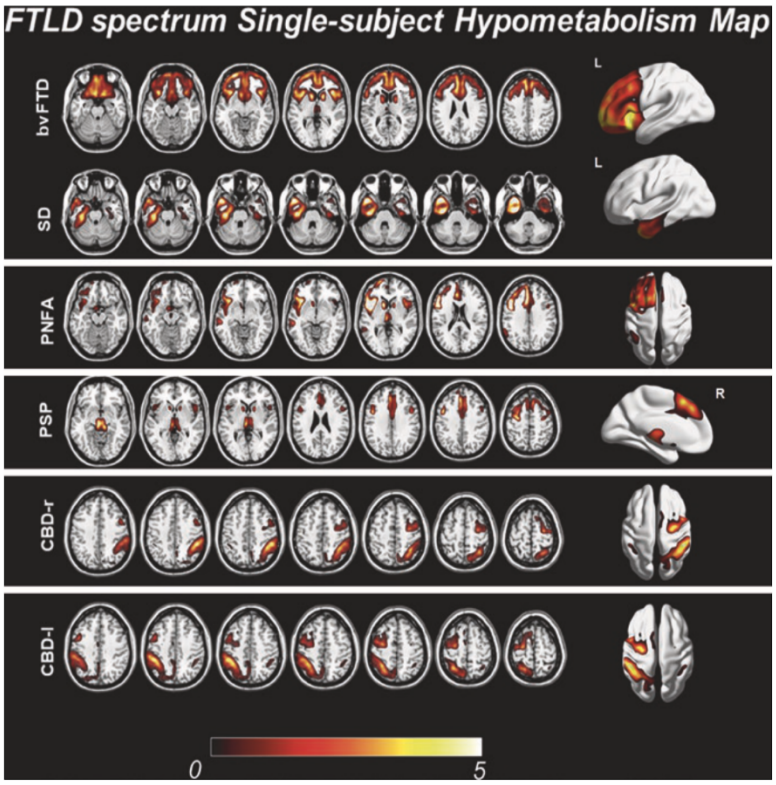
As demonstrated by various imaging studies, including those by Seeley et al. (Seeley, 2008; Seeley et al., 2011), bvFTD begins with extremely focal neural involvement. The initial neural deterioration starts in the pregenual anterior cingulate cortex (pACC) and the fronto-insular (FI) region, while the dorsolateral prefrontal cortex, primarily implicated in executive functions, remains relatively spared initially (Funahashi & Andreau, 2013). The pACC and FI are key regions of the salience network (Seeley et al., 2011), a functional circuit activated in response to environmental stimuli and emotionally significant events such as pain, thirst, hunger, social rejection, embarrassment, cooperation, and adoration (Craig, 2002; Critchley, 2005). More specifically, according to Seeley et al. (Seeley, 2008; Seeley et al., 2011), the selective vulnerability in bvFTD may be attributed to a population of neurons almost exclusively located in the pACC and FI: the Von Economo neurons (VENs), named after the researcher who characterized this

subtype (Von Economo, 2009). VENs have been identified as the primary target of the degenerative process occurring in bvFTD (Seeley, 2008).

A meta-analysis by Schroeter et al. (2014) provided crucial insights on structural and functional metabolic correlates of socio-cognitive dysfunctions in FTD. Based on studies utilizing MRI and FDG-PET, the authors observed a regional dissociation between atrophy and hypometabolism in bvFTD patients arguing a need for revision of the supportive imaging features suggested in the current diagnostic criteria (Rascovsky et al., 2011). Besides confirming the centrality of the ACC and anterior insula in empathy, Schroeter and colleagues also highlighted the involvement of subcortical regions in bvFTD patients. These regions include the basal ganglia, particularly the caudate nucleus, nucleus accumbens (the "ventral striatum"), putamen, and globus pallidus (lentiform nucleus), all part of the emotional network and the reward circuit. Another interesting finding of this meta-analysis is that, despite expecting a strong correlation between alterations in the medial anterior frontal cortex (Brodmann areas 9/32) and ToM impairments, the authors suggest ToM impairments as epiphenomenon of executive deficits, particularly of the inhibitory control system. According to Schroeter and colleagues, executive functions primarily depend on the activity of ACC and the left lateral prefrontal cortex, specifically the inferior frontal junction (IFJ).

FDG-PET imaging results in bvFTD notably contributed in the definition of patterns of neurodegeneration in this neurocognitive syndromes showing severe hypometabolism of the limbic system, frontal lobe, insular and temporal areas which is also due to the dysfunction of connected subcortical structures (see Figure 3) (Diehl et al., 2004; Jeong et al., 2005; Salmon et al., 2003; Schroeter et al., 2008; Cerami et al., 2016; Franceschi et al., 2005).

Figure 3. *FDG-PET patterns in bvFTD compared to other neurocognitive syndromes.*



Note. *Modified from PET and SPECT in neurology, 2nd Edition, by Dierckx et al., 2020, p. 223*

Representative SPM-t-map at the single-subject level in the FTLD spectrum. Figure shows prototypical examples of hypometabolism patterns in different variants of FTLD, from top to the bottom: behavioural variant of FTD-like hypometabolism pattern; semantic dementia-like hypo- metabolism pattern; PNFA-like hypometabolism pattern; PSP-like hypometabolism pattern; CBD left-like hypometabolism pattern; CBD right-like hypometabolism pattern. FTLD frontotemporal lobar degeneration, bvFTD behavioural variant of frontotemporal dementia, SD semantic dementia, PNFA primary non-fluent aphasia, PSP progressive supranuclear palsy, CBD-l corticobasal degeneration left, CBD-r corticobasal degeneration right.

Based on the FDG-PET hypometabolic patterns, two bvFTD variants, i.e. frontal and temporo-limbic variants, have been described (Cerami et al., 2016). Frontal bvFTD variant is characterized by widespread hypometabolism in the dorsolateral and ventromedial frontal cortex, whereas the temporo-limbic variant exhibits temporal lobes, including the poles, hippocampal structures, and amygdala hypometabolism with selective sparing of the dorsolateral prefrontal cortex (Cerami et al. 2016).

2.3 The bvFTD as model of Social Brain Dysfunction

The term "social brain dysfunction" describes deficiencies or anomalies in the neural networks and mechanisms underlying social cognition and behavior (see Chapter I). It includes a wide spectrum of conditions in which people struggle to interpret, comprehend, or react normally or expectedly to social cues and interactions. Aspects of social cognition that are affected by disruptions include theory of mind, emotional recognition and processing, empathy, social perception, social judgment, and social behavior.

Behavioral variant frontotemporal dementia (bvFTD) is an excellent *in vivo* model for studying social brain dysfunctions in neurocognitive disorders. Changes in social behavior and emotion recognition, noticeable from the early stages of the disease, correlate with progressive neurodegeneration in the frontotemporal and limbic regions responsible for these functions (Dodich et al., 2017; Eslinger et al., 2011; Ibañez & Manes, 2012; Schroeter et al., 2014). The direct relationship between damage of specific brain areas and social cognition deficits in bvFTD is evident from the most common initial manifestations of the condition, such as subtle changes in personality, interpersonal relationships, and emotional regulation (Piguet et al., 2011; Neary et al., 1998; Rascovsky et al., 2011). These changes occur even in the absence of significant impairment in traditional cognitive abilities such as memory, visuospatial functions (Rascovsky et al., 2011), and attentional/executive functions (Cerami & Cappa, 2013; Taragano et al., 2009). Clinically, the hallmark symptoms of bvFTD, as previously described, include loss of empathy/compassion, apathy, and inertia (lack of motivation to engage in previously gratifying activities or hobbies), behavioral disinhibition/socially inappropriate behaviors, and social withdrawal (Cerami & Cappa, 2013; Zamboni et al., 2008). Patients

with bvFTD progressively lose the ability to correctly identify social and emotional stimuli from their environment, such as potential rewards or punishments, leading them to act without considering the negative consequences of their actions. These actions are driven by excessive impulsivity, which can lead to harassing strangers, making offensive jokes, and sexual comments, sometimes resulting in criminal or morally inappropriate acts. Alongside these behavioral disturbances, individuals with bvFTD may exhibit hyperorality, hyperphagia, and dietary changes (Piguet et al., 2010). Overall, these factors result in a significant change in personality (Mahoney et al., 2012), dramatically impacting the patient's social, work, and family spheres.

Based on the neuroimaging evidence produced over the past twenty years and the known neural correlates of social cognition processes, particularly in emotional processing and recognition, researchers' interest in studying social cognition deficits in bvFTD has exponentially increased in recent years. As a natural consequence, there has been a progressive push towards the development and validation of tasks, questionnaires, and neuropsychological scales to explore various subdomains of social cognition (Dodich et al., 2017; Bertoux et al., 2012; Couto et al., 2013; Kumfor et al., 2017; Kumfor et al., 2013) and, consequently, the early identification of social brain dysfunction (Eslinger et al., 2011; Ibañez & Manes, 2012). Cognitive tests that explore the aforementioned social cognition subcomponents are considered helpful in the early diagnosis of bvFTD, as they often allow for the differential diagnosis with other neurodegenerative conditions. Therefore, the development of social cognition measures for the clinical diagnosis of bvFTD has become increasingly prioritized, despite the current diagnostic guidelines for bvFTD not requiring the formal neuropsychological assessment of any social cognition domains (Dodich et al., 2020).

BvFTD patients often present impairments at theory of mind (ToM) or emotional recognition and processings (Dickerson, 2016). In bvFTD, these abilities are often significantly impaired, leading to misinterpretations of social interactions and inappropriate responses, as well as difficulties in recognizing and appropriately responding to emotional cues. Socio-cognitive deficits can be explored with neuropsychological tests, such as the Reading the Mind in the Eyes Test (RMET) (Baron-Cohen, 2001), the Story-based Empathy Task (SET) (Perry, Mankuta, & Shamay-Tsoory, 2015), the First and Second-Order False Belief Tasks (Wimmer & Perner, 1983), the Faux Pas Test (Baron-Cohen, Leslie, & Frith, 1999) and the Ekman 60 Faces Test (Ekman & Friesen, 1976), or with scales or questionnaires as the Interpersonal Reactivity Index (IRI) (Davis, 1980), the revised Self-Monitoring Scale (r-SMS) (Snyder, 1974) and the SNQ (Kramer et al., 2013). This latter has been proved particularly useful in differential diagnosis of bvFTD from early onset AD (Panchal et al., 2015). By utilizing these neuropsychological assessments, clinicians can comprehensively evaluate the social cognition impairments in bvFTD patients (Dickerson, 2016; Panzavolta et al., 2024; Dodich et al., 2017; Dodich et al., 2020; Diehlschmid et al., 2007). This thorough evaluation aids in the accurate diagnosis and effective management of the condition.

2.4 The differential diagnosis with Alzheimer's disease

Due to its intrinsic heterogeneity, diagnosing FTD is a challenge even for specialists. This complexity is compounded by the overlap of signs and symptoms with other pathological conditions that must be considered in differential diagnosis. This intricate process is particularly challenging in the very early stage of the disease, known as the

prodromal phase. In the context of a progressive neurodegenerative disease, this phase corresponds to the interval between the onset of the first symptoms and the full development of the syndrome or disease, as defined by clinical diagnostic criteria (Boeve et al., 2022). A correct differential diagnosis yet at the prodromal phase is crucial to enable pharmacological and non-pharmacological interventions able to modify the disease course. This is particularly important for cases with known familial history (Greaves & Rohrer, 2019).

The most challenging differential diagnosis is with behavioral/executive atypical AD presentations (Dickerson, 2016). Although AD typically affects old individuals, several studies showed that AD is the most common cause of early-onset dementia, overlapping with the mean age of onset of bvFTD (Mercy et al., 2008; Garre-Olmo et al., 2010). A validation study on diagnostic criteria of bvFTD found that AD is the primary neuropathological etiology of patients *in vivo* classified as bvFTD (Harris et al., 2013). Neuropsychological testing revealed normal AD deficits in memory and visuospatial impairments in several of these cases, but the patients' behavioral changes and executive dysfunction met the criteria for bvFTD. The study did, however, also identify instances in which individuals had post-mortem AD pathology despite presenting with a restricted frontal lobe syndrome and even frontal atrophy on structural imaging. It is also known that bvFTD-like profile can manifest in early-onset AD due to *PSEN1* mutations (Mendez & McMurtray, 2006). With 10-15% of cases in autopsy series fitting criteria for bvFTD but turning out to have Alzheimer's pathology, focal forms of AD typically enter the differential for all the FTD/Pick complex clinical syndromes (Dickerson, 2016).

Since the diagnosis of bvFTD is based on a set of consensus diagnostic criteria developed by a panel of experts in the field (Rascovsky et al., 2011), the likelihood of a correct diagnosis increases with the number of converging indicators which

simultaneously reduce the possibility of alternative conditions. Therefore, in a differential diagnosis setting, one cannot rely solely on clinical assessment, although it is indispensable. The final evaluation must be corroborated by a comprehensive approach (Bang et al., 2015) that includes:

1. Thorough family, personal, and psychological histories to assess any changes in personality and behavior;
2. In-depth neuropsychological assessment;
3. Comprehensive laboratory and instrumental examinations to identify any ongoing proteinopathy (e.g., blood and cerebrospinal fluid tests for toxic proteins, imaging studies);
4. Genetic investigations.

This multifaceted diagnostic approach ensures a higher probability of an accurate and early diagnosis of FTD, which is essential for effective patient management (Bang et al., 2015).

Chapter 3
Materials and Methods

3.1 Aim of the study

Taking into account of above mentioned about the challenging differential diagnosis of bvFTD from AD and the usefulness of socio-cognitive measures assessing social norm knowledge in clinics (see Chapter 1 and 2), in this study we aimed at assessing diagnostic performance of the Italian version of the SNQ-22 questionnaire, i.e., SNQ-IT, for the early and differential diagnosis of bvFTD compared to AD patients and healthy controls (HC) individuals. The hypothesis is to prove the clinical validity of the use of SNQ-IT and of the social norm error pattern analysis in the diagnostic framework of bvFTD with a specific breaking-error profile in bvFTD with increased violation of social norms.

3.2 Sample selection

A total of 73 participants were enrolled in this study, divided into three sub-groups: 33 patients with probable bvFTD, 20 patients with prodromal or mild AD, and 20 healthy controls (HC) matched by age, education, and gender. Patients were enrolled at the Center for Dementia and Cognitive Disorders (CDCD) at the Mondino Foundation in Pavia, Italy. Only patients in the early stages of the disease with a Clinical Dementia Rating (CDR) global score of ≤ 1) and with a confirmed clinical diagnosis based on current diagnostic criteria (Rascovsky et al., 2011; Albert et al., 2013; McKhann et al., 2011) were included. Expert clinicians, unaware of the patients' performance on social

questionnaires, carried out the clinical diagnoses. The diagnoses were supported by standard neurological examinations, comprehensive neuropsychological testing, and neuroimaging assessments (MRI and/or FDG-PET).

The HC group consisted of individuals recruited from local community centers. We included only those with no history of neuropsychiatric disorders, normal neurological examinations, no medications affecting neurobehavioral functions, a CDR global score of 0, and a Mini-Mental State Examination (MMSE) score greater than or equal to 27. All patients, caregivers, and HCs provided informed consent for the experimental procedures, which were approved by the local ethics committee. For more details on the demographic and clinical characteristics of the sample, refer to Table 2.

Table 2. *Demographic and clinical features of the sample*

	bvFTD	**AD**	**HC**	**Statistics**	**Post-hoc**
Number of subjects (male/female ratio)	25/8	9/11	11/9	$X^2(2) = 5.5$, p=0.06	-
Age in years (mean±st.dev.)	65.8±8.3	68.7±8.9	62.9±6.2	F(2,70)=2.5, p=0.08	-
Education in years (mean±st.dev.)	10.5±3.6	10.8±4.2	13.1±4.4	F(2,70)=2.73, p=0.07	-
Disease duration in months) (median[interquartile range])	36 [12-156]	37.5 [6-96]	-	U(315), p=0.7	-
CDR sum of boxes (median[interquartile range])	1 [0.5-1]	1 [0.5-1]	-	U(227), p=0.7	-
MMSE score (mean±st.dev.)	24.5±2.6	21.6±3.3	29.4±0.8	F(2,70)=47.9, p<0.001	*bvFTD<HC****AD<HC*** AD<bvFTD***

*bvFTD: behavioural variant of frontotemporal dementia; AD: Alzheimer's disease; HC: healthy controls; CDR: Clinical Dementia Rating Scale;MMSE: Mini Mental State Examination; * p<0.05; ** p<0.01; *** p <0.001*

3.3 SNQ-IT Questionnaire

Patients were administered with a SNQ-IT questionnaire. It is an easy-to-administered questionnaire adapted for the Italian population from the original version (Kramer et al., 2013) and consisting of 22 binary yes/no questions. Questions were checked in cultural content by two independent raters and translated in Italian language. Since the questionnaire has been developed to assess social norm knowledge in the US, it was easily adapted for the Italian context with minimal changes. Content validity was preliminary assessed in a sample of healthy controls. Minimal discrepancies in translation were settled by consensus. It lasts about 5 minutes. The SNQ-IT provides three different scores. The global score (SNQ-gs) is the sum of the correct answers, with higher scores indicating better knowledge of social norms. Sample questions include, "Would it be socially acceptable and appropriate to... spit on the floor?" (No), "Tell a coworker your age?" (Yes), and "Talk out loud during a movie at the theater?" (No). See Table 3 for details on the original SNQ and the SNQ-IT questionnaire. The questionnaire provides two additional scores: the “Break” and the “Overadherence” error scores, i.e. SNQ-bes and SNQ-oes, according to the presence of errors made in breaking the social norm or in rigidly interpreting the social norm. While SNQ-bes score ranges from 0 to 12, SNQ-oes score ranges from 0 to 10.

Table 3. *Social Norm Questionnaires, US version (on the left) and Italian version (on the right)*

<u>The instructions for the subject:</u> Following is a list of behaviors that a person might engage in. Please decide whether or not it would be socially acceptable and appropriate to do these things in the mainstream culture of the United States (on the left) or Italy (on the right) and answer yes or no to each. Think about these questions as if they were occurring in front of or with a stranger or acquaintance, NOT a close friend or family member.

1	Tell a stranger you don't like their hairstyle?	NO YES	Dire a un estraneo che NON ti piace il suo taglio di capelli?	SI NO
2	Spit on the floor?	NO YES	Sputare per terra?	SI NO
3	Blow your nose in public?	NO YES	Soffiarsi il naso in pubblico?	SI NO
4	Ask a coworker their age?	NO YES	Chiedere a un tuo superiore la sua età?	SI NO
5	Cry during a movie at the theater?	NO YES	Piangere al cinema durante il film?	SI NO
6	Cut in line if you are in a hurry?	NO YES	Interrompere una conversazione se vai di fretta?	SI NO
7	Laugh when you yourself trip and fall?	NO YES	Ridere se tu inciampi e cadi?	SI NO
8	Eat pasta with your fingers?	NO YES	Mangiare la pasta con le mani?	SI NO
9	Tell a coworker your age?	NO YES	Dire a un tuo superiore la tua età?	SI NO
10	Tell someone your opinion of a movie they haven't seen?	NO YES	Dire a qualcuno la tua opinione su un film che quella persona non ha ancora visto?	SI NO
11	Laugh when someone else trips and falls?	NO YES	Ridere se vedi qualcun altro che inciampa e cade?	SI NO
12	Wear the same shirt every day?	NO YES	Indossare la stessa camicia ogni giorno?	SI NO
13	Keep money you find on the sidewalk?	NO YES	Raccogliere dei soldi trovati per strada?	SI NO
14	Pick your nose in public?	NO YES	Mettersi le dita nel naso in pubblico?	SI NO
15	Tell a coworker you think they are overweight?	NO YES	Dire a un collega che è ingrassato?	SI NO
16	Eat ribs with your fingers?	NO YES	Mangiare il pane con le mani?	SI NO
17	Tell a stranger you like their hairstyle?	NO YES	Dire a un estraneo che ti piace il suo taglio di capelli?	SI NO
18	Wear the same shirt twice in two weeks?	NO YES	Indossare la stessa camicia a distanza di due settimane?	SI NO
19	Tell someone the ending of a movie they haven't seen?	NO YES	Dire a qualcuno la fine di un film che lui non ha visto?	SI NO
20	Hug a stranger without asking first?	NO YES	Abbracciare uno sconosciuto senza averglielo chiesto prima?	SI NO
21	Talk out loud during a movie at the theater?	NO YES	Parlare ad alta voce al cinema durante il film?	SI NO
22	Tell a coworker you think they have lost weight?	NO YES	Dire a un collega che è dimagrito?	SI NO

3.4 Statistical Analysis

SPSS software was used to conduct statistical analysis. For every statistical test, $p<0.05$ was used to determine statistical significance. The following descriptive statistics were computed: mean and standard deviation for pseudo-continuous variables, median and interquartile range for normally distributed data, and frequency and percentage for categorical variables. ANOVA testing with Bonferroni adjustment for post-hoc comparisons and the chi square test were used to compare the groups' demographics, clinical traits, and SNQ-IT performances. The Mann-Whitney U test, a non-parametric test, was performed to assess clinical features between the two patient groups because of the non-normal distribution. The ANOVA's effect size was eta-squared, a scale from 0 to 1. Commonly encountered interpretation values published in the literature are: 0.01-0.06 (small effect), 0.06-0.14 (moderate effect), and >=0.14 (large effect) (Richardson, 2011).

To compare the main clinical features of the overall sample, we performed a one-way ANOVA and non-parametric test (Kruskal-Wallis) for the error score.

For testing the ability of the SNQ-IT scores in differentiating bvFTD from HC and AD, we used the Receiving operating curve (ROC) analyses. For those measures showing a significant discriminative effect, the cut points were derived from the Youden index (Sensitivity + Specificity - 1). Finally, a logistic regression (i.e., stepwise forward) analysis was performed in order to correctly classify bvFTD patients from HC and AD groups, entering in the model only those variables found to be significant with the statistic tests as predictor variables.

Chapter 4
Results

4.1 Clinical and demographic profile of the sample

No significant differences were observed in demographic variables (age, sex, and education) among the groups. Similarly, there were no significant differences in disease duration and CDR sum of boxes between the patient groups. As expected, both patient groups had lower MMSE scores compared to the HC group, with AD patients showing significantly lower scores than those with bvFTD. For more details on demographic and clinical features across the groups, see Table 2.

4.2 Social norm knowledge profile of the sample

Comparisons of the SNQ-IT performances across groups revealed significant differences in both SNQ-gs and error pattern profiles with worse performances in bvFTD compared to other groups. SNQ-gs score was significantly lower in bvFTD vs both HC ($p=0.001$) and AD ($p=0.001$). The SNQ-bes scores showed significant differences among the groups as well ($p<0.001$). Post-hoc analysis revealed significantly higher SNQ-bes scores in bvFTD compared to HC ($p<0.001$) and in comparison to AD as well, but this time even though significant, the difference was less pronounced ($p<0.05$). Finally, also the SNQ-oes scores showed differences among the three groups ($p=0.03$), but it was less pronounced compared to SNQ-gs and SNQ-bes. The bvFTD group showed significantly higher SNQ-oes than HC ($p<0.05$), but this did not significantly differ in bvFTD

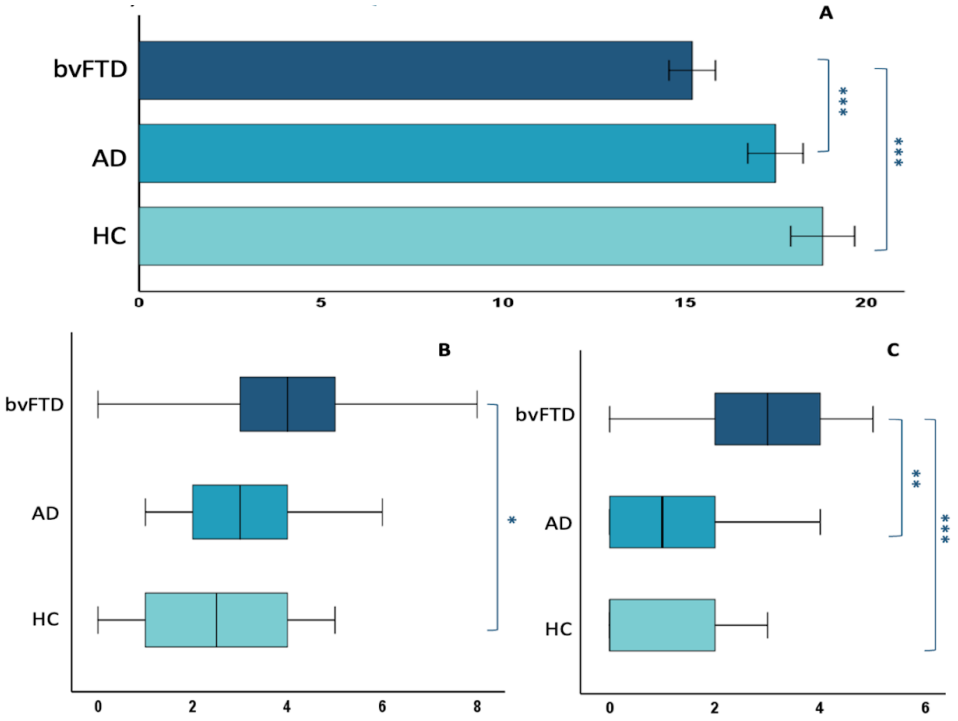
compared to AD. See Table 4 and Figure 4 for details on SNQ-IT comparisons across groups.

Table 4. *Comparisons of SNQ-IT performances in bvFTD, AD and HC groups*

	bvFTD	**AD**	**HC**	**Statistics**	**Post-hoc**
SNQ-gs (mean±st.dev.)	15.2±1.8	17.5±1.7	18.8±1.9	$F(2,70)=25.6$, $p<0.001$, $\eta^2=0.4$	*bvFTD<HC****, bvFTD<AD****
SNQ-bes (median[inter quartile range])	3[2-4]	1[0-2]	0[0-2]	$X^2(2)=17.2$, $p<0.001$	*bvFTD>HC****, bvFTD>AD*
SNQ-oes (median[inter quartile range])	4[3-5]	3[2-4]	2.5[1-4]	$X^2(2)=6.6$, $p=0.03$	*bvFTD>HC**

*bvFTD: behavioural variant of frontotemporal dementia; AD: Alzheimer's disease; HC: healthy controls; SNQ-gs: social norms questionnaire global score; SNQ-bes: social norms questionnaire break error score; SNQ-oes: social norms questionnaire overadhere error score; * p<0.05; ** p<0.01; *** p <0.001*

Figure 4. *Comparisons across groups at SNQ-gs (A), SNQ-oes (B) and SNQ-bes (C); * p<0.05; ** p<0.01; *** p <0.001*



4.3 Diagnostic accuracy of the SNQ-IT questionnaire and the added value of the error pattern analysis

The ROC analysis showed an excellent performance of SNQ-gs in discriminating bvFTD from HC (Area Under the Curve (AUC) = 0.90, p < 001, Standard Error (SE) = 0.04, Confidence Interval (CI) 95% = 0.82-99, cut-off = 17, Sensitivity = 0.93, Specificity 0.75, Accuracy = 0.86%). Considering subscale scores, SNQ-bes showed comparable excellent performance (AUC = 0.80, p < 0.001, SE = 0.04, CI 95% = 0.68-0.92, cut-off = 2, Sensitivity = 0.78, Specificity = 0.70, Accuracy = 87%), while SNQ-oes showed only a moderate performance (AUC = 0.70, p = 0.01, SE = 0.07, CI 95% = 0.55-0.84, cut off = 3, Sensitivity = 0.75, Specificity = 0.50, Accuracy = 65%).

ROC analysis showed good discriminating performance of SNQ-gs and SNQ-bes on differentiating bvFTD from AD (SNQ-gs: AUC = 0.82, $p < 0.001$, SE = 0.06, CI 95% = 0.71-94, cut off = 16, Sensitivity = 0.75, Specificity = 0.80, Accuracy = 76%; and SNQ-bes: AUC = 0.82, $p = 0.005$, SE = 0.07, CI 95% = 0.59-0.87, cut off = 2, Sensitivity = 0.78, Specificity 0.70, Accuracy = 74. See Table 5 and Figure 6 for details on ROC analysis.

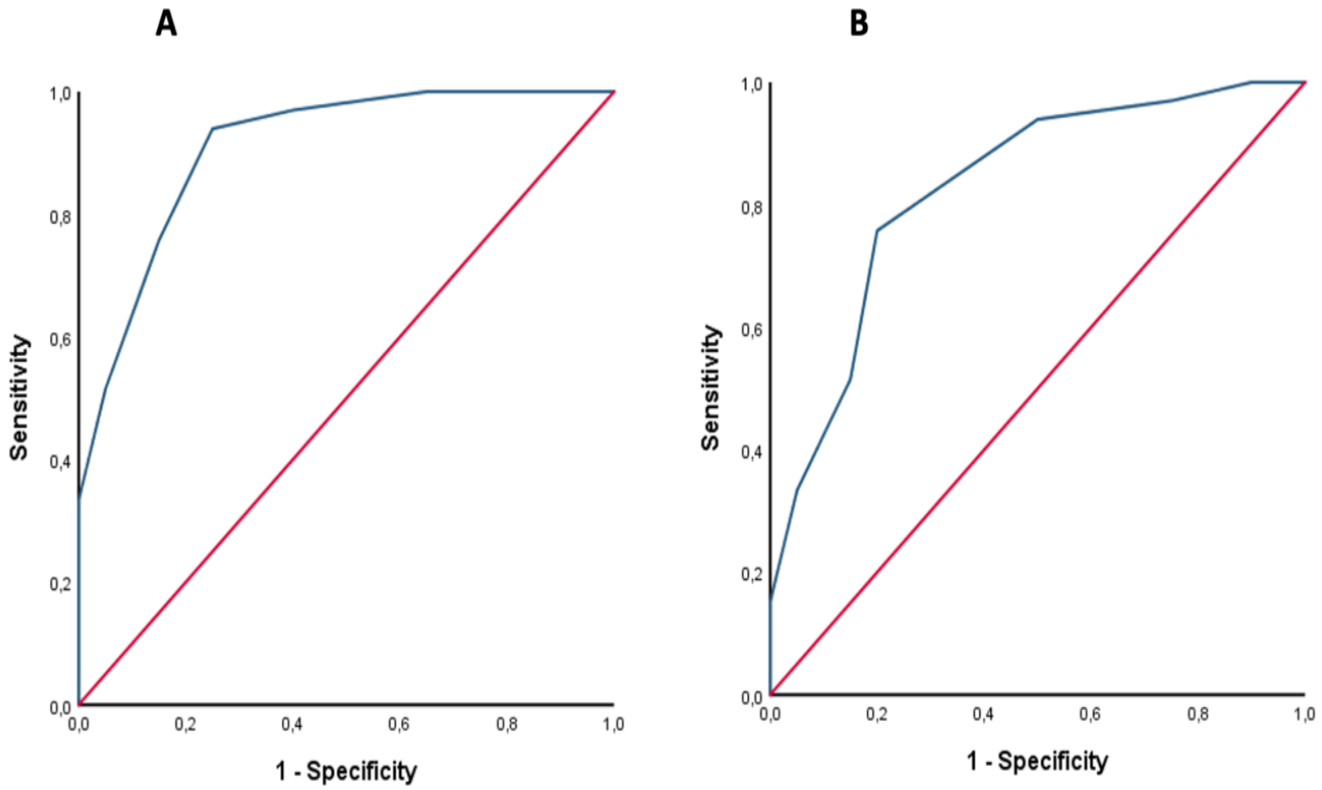
Logistic regression analysis identified SNQ-gs and SNQ-bes as the best combination in accurately distinguishing bvFTD from HC, managing to classify 93% of bvFTD patients. On the other hand, logistic regression analysis revealed that SNQ-bes score represents the main significant variable in distinguishing the group of patients with bvFTD from those with AD, classifying 90% of patients with bvFTD. According to this result, the SNQ-bes subscale provides the most informative score.

Table 5. *Coordinates for ROC curve in discriminating bvFTD from HC and AD*

	AUC	Standard error	Significance	CI 95%	Cut-off score	Sensitivity	Specificity	Accuracy
bvFTD vs HC								
SNQ-gs	0.90	0.04	**p<0.001**	0.82-99	17	0.93	0.75	86%
SNQ-bes	0.80	0.06	**p<0.001**	0.68-0.92	2	0.78	0.70	87%
SNQ-oes	0.70	0.07	**p=0.01**	0.55-0.84	3	0.75	0.50	65%
bvFTD vs AD								
SNQ-gs	0.82	0.06	**p<0.001**	0.71-94	16	0.75	0.80	76%
SNQ-bes	0.73	0.07	**p=0.005**	0.59-0.87	**2**	0.78	0.70	74%
SNQ-oes	-	-	**-**	-	**-**	-	-	-

*bvFTD: behavioural variant of frontotemporal dementia; AD: Alzheimer's disease; HC: healthy controls; SNQ-gs: social norms questionnaire global score; SNQ-bes: social norms questionnaire break error score; SNQ-oes: social norms questionnaire overadhere error score; * p<0.05; ** p<0.01; *** p <0.001*

Figure 5. *Receiving Operating Characteristic curve for the Social Norms Questionnaire (SNQ-IT) global score in the behavioral variant of frontotemporal dementia vs healthy controls (A) and Alzheimer's disease (B)*



Chapter 5
Discussion

Although the significant efforts made in the last decades for establishing more accurate criteria for bvFTD diagnosis, the early identification and differential diagnosis of this clinical syndrome in clinical settings is still a challenge. The lack of specific biological markers for FTD represents a main issue for clinicians and the limited accuracy of current neuropsychological batteries further complicates the diagnostic process (Rascovsky & Grossman, 2013). The presence of normal performance on standard neuropsychological tasks can lead indeed to a certain degree of uncertainty, especially in early and mild cases, resulting in a significant delay of accurately classifying subjects with subtle behavioral symptoms (Mendez et al., 2007). Conversely, more advanced cases may exhibit severe cognitive profiles making it difficult to differentiate bvFTD from AD and other FTD subtypes (Bertoux et al., 2016; Hutchinson & Mathias, 2007). Social cognition investigation may help in overcoming such limitation in clinics. Given that the social behavioral changes are frequently observed in bvFTD, researchers' interest in studying social cognition deficits in bvFTD has grown significantly over the last years. It was discovered that the direct relationship between damage to specific brain areas and social cognition deficits in bvFTD is evident from the early disease phases, causing subtle changes in personality, interpersonal relationships, and emotional regulation (Piguet et al., 2011; Neary et al., 1998; Rascovsky et al., 2011). This increased the interest lead to the development and validation of tasks, questionnaires, and neuropsychological scales to explore various subdomains of social cognition (Dodich et al., 2017; Bertoux et al.,

2012; Couto et al., 2013; Kumfor et al., 2017; Kumfor et al., 2013) and, consequently, to describe patterns of social brain dysfunctions in bvFTD patients (Eslinger et al., 2011; Ibañez & Manes, 2012).

Cognitive tests that evaluate social brain processes are useful in differentiating bvFTD from other neurodegenerative illnesses, which aids in the early diagnosis of the disease. For instance, language difficulties may point to Primary Progressive Aphasia (PPA), whereas long-term memory deficiencies may point to Alzheimer's Disease (AD) (Dubois et al., 2014; McKhann et al., 2011). On standard tests, however, patients with bvFTD frequently do not exhibit a distinct cognitive profile and may have episodic memory deficits resembling those of AD (Catricalà et al., 2012; Irish et al., 2012; Irish et al., 2013; Schubert et al., 2016; Ramanan et al., 2016; Fernández-Matarrubia et al., 2017). Therefore, even if the present recommendations do not mandate the assessment of these domains, the development of social cognition tests for the diagnosis of bvFTD has become increasingly important (Dodich et al., 2020). In this study, we explored the socio-cognitive deficits that are associated with bvFTD, with a particular interest in social norms adherence with a goal to evaluate the diagnostic utility of the Italian version of the Social Norm Questionnaire (SNQ-IT) and the clinical validity of the error pattern analysis with a focus on early and differential diagnosis. Our results showed excellent performances of the questionnaire in early diagnosis and good performance in differential diagnosis. More specifically, bvFTD patients scored significantly lower on the SNQ-gs indicating a more pronounced difficulty in comprehending social norms. Regarding the between group analysis, the SNQ clearly differentiated between control participants and patients, but also between patients with bvFTD and AD. This result is consistent to what is reported by previous studies (Panchal et al., 2015; Fong et al., 2016; Possin et al., 2013; Van Den Berg et al., 2021).

The most relevant finding is related to the error profile of bvFTD patients compared to both HC subjects and AD patients.

The SNQ-bes resulted particularly informative by showing that bvFTD patients were significantly more likely to make errors regarding the violations of social norms, compared to both AD patients and HC subjects. On the other hand, SNQoes did not show significant difference between bvFTD and AD patients. This result, while being in line with Van Den Berg et al. (2021), is different from what Panchal et al. (2015) reported. Their results for instance showed that the number of overadhere errors differs significantly between bvFTD and AD patients. At the opposite, in our analysis, SNQ-bes was more accurate in discriminating bvFTD from AD with respect to SNQ-oes, being a good predictor of correct patient classification, able to correctly identify 90% of bvFTD cases. This discrepancy could be associated with different sampling across our studies and Panchal et al. study, reporting severe damage on lateral anterior temporal lobe (aTL) (Panchal et al., 2015).

In line with other social cognition measures used in clinics (Panzavolta et al., 2024; Dodich et al., 2021; Diehlschmid et al., 2007; Dodich et al., 2017), SNQ-IT measure provides a good-to-excellent performance for early diagnosis, with high sensitivity and specificity according to the cut-off score derived from the Youden index analysis. The logistic regression analysis confirmed the diagnostic utility not only of the SNQ global score but also of the break score, with the combination of the two scores being able to correctly categorize the 93% of bvFTD patients and differentiate them from HC.

Excellent discriminative performance of the SNQ-IT, particularly of the SNQ-bes, indicates that this measure might add crucial information in the diagnostic pathway of bvFTD, especially in the early stages when symptoms may be mild and mimic those of

other neurodegenerative diseases, such as AD. This result supports the use of SNQ-IT alone or in combination with other social cognition measures to improve diagnosis

Main strengths of the present study are the use of culturally adapted socio-cognitive material and a robust statistical approach including ROC analysis and logistic regression analysis. Some limitations should however be considered, such as the relatively small sample size, which may limit the generalizability of data and take into account discrepancies with previous literature findings (Panchal et al., 2015). Future studies on larger sample are thus needed for further confirmation of the present data and better assessment of the clinical value of the SNQ-IT scores.

Chapter 6
Conclusion

In conclusion, the present study underlines the diagnostic value of the Italian version of the Social Norm Questionnaire (SNQ-IT) and its subscales for distinguishing bvFTD from both healthy controls and AD patients. Emphasis should be given to SNQ-gs and SNQ-bes subscale. The results of the present study observed that bvFTD patients are characterized by a specific socio-cognitive impairment in comprehending and respecting social norms, whereas in AD patients, the impairment is less evident. Strong discriminatory power of the SNQ enhances its role as a supplementary tool in clinics for the early and differential diagnosis of bvFTD. ROC and Logistic Regression Analysis supported this finding, therefore recommending its further utilization within clinical settings, however, variations in the efficiency within SNQ subscales among different studies suggests attention to further refinement research on this tool for enhancing diagnostic precision. Nonetheless, considering the sample size limitation, the culturally adapted SNQ-IT gives promise for the improvement of early identification and differential diagnosis of bvFTD. Further research should focus on exploring the SNQ's error patterns within larger and more diverse sample sizes considering also comparisons between frontal and temporo-limbic variants of bvFTD and exploring neural correlates of the error profiles (Cerami et al., 2016). Additionally, combining SNQ-IT information with other non-social and socio-cognitive information, as well as with biological marker information may enhance our comprehension of possible differential impairment patterns in social norms knowledge and understanding in bvFTD subgroup of patients.

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