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More than words: Social cognition across variants of primary progressive aphasia

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ABSTRACT

Although primary progressive aphasia (PPA) is clinically typified by linguistic impairments, emerging evidence highlights the presence of early deficits in social cognition. This review systematically describes the latter patterns, specifying their relation to the characteristic linguistic dysfunctions and atrophy patterns of non-fluent, semantic, and logopenic variants of the disease (nfvPPA, svPPA, and lvPPA, respectively), relative to closely related dementia types. Whereas the evidence on lvPPA proves scant, studies on nfvPPA and svPPA patients show consistent deficits in emotion recognition, theory of mind, and empathy. Notably, these seem to be intertwined with language impairments in nfvPPA, but they prove primary and independent of language disturbances in svPPA. Also, only the profile of svPPA resembles that of behavioral variant frontotemporal dementia, probably reflecting the overlap of fronto-temporal disruptions in both conditions. In short, the neurocognitive relationship between linguistic and socio-cognitive deficits cannot be precisely predicated for PPA as a whole; instead, specific links must be acknowledged in each variant. These emergent patterns pave the way for fruitful dimensional research in the field.

1. Introduction

Primary progressive aphasia (PPA) is a clinical syndrome mainly typified by linguistic deficits at symptom onset and in early stages (Mesulam, 2003). Current consensus criteria (Gorno-Tempini et al., 2011) discriminate among three disease subtypes: (i) non-fluent variant PPA (nfvPPA), whose core symptoms are effortful and/or agrammatic language production; (ii) semantic variant PPA (svPPA), also called 'semantic dementia' or 'temporal variant frontotemporal dementia', characterized by anomia and single-word comprehension deficits; and (iii) logopenic variant PPA (lvPPA), marked by word retrieval and sentence repetition deficits.

Of note, compromised brain regions across variants extend beyond classical language areas and none of them is exclusively devoted to linguistic functions (Adolfi et al., 2017; Amodio and Frith, 2006; Barrett et al., 2007; Binney et al., 2016b; Craig, 2009; Gallese, 2007; Gallese et al., 2004; Lamm et al., 2011; Olson et al., 2013; Pobric et al., 2016; Rice et al., 2015; Samson et al., 2004; Saxe, 2006; Saxe and Kanwisher, 2003). Moreover, while clinical diagnosis of PPA is basically anchored in linguistic disturbances, a proportion of cases cannot be easily classified based solely on language tests (Wicklund et al., 2014). Indeed, some presentations of PPA involve only minor or mixed linguistic alterations, hindering differential diagnosis (Mesulam et al., 2012). Evidence from other domains, such as memory (Eikelboom et al., 2018), executive functions (Macoir et al., 2017), and praxis (Johnen et al., 2018), proves critical in such circumstances. In this sense, and more particularly, an increasing amount of work underscores the relevance of behavioral and socio-cognitive assessments to improve early diagnostic accuracy (Binney et al., 2016a; Harris et al., 2018; Piguet et al., 2015; Pozzebon et al., 2018b; Rohrer and Warren, 2010; Rosen et al., 2006; Thompson et al., 2003; Van Langenhove et al., 2016).

Generally speaking, social cognition encompasses the

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psychobiological processes that allow us to comprehend and interact with other people (Adolphs, 2009). Predictably, such a broad and complex concept has been defined in various ways. For example, some classifications distinguish among emotion perception, social perception, and theory of mind (ToM) as three core socio-cognitive processes (Roelofs et al., 2017), while others advance key distinctions among emotion recognition, ToM, and empathy, alongside complementary components such as morality and social decision making (Arioli et al., 2018; Ibanez et al., 2016).[1] In this work we follow the latter approach, focusing on emotion recognition, ToM, and empathy as key socio-cognitive domains given their systematic assessment across studies on (at least some) PPA variants (Harciarek and Cosentino, 2013; Kumfor and Piguet, 2012; Shany-Ur and Rankin, 2011). Importantly, our focus is further justified by the existence of standardized and easily applicable instruments for all three domains, which renders them good candidates for prospective incorporation in clinical settings (Davis, 1983; Sarazin et al., 2012; Torralva et al., 2009).

Emotion recognition is the ability to identify how others are feeling based on social cues like facial expressions, voices, and body posture (Barrett et al., 2011). ToM is defined as the capacity to reason and make inferences about one's own mental states and those of others (Abu-Akel and Shamay-Tsoory, 2011; Shamay-Tsoory et al., 2006). Empathy is the ability to respond to others' affective experiences (Decety and Jackson, 2004; Decety and Lamm, 2006). Note that ToM and empathy share certain characteristics, as both hinge on the representation of others' mental or emotional states to predict behaviors and allow for successful social interactions (Singer, 2006). Additionally, both domains have cognitive and affective dimensions. Indeed, ToM is present when one infers or reasons about others' cognitive (e.g., beliefs, thoughts, intentions) or affective (e.g., emotions, feelings) states, each of these processes recruiting partially different neural substrates (Shamay-Tsoory et al., 2006). Similarly, empathy involves not only an affective component (often understood as emotional contagion), but also a cognitive component (namely, perspective taking, via explicit construals of the other person's feelings) (Decety and Michalska, 2010; Shamay-Tsoory et al., 2009), both of which can be partially doubly dissociated (Shamay-Tsoory et al., 2009). Yet, despite their similarities, ToM and empathy are widely recognized as different processes: ToM is mainly based on cognitive inferences about a subject's mental states (Baron-Cohen et al., 1994), which is not necessary for empathy. Instead, empathy entails an emotional response to the affective state of the other person (Singer, 2006), which is not necessary for ToM. Moreover, this fundamental difference between ToM and empathy is formally captured by validated measures which are often used to test each domain separately (Baron-Cohen et al., 1999; Baron-Cohen et al., 2001; Davis, 1983).

More crucially for present purposes, the distinction among emotion recognition, ToM, and empathy is widely present across multiple reports on early and mild stages of PPA (Harciarek and Cosentino, 2013; Hutchings et al., 2017; Kumfor and Piguet, 2012; Shany-Ur and Rankin, 2011). Indeed, these processes are critically associated with many brain regions that are systematically atrophied across PPA variants (Adolphs, 2002; Amodio and Frith, 2006; Decety and Jackson, 2004; Decety and Lamm, 2006; Gallagher and Frith, 2003; Gorno-Tempini et al., 2011; Lamm et al., 2011; Murphy et al., 2003; Samson et al., 2004; Saxe, 2006; Saxe and Kanwisher, 2003; Shamay-Tsoory et al., 2009, 2006; Vytal and Hamann, 2010). Moreover, the assessment of these socio-cognitive domains has the potential to help early clinical distinctions among them. Notably, combined measures of negative facial emotion recognition, episodic memory, and visual processing, independent of language performance, yield accurate diagnosis of early non-semantic PPA in over 85% of the cases (Piguet et al., 2015). Additionally, empathy, as measured through informant-based data, may help differentiate between nfvPPA and lvPPA (Van Langenhove et al., 2016). Finally, socio-cognitive symptoms in PPA syndromes, such as empathy loss (Hazelton et al., 2016; Hsieh et al., 2013) and reduced emotional memory (Kumfor et al., 2014), are intimately related to caregiver burden. Thus, the study of social cognition in PPA could have important implications not only for early differential diagnosis but also for treatment purposes, since having a comprehensive picture of alterations beyond the language domain could guide new interventions to assist patients and their families (Hazelton et al., 2016; Pozzebon et al., 2018a, b).

Furthermore, PPA variants are subsumed under the umbrella of frontotemporal dementia (Gorno-Tempini et al., 2011). This includes the behavioral variant of frontotemporal dementia (bvFTD), characterized by early and pervasive changes in personality and social behavior following atrophy of frontal, insular, and temporal regions (Piguet et al., 2011). Accordingly, the distinction between nfvPPA, svPPA and bvFTD can be challenging, since they are partially similar in their clinical manifestation and neural biomarkers (Gorno-Tempini et al., 2011; Hardy et al., 2016; Pan and Chen, 2013; Rohrer and Warren, 2010; Rosen et al., 2002a). More specifically, nfvPPA and svPPA present socio-cognitive deficits (e.g., in emotion recognition, ToM, and empathy) that partially resemble those of bvFTD (Couto et al., 2013; Harciarek and Cosentino, 2013; Kumfor et al., 2018; Van Langenhove et al., 2016). On the other hand, lvPPA is most commonly related to Alzheimer's disease (AD) pathology (Gorno-Tempini et al., 2011; Harciarek and Kertesz, 2011). In fact, both lvPPA and AD have a similar profile of behavioral change over time, mainly characterized by apathy (Van Langenhove et al., 2016). Thus, given the clinical and pathological heterogeneity and overlap across neurodegenerative disorders (Ahmed et al., 2016), differential diagnosis within the PPA spectrum requires not only discriminating among its variants, but also distinguishing them from other conditions such as bvFTD and AD. Social cognition assessments can be useful for this purpose (Piguet et al., 2015; Sarazin et al., 2012).

Against this background, we aim to systematically review evidence on social cognition deficits across PPA variants. While relevant research has been condensed in previous works (Harciarek and Cosentino, 2013; Kumfor and Piguet, 2012; Shany-Ur and Rankin, 2011), over 15 reports have been produced since these reviews were published, doubling the available corpus. Also, a more recent synthesis of the literature (Hutchings et al., 2017) has focused only on facial identity and expression processing, overlooking several other key domains, such as (i) emotion processing from bodies (Kumfor et al., 2018), auditory stimuli (Fletcher et al., 2015; Rohrer et al., 2012), or a combination of both (Downey et al., 2015; Kumfor et al., 2013; Multani et al., 2017; Rankin et al., 2009; Woolley et al., 2015), (ii) ToM (Bejanin et al., 2016; Couto et al., 2013; Duval et al., 2012; Irish et al., 2014); and (iii) empathy (Hazelton et al., 2016; Hsieh et al., 2013; Irish et al., 2013; Marshall et al., 2017; Rankin et al., 2005; Shdo et al., 2017). Lastly, while previous reports have exclusively targeted the relationship between behavioral performance and gray matter volume, recent studies offer novel evidence from diffusion tensor imaging (Downey et al., 2015; Multani et al., 2017), resting-state functional connectivity (Bejanin et al., 2016; Toller et al., 2018), and physiological measures (Balconi et al., 2015; Fletcher et al., 2015; Marshall et al., 2018a, b). Our comprehensive coverage contemplates and integrates all these strands of evidence, seeking to reveal whether and how linguistic and socio-cognitive outcomes interact in each PPA variant.

The remainder of the article comprises five sections. First, we describe our literature selection criteria. Next, we synthetize multidimensional evidence from the three PPA variants concerning emotion recognition, ToM, and empathy. Along that overview, we describe how socio-cognitive impairments relate to neuroanatomical and neurofunctional abnormalities in each variant, and how they interact with

[1] While both taxonomies recognize an explicit distinction among ToM, empathy, and emotion recognition, one of them (Ibanez et al., 2016) refers to the latter domain as a component in its own right, and the other (Arioli et al., 2018) places it alongside related processes such as the perception of faces, body language, and voices.

language deficits, highlighting the former's primary or secondary nature. These data are then recapped and jointly interpreted to distill whether there are distinctive socio-cognitive profiles within the PPA spectrum. Finally, we compare the socio-cognitive profile of each variant with those of bvFTD and AD, and outline outstanding challenges for future research. All in all, this comprehensive framework could open new avenues for reconsidering current diagnostic and research criteria on PPA.

2. Literature search criteria

Our literature search was conducted on PubMed and Google Scholar. Following Ibanez et al. (2016), we focused on three key social cognition domains (emotion recognition, ToM and empathy), introducing combinations of the following keywords: 'primary progressive aphasia', 'frontotemporal dementia', 'frontotemporal lobar degeneration', 'pick's disease', 'social cognition', 'emotion', 'empathy', 'theory of mind', 'moral cognition', 'morality', 'social decision making'. Also, citation lists in each paper were manually reviewed for additional relevant works. We included only literature published in English until November 15, 2018. Group-based studies and single-case reports were selected provided they included at least one relevant experimental task or questionnaire (patient- or informant-based) and reported a statistical comparison between groups or individuals.

Our final compilation comprised 47 papers, each of which was systematically reviewed in quest of the following information: (a) sample description; (b) social cognition tasks and/or questionnaires used; (c) language tests administered; (d) neuroimaging techniques applied; and (e) main behavioral and neuroimaging results, taking into account reported associations between socio-cognitive and linguistic performance, as well as comparisons with outcomes from other dementia groups. All this information is summarized in the Appendix (Tables A1 and A2).

In most papers published after 2011 (n = 30), patients met consensus criteria for PPA diagnosis as stated by Gorno-Tempini et al. (2011). Additionally, ten papers published between 2011 and 2012, as well as six papers published before 2010, followed criteria by Neary et al. (1998), and/or McKhann et al. (2001), and/or Gorno-Tempini et al. (2004). Lastly, one paper (Rosen et al., 2002b) included a group designated 'temporal variant of frontotemporal dementia' according to Brun and Passant's (1996) criteria –note that these consist in temporal lobe atrophy together with empty speech and impairments in naming and word comprehension abilities, thus resembling current criteria for svPPA. The exact number of samples diagnosed according each set of criteria can be found in the Appendix (Table A3).

3. Social cognition deficits in primary progressive aphasia

3.1. Emotion recognition

Emotion recognition from social cues (e.g., facial expressions, voices, body posture) allows identifying how others are feeling to promote adequate behavior and social functioning (Barrett et al., 2011). Neuroimaging evidence has related this ability to structures such as the amygdala, the insula, and the orbitofrontal cortex (Adolphs, 2002; Murphy et al., 2003; Vytal and Hamann, 2010). As will be shown below, emotion recognition is the most widely investigated social cognition domain in PPA.

3.1.1. Emotion recognition in nfvPPA

This domain is affected in nfvPPA patients, as revealed via picture-based tasks (e.g., Ekman Test) (Hazelton et al., 2016; Johnen et al., 2018; Kumfor et al., 2013, 2011; Piguet et al., 2015). Of note, such deficits seem to be specific for negative emotions (anger, disgust, fear, sadness) (Piguet et al., 2015), although spared disgust recognition has also been reported (Kumfor et al., 2013, 2011). However, facial emotion recognition impairments in nfvPPA are accompanied by abnormalities in face perception (Couto et al., 2013), and patients actually improve their performance when the intensity of the emotional expressions is increased by digitally manipulating critical features of the photographs (e.g., in Ekman Caricatures). Therefore, this impairment may be at least partially explained by the (dys)functionality of perceptual and attentional mechanisms (Kumfor et al., 2013, 2011).

Patients with nfvPPA also show deficits in recognizing basic emotions in videos of dynamic facial expressions (Marshall et al., 2018a,b). However, correctly identified trials are accompanied by a significant increase in autonomic reactivity (measured with electromyography), implying that preserved facial mimesis may underlie the ability to recognize emotions in this group (Marshall et al., 2018b). Although this result points to a normal matching between explicit and implicit emotional processing, contrary evidence also exists. Indeed, Balconi et al. (2015) found that, in nfvPPA, valence/arousal ratings of affective pictures (tapped by the International Affective Picture System) were unrelated to autonomic reactivity, as indexed through heart rate and electrodermal response. Nonetheless, the authors note, this result may be confounded with language deficits in that nfvPPA sample. More specifically, both implicit emotional responsiveness (indexed by self-assessment of arousal/HR ratio) and verbal fluency were related to left putamen atrophy in this group, but not in others (Balconi et al., 2015). Finally, a neuroimaging study found that reduced recognition of facial emotions in nfvPPA was associated with atrophy of the right temporal pole and the bilateral insula (Couto et al., 2013).

Regarding the auditory modality, nfvPPA patients show difficulty recognizing affective prosody in all basic emotions (Rohrer et al., 2012). However, they also fail in the recognition of acoustic and linguistic dimensions of prosody, suggesting the involvement of an early generic perceptual deficit that impacts on higher levels of prosodic processing (Rohrer et al., 2012). In another study, although overall autonomic reactivity to sound was reduced in nfvPPA, these patients exhibited greater pupil responses for both highly pleasant (e.g., baby laughing) and unpleasant (e.g., person spitting) non-verbal sounds, compared to neutral ones (e.g., telephone ringing) (Fletcher et al., 2015). Therefore, nfvPPA patients seem to retain a normal coupling between implicit (autonomic reactivity) and explicit (behavioral coding) measures when processing emotions from sounds (Fletcher et al., 2015), in line with findings for visual stimuli (Marshall et al., 2018b).

The performance of nfvPPA patients is less consistent on The Awareness of Social Inference Test (TASIT) (McDonald et al., 2003), a more ecological instrument that employs short video-vignettes to assess emotion recognition from a combination of facial expressions, vocal sounds, and paralinguistic cues. While one work based on this task reported deficits in the recognition of basic emotions (Multani et al., 2017), others found no such impairments (Gola et al., 2017; Rankin et al., 2009; Woolley et al., 2015) and one study reported a preservation of disgust recognition (Woolley et al., 2015). Overall, it is not clear whether emotion recognition difficulties in nfvPPA extend to naturalistic situations. Taking into account the presumed impact of perceptual, attentional (Kumfor et al., 2013, 2011; Rohrer et al., 2012), and linguistic (Balconi et al., 2015) factors on these patients' performance in modality-specific emotion recognition tasks, it is plausible that they may benefit from a combination of different sources of socio-emotional information (as offered by TASIT). Note, however, that patients with nfvPPA display deficits in the recognition of emotions in abstract paintings, suggesting their impairments in this domain are not circumscribed to socially-laden stimuli (Cohen et al., 2016).

To sum up, nfvPPA patients show deficits in their ability to label the emotions seen in others and this is associated with temporo-insular atrophy. Impairments in their ability to explicitly code emotions cannot be fully disentangled from perceptual, attentional, and verbal deficits. Indeed, a combination of social cues from different modalities may help patients compensate their difficulties. Finally, although they may show a diminished overall autonomic reactivity to emotional stimuli, they would seem to display a normal coupling between implicit and explicit measures of emotion recognition.

3.1.2. Emotion recognition in svPPA

A larger number of studies have addressed emotion recognition in svPPA, revealing deficits in the identification of facial emotional expressions from static photographs, particularly for negative emotions (Binney et al., 2016a; Calabria et al., 2009; Hsieh et al., 2012b, 2013; Hutchings et al., 2015; Irish et al., 2013; Johnen et al., 2018; Kamminga et al., 2015; Kumfor et al., 2018, 2013; Kumfor et al., 2016, 2011; Lindquist et al., 2014; Miller et al., 2012; Omar et al., 2011b; Perry et al., 2001; Rosen et al., 2004, 2002b). In contrast to nfvPPA, svPPA patients do not improve their performance when stimulus salience is increased (Ekman Caricatures) (Kumfor et al., 2013, 2011). This may reflect a primary deficit in facial emotion recognition, which cannot be overcome through reductions in the task's attentional and perceptual demands (Kumfor et al., 2013, 2011). Further evidence of the primary nature of these deficits in svPPA comes from studies showing that they prove independent of face perception skills (Irish et al., 2013; Kamminga et al., 2015; Miller et al., 2012; Rosen et al., 2004, 2002b) and language abilities (indexed by confrontation naming and semantic comprehension tests) (Irish et al., 2013; Kumfor et al., 2018; Rosen et al., 2002b). Importantly, while facial emotion recognition impairments in some tasks (Ekman 60 and Emotion Selection) are influenced by verbal/semantic dysfunctions, deficits in other measure (Emotion Matching) remain significant after covarying for a relevant perceptual task (Face Matching) (Miller et al., 2012). According to the authors, this suggests that svPPA patients exhibit primary emotion processing disturbances that cannot be explained by other cognitive factors. Furthermore, the sample in this work was composed exclusively by svPPA patients with predominant left temporal atrophy, which may partially account for the observed outcomes (see below).

Facial emotion labeling deficits in svPPA also prove significant in the presence of dynamic videos (Marshall et al., 2018a,b), despite preserved autonomic responses (heart rate) during the task (Marshall et al., 2018a). This pattern suggests that emotion recognition deficits may partly reflect difficulties in the bottom-up processing of autonomic (cardiac) signals elicited by the social stimuli (Marshall et al., 2018a). Additional physiological evidence aligns with that conclusion; unlike nfvPPA patients, those with svPPA do not exhibit higher electromyographic responses during correct emotion identification trials (Marshall et al., 2018b), suggesting a variant-specific abnormality in the coupling between autonomic responsivity and facial expression identification.

Facial emotion recognition deficits in svPPA have been related mainly to right ATL atrophy (Binney et al., 2016a; Kamminga et al., 2015; Kumfor et al., 2016; Perry et al., 2001). In fact, they are more profound in patients whose initial ALT atrophy is predominantly right-sided (Binney et al., 2016a; Kamminga et al., 2015; Kumfor et al., 2016; Perry et al., 2001), whereas those with predominant left ATL atrophy at symptom onset tend to display more pronounced language difficulties (Binney et al., 2016a; Kumfor et al., 2016; Perry et al., 2001). However, with disease progression, an involvement of the contralateral hemisphere becomes evident, affecting both domains in both phenotypes (Kumfor et al., 2016). Indeed, longitudinal evidence suggests that progressive right ATL deterioration in left svPPA patients accounts for their worsening emotion recognition deficits (Kumfor et al., 2016). Instead, in right svPPA, greater emotion-processing difficulties over time would be related to sustained thinning of the right orbitofrontal and anterior cingulate cortices (Kumfor et al., 2016).

Moreover, emotion identification difficulties in svPPA have been related to abnormal diffusivity in the anterior thalamic radiation (Downey et al., 2015). Also, greater emotion recognition impairments in svPPA compared to nfvPPA and lvPPA may be related to more severe focal damage of the right uncinate fasciculus in the former group (Multani et al., 2017).

Beyond facial stimuli, svPPA patients manifest deficits in recognizing emotions from bodies (Kumfor et al., 2018), abstract visual patterns (Cohen et al., 2016), music (Hsieh et al., 2012b; Omar et al., 2011a), verbal prosody (Perry et al., 2001), and non-verbal vocal sounds (Omar et al., 2011a). Moreover, Fletcher et al. (2015) reported an overall reduced autonomic reactivity to sound in svPPA, but also an altered coupling between autonomic (pupillary) and affective behavioral responses to emotionally salient sounds (when referenced to healthy individuals). Instead, no such deficit was observed in nfvPPA. More specifically, when referenced to the affective valence ratings of the corresponding patient group, svPPA and nfvPPA patients showed significantly increased pupil responses to highly valenced pleasant (e.g., baby laughing) and unpleasant (e.g., person spitting) sounds relative to neutral ones (e.g., telephone ringing). However, this correlation was disrupted in the svPPA group when pupil responses were referenced to valence ratings from healthy controls. This result aligns with that of Marshall et al. (2018b) for visual stimuli, further suggesting that svPPA patients may be unable to use implicit autonomic reactions in guiding emotion recognition.

Emotion recognition deficits in svPPA patients have also been evinced through a video-based task requiring identification of basic emotions in a realistic context (i.e., TASIT) (Binney et al., 2016a; Downey et al., 2015; Gola et al., 2017; Irish et al., 2013; Multani et al., 2017; Rankin et al., 2009; Woolley et al., 2015). Importantly, such impairments persist when controlling for lexico-semantic processes, as measured through auditory single-word comprehension (Multani et al., 2017) and vocabulary (Downey et al., 2015) tests, further highlighting their primary nature. Of note, in these naturalistic tasks, patients with svPPA perform worse than those with nfvPPA and lvPPA (Multani et al., 2017), pointing to a more profound difficulty in the contextual integration of social cues. However, a recent study reported that, when faces are embedded in a body posture context, the performance of svPPA patients in face emotion recognition matches that of healthy controls, indicating some degree of preserved contextual integration abilities (Kumfor et al., 2018). This counterintuitive result regarding facial emotion recognition may be explained by the prominence of left-hemisphere temporal lobe atrophy in the cohort assessed. Finally, note that emotion recognition deficits in svPPA are not only tapped via laboratory-based measures but also acknowledged by informants, as revealed through ratings in the emotion recognition dimension of the Socio-emotional questionnaire (Hutchings et al., 2015).

In conclusion, svPPA patients seem characterized by emotion recognition deficits in visual and auditory paradigms as well as in naturalistic tasks requiring the integration of various modalities. Such impairments are possibly related to right ATL, orbitofrontal and anterior cingulate atrophy, as well as damage to with matter connections. More notably, they appear to be primary, as they prove independent of perceptual, attentional, and linguistic disturbances. Deficits in emotion recognition may be partially related to an impairment in the afferent processing of autonomic responses elicited by social stimuli.

3.1.3. Emotion recognition in lvPPA

Emotion recognition has been only recently studied in lvPPA. While a study reported spared performance in this population through a task requiring identification of emotional expressions in static faces (Piguet et al., 2015), contradictory evidence found comparable deficits between lvPPA and nfvPPA in a similar task (Hazelton et al., 2016). In addition, lvPPA patients display significant receptive prosody deficits for emotional, acoustic, and linguistic stimuli, similar to nfvPPA (Rohrer et al., 2012). Lastly, although an emotion recognition task involving naturalistic scenes (i.e., TASIT) revealed better performance in lvPPA than nfvPPA, the difference was not significant (Multani et al., 2017). However, in that study, lvPPA patients significantly outperformed those with svPPA (Multani et al., 2017). Thus, it can be hypothesized that emotion recognition deficits in lvPPA (if present) may be milder than in other PPA variants.

3.1.4. Interim conclusion: Emotion recognition in primary progressive aphasia variants

To conclude, the three PPA variants show deficits in emotion recognition abilities, although they may be related to different underlying mechanisms. In nfvPPA, available evidence is not enough to disentangle

such impairments from perceptual, attentional, and linguistic difficulties. In contrast, emotion recognition deficits in svPPA seem to be primary (independent of perceptual, attentional, and linguistic impairments) for both explicit and implicit processing, and possibly related to ATL and prefrontal damage together with abnormalities in white matter tracts that connect frontal and limbic structures. Evidence is sparse regarding emotion recognition dysfunctions in lvPPA, and their relationships with language and brain measures are hitherto unexplored in this variant.

3.2. Theory of mind

ToM is the ability to reason about one's own mental states and those of others, and it involves two processes: the inference of others' cognitive states (e.g., beliefs, thoughts, intentions) and the understanding of others' affective states (e.g., emotions, feelings) (Abu-Akel and Shamay-Tsoory, 2011; Shamay-Tsoory et al., 2006). Overall, key structures related with ToM include the medial and orbital prefrontal cortex, the superior temporal sulcus, the temporo-parietal junction, and the temporal poles bilaterally (Amodio and Frith, 2006; Gallagher and Frith, 2003; Samson et al., 2004; Saxe and Kanwisher, 2003; Saxe and Wexler, 2005). During the last decade, evidence regarding ToM has been produced in reports of nfvPPA and (more frequently) in svPPA.

3.2.1. Theory of mind in nfvPPA

To our knowledge, only one study has explicitly addressed ToM and its neural correlates in nfvPPA (Couto et al., 2013). The paradigm used was an affective ToM task that requires inferring complex emotional states in others through the observation of the eye region. Results showed a significant deficit in the patients relative to healthy subjects, which correlated with gray matter volume of the bilateral insula, temporal pole, and amygdala. However, as temporo-insular atrophy was also related to face perception and facial emotion recognition in that study, reported ToM deficits could be explained by basic level impairments (Couto et al., 2013).

Another approach to study ToM is through sarcasm detection tasks, which tap the ability to interpret an ironic message from the integration of various contextual cues. Using a naturalistic video-based test (i.e., TASIT), Rankin et al. (2009) reported preserved sarcasm recognition in nfvPPA. Indeed, in that work, poorer sarcasm comprehension was predicted by atrophy in bilateral posterior parahippocampi, temporal poles, and right medial frontal pole. Note, however, that the analysis conflated patients with varied neurodegenerative diseases, and the affected regions are not systematically damaged in nfvPPA. Moreover, the nfvPPA subsample included only four participants, which is insufficient to draw firm conclusions.

To sum up, nfvPPA patients may have difficulty in inferring others' complex emotional states (at least in visual tasks). This pattern has been related to more basic impairments in face perception and emotion recognition, in association with temporo-insular atrophy. However, this conclusion must be taken with reservations since it stems from only one study.

3.2.2. Theory of mind in svPPA

Few works have empirically investigated ToM in svPPA, finding deficits in cognitive as well as affective dimensions. Across studies examining cognitive ToM, svPPA patients display deficits in their ability to infer the intentions, false beliefs, and humoristic intentions of characters in social scenarios (Bejanin et al., 2016; Duval et al., 2012; Irish et al., 2014), alongside difficulties in understanding sarcasm (Binney et al., 2016a; Downey et al., 2015; Rankin et al., 2009). Regarding affective ToM, these patients show difficulties for inferring others' complex emotional states upon observation of their eye region (Bejanin et al., 2016; Chen et al., 2018; Duval et al., 2012). Deficits in ToM tasks persist when controlling for language deficits, as measured with categorical fluency (Bejanin et al., 2016), and semantic comprehension tests (Irish et al., 2014), suggesting a primary difficulty in social inference.

Interestingly, in a subjective self-report questionnaire, patients with svPPA demonstrated that they were aware of their affective ToM impairment but not of their cognitive ToM deficit –that is, a form of anosognosia, as they were specifically impaired in recognizing their poor reasoning about others' intentions and beliefs (Duval et al., 2012).

Early works have suggested associations between ToM impairments and right ATL atrophy in svPPA (Downey et al., 2015; Irish et al., 2014; Michel et al., 2013; Rankin et al., 2009). However, a more recent study found no relation between ToM performance and right temporal lobe volume in this population (Bejanin et al., 2016). Yet, cognitive ToM was related to medial parietal and prefrontal regions (including the anterior insular, inferior frontal, and orbitofrontal cortices) and affective ToM was associated with the left medial temporal lobe (including the amygdala, the anterior hippocampus, and the parahippocampal gyrus) (Bejanin et al., 2016). Resting-state functional connectivity evidence further suggested that higher-order socio-cognitive deficits in svPPA patients could reflect a disconnection between the ventral medial prefrontal cortex and amygdala/hipocampal complex (Bejanin et al., 2016). However, this claim should be taken as conjectural, since the study's low statistical power prevented the authors from correlating functional connectivity results and ToM outcomes (Bejanin et al., 2016). Finally, further evidence against a predominant role of the right ATL subserving ToM in this variant comes from studies reporting no differences between right and left svPPA in cognitive and affective dimensions (Bejanin et al., 2016; Chen et al., 2018) –although Binney et al. (2016a) reported a near-significant difference between those subvariants, with right svPPA patients performing worse at sarcasm comprehension as assessed through TASIT.

To conclude, svPPA patients present deficits in cognitive and affective ToM that seem independent of language disturbance and associated with fronto-temporo-insular and parietal hubs. Also, reported alterations seem independent of the primary site of atrophy (right vs left) at initial presentation.

3.2.3. Interim conclusion: Theory of mind in primary progressive aphasia variants

There is evidence of affective ToM deficits in nfvPPA and cognitive and affective ToM impairments in svPPA. However, they may be explained by different underlying mechanisms. While ToM impairments may arise from more basic face perception and visual emotion recognition deficits in nfvPPA, they seem primary and independent of perceptual and language functioning in svPPA –and related with fronto-temporo-insular and parietal hubs. No study has examined this ability in lvPPA, and no study has explicitly compared ToM across the different PPA variants.

3.3. Empathy

Empathy is defined as the capacity to respond to others' affective experiences (Decety and Jackson, 2004; Decety and Lamm, 2006). This ability encompasses an affective component –which may entail sharing emotional experiences with others (emotional contagion)– and a cognitive component –associated with ToM, consisting of the ability to intentionally take others' perspectives and imagining how they would feel (Decety and Jackson, 2004; Decety and Lamm, 2006; Melloni et al., 2014; Shamay-Tsoory et al., 2009). Neurally speaking, empathy has been related to an extended neural network, involving the bilateral insula, the somatosensory cortex, the periaqueductal gray, and the anterior cingulate cortex (Decety and Jackson, 2004; Decety and Lamm, 2006; Lamm et al., 2007; Melloni et al., 2014). In addition, the amygdala seems to be the region with the earliest selective response to affective empathy (Hesse et al., 2016). In PPA, both affective and cognitive empathic abilities have been explored exclusively via self-and/or informant reports.

3.3.1. Empathy in nfvPPA

Although patients with nfvPPA have shown reduced (Hazelton et al., 2016) or widely varying (Rankin et al., 2006) performance in the cognitive dimension of empathy, the informant version of the Interpersonal Reactivity Index (IRI) consistently reveals normal affective empathy compared to controls (Gola et al., 2017; Hazelton et al., 2016; Rankin et al., 2006; Shdo et al., 2017; Sollberger et al., 2014). Moreover, evidence on spared affect-sharing capacity in nfvPPA is supported by studies that employed the Sensitivity to Expressive Behavior Subscale of the Revised Self-Monitoring Scale (RSMS-EX) (Marshall et al., 2017; Shdo et al., 2017). Another work also reported normal RSMS total scores (as a measure of socioemotional sensitivity) in a nfvPPA sample, although the authors did not differentiate between subscales (Toller et al., 2018).

However, in comparison to pre-morbid functioning, analysis of informants' ratings in the IRI revealed a significant reduction in both cognitive and affective empathy following disease onset in nfvPPA (with a mean illness duration of 3.3 years) (Hazelton et al., 2016). This finding is in line with a one-year longitudinal study reporting a significant loss of empathy (measured with the Cambridge Behavioral Inventory Revised; CBI-R) in nfvPPA relative to lvPPA –a pattern that may have diagnostic value (Van Langenhove et al., 2016). Moreover, as reported by Hazelton et al. (2016), a reduction in cognitive empathy correlated with facial emotion recognition ability in nfvPPA but not in lvPPA. Finally, scores from nfvPPA patients and informants on the IRI subscales reveal virtually no differences, suggesting an accurate self-awareness of empathy loss in nfvPPA (Eslinger et al., 2011; Sollberger et al., 2014).

To summarize, nfvPPA presents normal affective empathy in comparison to controls, while findings about cognitive empathy remain inconclusive. However, these patients may exhibit a reduction in their empathic abilities if compared with ratings before diagnosis. Still, nfvPPA patients show awareness of their empathic loss, in line with caregivers' reports. Neural correlates of the empathic profile have not been addressed in nfvPPA separately from other dementia groups.

3.3.2. Empathy in svPPA

Studies in svPPA have found impairments in cognitive and/or affective empathy, as revealed by the IRI (Binney et al., 2016a; Henry et al., 2014; Hsieh et al., 2013; Irish et al., 2014, 2013; Rankin et al., 2006, 2005; Shdo et al., 2017; Sollberger et al., 2014), the RSMS total score (Toller et al., 2018), the RSMS-EX (Marshall et al., 2017; Shdo et al., 2017), the Empathy dimension of the Socio-emotional questionnaire (Hutchings et al., 2015), and the Empathic Scale of the CBI-R (Van Langenhove et al., 2016).

Empathy deficits in this variant have been related to right anterior temporal atrophy (Binney et al., 2016a; Henry et al., 2014; Irish et al., 2013; Perry et al., 2001; Rankin et al., 2006). Binney et al. (2016a) found that, although svPPA patients presented reduced cognitive empathy when taken as a whole, only the right svPPA subsample scored significantly lower than controls. Interestingly, while both subgroups showed severe naming and single-word comprehension impairments and surface dyslexic errors, linguistic deficits were significantly more profound in left svPPA (Binney et al., 2016a). Thus, empathic deficits in svPPA seem independent of language impairments. In this line, Irish et al. (2013) also found that right svPPA patients were significantly impaired in affective empathy as compared to left svPPA, in the context of a similar cognitive and linguistic profile. Lastly, a single-case study reported impaired cognitive empathy but preserved affective empathy in a left svPPA patient (Calabria et al., 2009). Taken together, these findings suggest that empathic deficits are more common in right svPPA, and not related to language impairments.

In Marshall et al.'s (2017) study, reduced emotional empathy in svPPA (measured with RSMS-EX) was related to impairments in interoception (i.e., the sensing of bodily signals) in a heartbeat counting task. Importantly, interoceptive accuracy was not related to semantic deficits, as captured by a vocabulary test, but it was associated with gray matter volume of right cingulo-insulo-amygdalar regions (Marshall et al., 2017). Taken together, these results suggest that svPPA is characterized by a primary deficit in the ability to decode autonomic responses, which may undermine the capacity to empathize with others (Marshall et al., 2017), in line with reports on emotion recognition impairments (Marshall et al., 2018b).

Also, according to some studies, svPPA patients tend to overestimate their level of empathic concern (affective empathy) relative to their informants' reports (measured as discrepancy score) (Sollberger et al., 2014). More specifically, self-ratings are close to their premorbid level of empathic concern according to their informant reports (Sollberger et al., 2014). Overestimation of one's empathic concern correlated with gray matter volume in the right ATL, the right posterior insula, and the left anterior fusiform gyrus (Sollberger et al., 2014). In contrast, an earlier study found no significant differences between svPPA patients and informants' ratings in IRI subscales (Eslinger et al., 2011). Finally, compared to nfvPPA and lvPPA patients, those with svPPA show more profound empathic loss at baseline and at one-year follow-up (Van Langenhove et al., 2016). Moreover, empathic deficits in this variant have been correlated with disease severity and behavioral abnormalities (Hsieh et al., 2013; Irish et al., 2013).

To sum up, svPPA patients present impairments in cognitive and affective empathy that seem independent from language. Empathic deficits would be related to right ATL damage.

3.3.3. Empathy in lvPPA

Hazelton et al. (2016) reported reduced cognitive empathy but normal affective empathy (as measured with the IRI) in lvPPA compared to controls. Moreover, when compared to pre-morbid results, cognitive empathy outcomes evidence a significant decline in these patients, alongside a marginal reduction of affective empathy (Hazelton et al., 2016). Although the empathic profile of lvPPA resembles that of nfvPPA (Hazelton et al., 2016), some differences must be noted. First, Van Langenhove et al. (2016) reported that, while both PPA variants presented a similar behavioral profile at baseline, a significant empathy loss (tapped by the CBI-R subscale) was registered after one year in nfvPPA but not in lvPPA –this pattern being potentially informative for differential diagnosis. Second, in the study of Hazelton et al. (2016), changes in cognitive empathy over time correlated with visuospatial abilities in lvPPA and with emotion recognition in nfvPPA.

In sum, though evidence regarding empathy in lvPPA is sparse and so far inconclusive, it seems that deficits in such a dimension (if present) differ from those observed in nfvPPA in terms of their neural correlates and progression.

3.3.4. Interim conclusion: Empathy in primary progressive aphasia variants

In conclusion, there is evidence of deficits in cognitive empathy in all three variants, although these prove more marked in svPPA. This condition also involves early affective empathy impairments, which seem to emerge later in nfvPPA. Empathy loss is more evident in svPPA than in the other variants, and more pronounced in nfvPPA than in lvPPA over time. Also, svPPA patients (but not those with nfvPPA) show anosognosia for their change in empathic behavior. Possibly, empathic deficits are independent from language in svPPA, and may be associated with right temporal structures. No similar claims can be advanced for either nfvPPA and lvPPA, as evidence on the neural correlates of empathic deficits is lacking in both variants.

4. Brain-behavior associations across socio-cognitive and linguistic deficits in primary progressive aphasia variants

The main neural hubs affected across PPA variants play undisputed roles in language processing. Yet, as seen above, they also prove critical for various socio-cognitive domains, which may account for their widespread disturbance in these conditions. Importantly, as summarized in Fig. 1, these deficits do not manifest identically in all forms of PPA. In this section, we recap and critically discuss the available

Social cognition domain / stimuli		PPA variant: nfvPPA	svPPA	lvPPA
EMOTION RECOGNITION	Static faces	Impaired (5 reports) - Related to perception and attention - Possibly related to language - Related to right temporal pole and bilateral insula	Impaired (18 reports) - Independent of perception and attention - Independent of naming and semantic comprehension - Related to right ATL, OFC and ACC	Mixed evidence (Impaired: 1 report; Preserved: 1 report)
	Dynamic faces	Impaired (2 reports)	Impaired (2 reports)	Unexplored
	Bodies	Unexplored	Impaired? (1 report)	Unexplored
	Prosody / vocal sounds	Impaired? (1 report) - Related to generic perceptual deficits	Impaired (2 reports)	Impaired? (1 report) - Related to generic perceptual deficits
	Naturalistic scenes	Mixed evidence (Impaired: 1 report; Preserved: 3 reports)	Impaired (7 reports) - Independent of vocabulary and semantic comprehension - Possible related to anterior thalamic radiation and right uncinate fasciculus	Impaired? (1 report)
TOM	Cognitive	Unexplored	Impaired (3 reports) - Independent of categorical fluency and comprehension - Related to right temporal lobe, medial parietal and prefrontal regions - Deficits independent of primary site of atrophy (right vs left) at initial presentation	Unexplored
	Affective	Impaired? (1 report) - Possibly related to face perception and facial emotion recognition - Related to bilateral insula, temporal pole, and amygdala	Impaired (3 reports) - Independent of categorical fluency - Related to right and left-medial temporal regions - Deficits independent of primary site of atrophy (right vs left) at initial presentation	Unexplored
EMPATHY	Cognitive	Impaired? (1 report) - Related to emotion recognition	Impaired (6 reports) - More profound in right svPPA but also present in left svPPA - Not related to language impairments	Impaired? (1 report) - Related to visuospatial abilities
	Affective	Preserved (6 reports) - Decreasec when compared to premorbid functioning (1 report)	Impaired (8 reports) - More profound in right svPPA but also present in left svPPA - Not related to language impairments	Preserved? (1 report) - Decreased when compared to premorbid functioning (non-significant)

Fig. 1. Performance in social cognition domains across variants of primary progressive aphasia. The color bar represents the strength of evidence according to number of reports. ACC: anterior cingulate cortex; ATL: anterior temporal lobe; lvPPA: logopenic variant primary progressive aphasia; nfvPPA: non-fluent variant primary progressive aphasia; OFC: orbitofrontal cortex; svPPA: semantic variant primary progressive aphasia; ToM: theory of mind.

evidence, distilling the distinctive patterns of socio-cognitive deficits in each variant, assessing their relation to linguistic dysfunctions, and distilling their specific neural bases.

As shown in Section 3, the socio-cognitive profile of nfvPPA includes deficits in emotion recognition, affective ToM, and cognitive empathy, alongside a relative preservation of affective empathy (see Fig. 1). Briefly, nfvPPA patients may present difficulties in identifying and inferring how others feel, which may reflect the overlap in the affective component of ToM (intentionally reasoning about others' affective states) and the cognitive component of empathy (imagining how others feel) (Singer, 2006). However, these patients seem partially spared in their capacity to resonate with others' emotional experiences (affective empathy), at least in early disease stages. Indeed, longitudinal evidence (Van Langenhove et al., 2016) and caregivers' reports (Pozzebon et al., 2018b) indicate that deficits in relevant socio-cognitive skills emerge one or two years after nfvPPA diagnosis. This suggests that specific disturbances of social cognition in this variant may appear *after* evident linguistic deficits (as required for diagnosis), and not concomitantly with them. Furthermore, experimental studies show that socio-cognitive deficits in nfvPPA cannot be fully disentangled from perceptual, attentional, and linguistic dysfunctions (Balconi et al., 2015; Couto et al., 2013; Kumfor et al., 2013, 2011; Rohrer et al., 2012), and they may be affected by language processing confounds (Couto et al., 2013; Rohrer et al., 2012).

In brief, since they become evident only after language impairments and are intertwined with other cognitive dysfunctions, socio-cognitive deficits do not seem to represent primary disturbances in nfvPPA. Conceivably, the secondary nature of such alterations might partially explain why patients could compensate particular socio-cognitive deficits in naturalistic situations featuring rich multimodal (including various non-linguistic) cues (Gola et al., 2017; Rankin et al., 2009; Woolley et al., 2015). Nonetheless, these tentative conclusions should be systematically tested in the future.

Regarding the neural bases of socio-cognitive deficits in nfvPPA, there is evidence of emotion recognition and affective ToM being related to the insular cortex (Couto et al., 2013), one of the main structures atrophied in these patients, together with the inferior frontal gyrus (Gorno-Tempini et al., 2011). These regions are critically involved in stimulus triggered attentional reorientation (Weissman et al., 2006) and salience processing (Ibanez et al., 2010; Seeley et al., 2007).

Thus, neural damage in these sites may impair relevant attentional mechanisms, negatively impacting on the performance of nfvPPA patients. In fact, when attention allocation is facilitated in nfvPPA through increased stimulus salience, socio-cognitive deficits are minimized (Kumfor et al., 2013, 2011).

Surprisingly, insular damage in nfvPPA does not seem to yield deficits in particular putative domains. This structure is critically involved in affective and socio-cognitive processes, including disgust recognition (Wicker et al., 2003), interoception (García-Cordero et al., 2016; Zaki et al., 2012), emotional awareness (Craig, 2009), and affective empathy (Adolfi et al., 2017; Lamm et al., 2007), among others (Ibanez et al., 2010). However, nfvPPA patients seem characterized by a preserved ability to recognize disgust (Kumfor et al., 2013, 2011; Woolley et al., 2015) and process affective dimensions of empathy (Gola et al., 2017; Hazelton et al., 2016; Rankin et al., 2006; Shdo et al., 2017; Sollberger et al., 2014). Both counterintuitive results may be explained following Kumfor et al. (2013). The authors noted that different parts of the insula are specialized for different functions, the dorsal region being more devoted to language expression and the antero-ventral region to emotional processing (Mutschler et al., 2009). Indeed, imaging-based nfvPPA diagnosis requires predominant left posterior fronto-insular atrophy (Gorno-Tempini et al., 2011). Thus, given that the patients evaluated were in early disease stages (between 2 and 5 years when reported), these unexpected findings may reflect the lack of antero-ventral insular atrophy. Moreover, socio-cognitive impairments in nfvPPA are also partially related to temporal pole damage (Couto et al., 2013), but atrophy of this region is not critical for diagnosis. Therefore, socio-cognitive deficits in nfvPPA seem related to structures not necessarily compromised at disease onset.

In conclusion, socio-cognitive deficits in nfvPPA patients may emerge after language impairment, initially reflecting a difficulty in attending to socially relevant information, in association with their primary site of atrophy. The lack of anterior insula and temporal damage may explain the relative preservation of particular socio-cognitive functions (i.e., disgust recognition and affective empathy) at early stages of the disease.

Concerning svPPA, the evidence shows consistent deficits in emotion recognition (even in naturalistic situations), cognitive and affective ToM, and cognitive and affective empathy (see Fig. 1). These disturbances appear alongside manifest behavioral disturbances (e.g., egocentrism) and can be tracked in very early disease stages, matching the onset of verbal symptoms (Pozzebon et al., 2018b; Van Langenhove et al., 2016). Moreover, experimental evidence suggests that socio-cognitive deficits in svPPA are independent from language comprehension skills. Indeed, multiple works have shown that such dysfunctions (e.g., in emotion recognition and ToM) remain significant even when controlling for semantic impairments (Bejanin et al., 2016; Irish et al., 2014; Rosen et al., 2002b) –but see Hsieh et al. (2012a). These observations, together with evidence that the reported impairments are uninfluenced by perceptual and attentional factors (Kumfor et al., 2013, 2011), suggest that socio-cognitive alterations in svPPA are primary in nature –i.e., not epiphenomenal to other consequences of the disease.

In neural terms, most svPPA patients are characterized by ATL atrophy, predominantly in the left hemisphere at initial presentation (Gorno-Tempini et al., 2011) –a pattern that is accompanied by typical language difficulties (Binney et al., 2016a; Kumfor et al., 2016; Perry et al., 2001). However, approximately 25–30% of the patients present with predominantly right ATL atrophy at symptom onset (Chan et al., 2009; Hodges et al., 2009). Of note, socio-cognitive deficits are more prominent in right svPPA (Binney et al., 2016a; Henry et al., 2014; Irish et al., 2013; Kamminga et al., 2015; Michel et al., 2013; Perry et al., 2001), probably reflecting the more critical role of right ATL structures in socio-emotional behavior (Olson et al., 2013; Pobric et al., 2016; Rice et al., 2015).

Such a dissociation has been interpreted to reflect the relative differential contributions of right and left temporal structures to socio-emotional and lexico-semantic/conceptual processes, respectively (Gainotti, 2015; Pobric et al., 2016). However, with disease progression, socio-cognitive deficits become evident in left svPPA patients as well (Kumfor et al., 2016). Indeed, right ATL degradation has been proposed as an underlying mechanism accounting for emotion recognition (Kumfor et al., 2016), ToM (Irish et al., 2014), and empathy (Rankin et al., 2006) impairments in this subpopulation.

Beyond the right ATL, other structures also seem to be important for social cognition in svPPA, including the right orbitofrontal cortex, the right anterior cingulate cortex, the bilateral amygdala, and the insular cortex –in addition to less typical regions, such as the anterior thalamic radiation (Bejanin et al., 2016; Downey et al., 2015; Hsieh et al., 2012b; Irish et al., 2014; Kumfor et al., 2016). Of note, patients with svPPA present with atrophy in orbitofrontal and ventromedial prefrontal cortices, a pattern that does not correlate with semantic memory impairments (Mummery et al., 2000; Rosen et al., 2002a). Damage to these sites may explain the greater pervasiveness of socio-cognitive deficits in svPPA relative to nfvPPA. Indeed, it has been suggested that socio-cognitive deficits in svPPA (as opposed to nfvPPA) would reflect difficulties in the bottom-up processing of autonomic signals to guide the recognition of and responsiveness to others' emotions (Marshall et al., 2018a, 2017; Marshall et al., 2018b). In this sense, the orbitofrontal and ventromedial cortices are critical for interpreting somatic sensations that underlie decision-making and self-monitoring functions, so that their disruption can compromise adaptive interpersonal behavior (Beer and Ochsner, 2006; Ibanez et al., 2017; Melloni et al., 2016).

The presence of more severe socio-cognitive deficits in svPPA relative to nfvPPA (and also lvPPA) has been proposed to reflect abnormal functional connectivity between temporal and frontal structures (Bejanin et al., 2016) as well as structural damage to the uncinate fasciculus (Multani et al., 2017). In this sense, note that the ATL is connected to regions devoted to higher-order socio-cognitive processing, namely the orbitofrontal cortex, via the uncinate fasciculus (Papinutto et al., 2016; Von Der Heide et al., 2013) –a white matter tract that is more altered in svPPA than other variants (Galantucci et al., 2011). Also, as reported by Multani et al. (2017), right uncinate fasciculus integrity can contribute more to naturalistic emotion recognition than gray matter regions surrounding that tract (i.e., orbitofrontal cortex and ATL gray matter volume). This finding highlights the relevance of specific neuroimaging techniques, such as diffusion tensor imaging, to explore the neural correlates of social cognition in aphasia.

In sum, svPPA would be mainly characterized by primary socio-cognitive deficits, which are independent from linguistic and domain-general dysfunction but possibly related to interoceptive impairments. Moreover, such socio-cognitive difficulties seem more severe in this variant than in the other two, possibly reflecting the greater disruption of prefrontal and temporal regions and their connections.

Finally, evidence is scarce for lvPPA. It has been suggested that these patients would exhibit less severe emotion recognition deficits compared to those of nfvPPA and svPPA (Multani et al., 2017). Additionally, much like nfvPPA patients, subjects with lvPPA would display reduced cognitive empathy but normal affective empathy as compared to controls (Hazelton et al., 2016) –see Fig. 1. However, lvPPA seems characterized by fewer behavioral disturbances compared to the other PPA variants (Van Langenhove et al., 2016). In fact, in the study of Van Langenhove et al. (2016), empathy loss was less pronounced in lvPPA as compared to nfvPPA and svPPA, suggesting a possible phenotypical distinction.

Details are also scant concerning the brain correlates of socio-cognitive performance in lvPPA. This variant is crucially typified by atrophy of the temporo-parietal junction (Gorno-Tempini et al., 2011), which has been related to perspective taking and ToM (Samson et al., 2004; Saxe, 2006; Saxe and Kanwisher, 2003; Saxe and Wexler, 2005). However, no study has explicitly explored the brain correlates of social cognition in lvPPA, which leaves open a promising space for fruitful research in future years.

5. Socio-cognitive profile in PPA variants in comparison to other dementia groups

Current diagnostic criteria consider PPA variants as part of the frontotemporal dementia spectrum, which includes bvFTD (Gorno-Tempini et al., 2011). However, lvPPA is most commonly related to AD pathology (Gorno-Tempini et al., 2011; Harciarek and Kertesz, 2011). Thus, considering the clinical and pathological heterogeneity and overlap across neurodegenerative disorders (Ahmed et al., 2016), differential diagnosis within the PPA spectrum also requires considering the profile of closely related dementia groups, such as bvFTD and AD, across different levels of manifestation.

Patients with bvFTD may show disinhibition, compulsivity, impulsivity, changes in eating behavior, depression, empathy loss, and inappropriate conduct, even before the emergence of cognitive dysfunction (Piguet et al., 2011; Santamaria-Garcia et al., 2016). In experimental tasks, the socio-cognitive profile of bvFTD involves deficits in emotion recognition, interoception, ToM, sarcasm detection, empathy, moral judgment, social cooperation, social emotions and social decision making (Baez et al., 2014a,b; Baez et al., 2016a, b; García-Cordero et al., 2016; Harciarek and Cosentino, 2013; Ibanez, 2018; Ibanez et al., 2017, 2016; Ibanez et al., 2014; Ibanez and Manes, 2012; Melloni et al., 2016; Santamaría-García et al., 2017). These deficits could be only partially related to executive dysfunction (Torralva et al., 2007). In contrast, AD is primarily characterized by episodic memory loss at early stages, related to medial temporal lobe atrophy (McKhann et al., 2011). Though social cognition impairments have been reported in AD, they are milder than in FTD syndromes and probably related to cognitive dysfunction and with the progression of degeneration to other structures (Klein-Koerkamp et al., 2012; Kumfor and Piguet, 2013; Lavenu and Pasquier, 2005; Shany-Ur and Rankin, 2011; Torralva et al., 2000).

Behaviorally, unlike nfvPPA, lvPPA, and AD, svPPA involves severe behavioral dysfunctions typical of bvFTD, including disinhibition, aberrant motor behavior, empathy loss, and eating disorders (Harris et al., 2018; Kamminga et al., 2015; Rosen et al., 2006; Van Langenhove et al., 2016). This pattern may be explained by the common involvement of medial and orbital frontal structures (especially on the right hemisphere) in svPPA and bvFTD (Rosen et al., 2006). In contrast, according to a longitudinal study, nfvPPA and lvPPA patients do not present with behavioral disturbances at baseline. Over a one-year period, however, nfvPPA patients show a decline in empathy, while those with lvPPA present a profile of behavior change similar to AD, characterized by apathy (Van Langenhove et al., 2016).

Results from experimental studies are in line with the above observations. The socio-cognitive profile of svPPA patients tends to resemble that of bvFTD, especially when atrophy is predominantly right-sided (Downey et al., 2015; Fletcher et al., 2015; Hsieh et al., 2013; Hutchings et al., 2015; Irish et al., 2014; Kamminga et al., 2015; Kumfor et al., 2013; Marshall et al., 2018b; Omar et al., 2011a, b; Rankin et al., 2006; Shdo et al., 2017; Sollberger et al., 2014; Woolley et al., 2015). Yet, impairments are typically greater for bvFTD (Eslinger et al., 2011; Gola et al., 2017; Kumfor et al., 2018; Rosen et al., 2004). For example, while svPPA and bvFTD show similar profiles in recognizing facial emotional expressions in isolation or in a congruent context (e.g., an angry face in an angry body posture), differences emerge when faces appear in incongruent contexts (i.e., a sad face in an angry body posture) (Kumfor et al., 2018). In those trials, bvFTD patients perform worse than svPPA patients in the recognition of facial emotional expressions. Also, bvFTD patients show greater contextual influence, marked by an increased tendency to label the facial emotion as that displayed by the body, in line with the 'environmental dependency syndrome' (Kumfor et al., 2018) and related disinhibited behavior (Ibanez, 2018), commonly reported in this group. This result suggests that svPPA, in contrast to bvFTD, would entail a relatively greater sparing of contextual integration skills. Nonetheless, the sample of that study was composed mainly by left svPPA patients, calling for further research in subjects with predominant right atrophy.

Another commonality between svPPA and bvFTD concerns fundamental deficits in interoception in the latter populations, which may negatively impact their socioemotional sensitivity through damage in the anterior insula, anterior cingulate and amygdala hubs (García-Cordero et al., 2016; Marshall et al., 2017; Toller et al., 2018). Indeed, processing of interoceptive sensitivity would provide the building blocks of the awareness of self and others' emotions (Craig, 2009). In contrast, one study reported preserved interoception and emotional empathy in nfvPPA (Marshall et al., 2017).

Finally, as bvFTD patients, those with svPPA demonstrate reduced insight for their socio-emotional disturbances (Hornberger et al., 2014; Hutchings et al., 2015; Sollberger et al., 2014), while normal self-awareness has been reported in nfvPPA (Hornberger et al., 2014; Sollberger et al., 2014). This is in line with other studies reporting anosognosia for progressive language impairments in svPPA, a pattern that was not present in nfvPPA (Kertesz, 2010). Furthermore, insight loss has been related to fronto-temporo-insular regions (Hornberger et al., 2014; Sollberger et al., 2014).

While some studies suggest different neural correlates of social cognition impairments in bvFTD and svPPA (Kamminga et al., 2015; Rankin et al., 2006), more recent evidence offers novel insights. According to Downey et al. (2015), socio-cognitive deficits in emotion recognition and ToM (i.e., sarcasm comprehension) in bvFTD and svPPA are related to widely distributed, overlapping networks that subserve those processes in the healthy population. In other words, data do not support the notion of separable, syndrome-specific neural correlates of social cognition; rather, neural substrates of social cognition impairments would be 'trans-syndromic' (Downey et al., 2015; Ibanez et al., 2016). Thus, social cognition impairments in bvFTD and svPPA would be primary, early, and independent of other cognitive functions, in relation to orbitofrontal, ventromedial and ATL gray matter hubs, and white matter tracts (e.g., uncinate fasciculus) that connect them.

Another picture emerges when comparing bvFTD with nfvPPA. While both groups show difficulties in recognizing emotions and in ToM, these may be explained by different underlying mechanisms. Couto et al. (2013) showed that, while ToM deficits in nfvPPA would be secondary to face perception and basic emotion recognition deficits, they would be *sui generis* in bvFTD, where basic facial recognition is preserved. This conclusion stems from the finding that social cognition deficits were related to atrophy in temporo-insular regions in nfvPPA and to fronto-insular regions in bvFTD (Couto et al., 2013). This reinforces the view that, in contrast to bvFTD and svPPA, socio-cognitive deficits in nfvPPA are not independent of other cognitive functions.

Regarding lvPPA, the evidence is not enough to draw firm conclusions. Socio-cognitive disturbances seem milder in this group than those in bvFTD, svPPA, and nfvPPA (Multani et al., 2017; Piguet et al., 2015; Van Langenhove et al., 2016). Considering that lvPPA tends to be related to AD pathology (Gorno-Tempini et al., 2011; Harciarek and Kertesz, 2011), its socio-cognitive profile may prove more similar to that of AD than frontotemporal disorders. However, to date, no study has compared both populations.

To sum up, evidence suggests that, in svPPA and bvFTD, social cognition impairments would be primary and related to overlapping neural correlates, while in nfvPPA they would be secondary to more basic deficits triggered by damage in non-ventral-frontal structures.

6. Future directions

Social cognition assessment may be useful for differential diagnosis between PPA variants (Piguet et al., 2015), but more research is needed. Complex social cognition domains, such as moral cognition, social emotions, and social decision-making, have not yet been studied in PPA. These abilities are critical to guide socially adequate behavior, and have been reported to be impaired in other neurological conditions, such as bvFTD (e.g., Baez et al., 2016a; Melloni et al., 2016;

Santamaría-García et al., 2017), in association with atrophy and connectivity atypicalities in extended networks involving prefrontal cortices and limbic regions. The exploration of these domains in PPA would be useful to further delineate the patients' profile.

Also, studies employing ecological tasks that integrate contextual information are needed to better understand the social functioning of PPA patients in real life. Social interaction is influenced by context (Adolphs, 2009; Barrett et al., 2007; Ibáñez and García, 2018). Integrating relevant external and internal signals that surround a social event is critical to adequately assess social meaning and behave accordingly (Ibáñez and García, 2018). It is well-established that this ability is impaired in bvFTD, reflecting abnormalities in fronto-temporo-insular networks (Baez et al., 2017; Ibanez and Manes, 2012; Ibáñez and García, 2018). How context influences socio-cognitive processing in PPA and how it relates to atrophied regions in these populations remains to be explored.

Research on empathy in this condition would also profit from the use of experimental paradigms. Although self-report questionnaires, such as the IRI, have the advantage of capturing behavior in real life, experimental designs allow manipulating conditions and studying empathic abilities objectively. For example, empathy-for-pain paradigms are robust to explore the associated neural correlates (Bernhardt and Singer, 2012), and have shown great sensitivity in bvFTD (Baez et al., 2014b, b).

Another relevant avenue for further research is interoception, which is related to emotional processing and social cognition (Adolfi et al., 2017; Craig, 2009). Indeed, disruptions of this domain have been implicated in svPPA and bvFTD deficits (García-Cordero et al., 2016; Marshall et al., 2017), and may constitute a protentional biomarker of fronto-temporo-insular disfunction in neurodegenerative diseases (García-Cordero et al., 2016; Van den Stock and Kumfor, 2017).

Moreover, the study of social cognition is enriched through the combination of different methodological and technical approaches. As evidenced in the present review, brain-behavior associations underlying socio-cognitive impairments in PPA can be tapped via neuroimaging techniques (e.g., voxel-based morphometry, functional connectivity, diffusion tensor imaging) and autonomic measures (e.g., electromyography, pupillometry). However, no study has yet integrated various of these approaches to provide multidimensional markers of the observed impairments. Research along these lines could greatly enhance current understanding of the profiles identified above. Finally, longitudinal works in PPA are lacking. Studies assessing progressive changes in social cognition and its underlying neural correlates, such as that of Kumfor et al. (2016), are necessary to understand how deficits emerge and evolve from early to late stages of the disease.

To summarize, it is necessary to continue exploring social cognition in PPA, including complex domains, and employing ecological tasks, to better delineate differential profiles.

7. Conclusions

Although PPA is a clinical syndrome mainly recognized by language impairments, emerging experimental works are revealing impairments in diverse socio-cognitive processes in these patients, in association with brain measures. Moreover, to better understand the socio-cognitive characteristics of PPA, these must be understood in relation to cognitive and language functioning in each of the three variants, relative to other closely related dementia groups.

Available evidence indicates that nfvPPA and svPPA patients show deficits in emotion recognition, ToM, and empathy, attributable to different underlying mechanisms. In nfvPPA, socio-cognitive deficits seem to be driven by perceptual and attentional dysfunction, and they prove intertwined with language impairments. Atrophy in insular and inferior frontal cortices would explain patients' difficulties in guiding attention to socially-relevant information, which can be overcome by increasing the salience of the task-stimuli. Note that inferences about nfvPPA are based on fewer empirical works in comparison to svPPA. Thus, ensuing conclusions must be taken with reservations due to their sometimes incipient empirical support.

In contrast, in svPPA, socio-cognitive deficits seem to be primary and more severe than in the other PPA variants, and they would be concomitant to, but independent of, language disturbances (i.e., semantic deficits). Deficits are evident when applying both explicit and implicit measures and may be associated with interoceptive impairments. The involvement of ATL and prefrontal regions (e.g., orbitofrontal cortex), together with damage in relevant white matter connections between these structures may explain the more pervasive deficits observed in svPPA, as well as anosognosia for their difficulties. This profile resembles that of bvFTD.

Also, evidence for lvPPA proves scant so far. While a few studies reported deficits in emotion recognition and empathy in this population, none has addressed ToM abilities, which is surprising considering that the main area of atrophy in these patients is left temporo-parietal junction, a region previously implicated in ToM performance. The neural correlates of social cognition in lvPPA have not been explored.

The exploration of more complex social cognition domains, the administration of ecological tasks, the combinations of different neuroscientific techniques, and the conduction of longitudinal studies could help to further specify the differential cognitive, linguistic, and socio-cognitive profiles in PPA variants.

8. Limitations

Two limitations must be acknowledged in this review. First, while most works adhere to current consensus criteria for PPA (Gorno-Tempini et al., 2011), some have followed other diagnostic guidelines (Brun and Passant, 1996; Gorno-Tempini et al., 2004; McKhann et al., 2001; Neary et al., 1998). While this could have resulted in possible inconsistencies across studies, the systematicity of findings (especially for nfvPPA and svPPA) highlights their robustness. Moreover, note that actual criteria for specific variants in some guidelines (Gorno-Tempini et al., 2011; Gorno-Tempini et al., 2004; Neary et al., 1998) are markedly similar, further reducing potential heterogeneity among reports. Second, note that various studies have been conducted by the same research groups. As confirmed by personal communications with the corresponding authors, this has resulted in partial overlap between some patient samples, especially in works published close in time. Although this may limit the strength and generalizability of some conclusions, the key patterns detected prove consistent throughout a wide time frame (from 2001 to 2018), attesting to their consistency. Nevertheless, future efforts should be made to assess our main conclusions via independent replication studies.

Conflict of interest

None to declare.

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Appendix A

Table A1
Group-based experimental studies.

Study	Sample (mean age; years of disease duration)	Social cognition tasks or questionnaires	Language and semantic processing assessment	Brain measures	Behavioral results	Neuroimaging results
Toller et al. (2018)	14 bvFTD (57.7) 29 AD (61.9) 20 PSP (68.9) 21 svPPA (62.1) 19 nfvPPA (66.3) 65 HC (68)	RSMS (informant version)	–	Resting state-fMRI (intrinsic connectivity)	bvFTD, svPPA, PSP < HC; AD, nfvPPA = HC in socioemotional sensitivity (RSMS score)	In the full sample and in HC alone: significant positive association between RSMS score and salience network connectivity Exploratory analysis in diagnostic subgroups did not reach statistical significance
Johnen et al. (2018)	31 bvFTD (64; 2.3) 21 svPPA (67; 2.8) 14 nfvPPA (68; 2) 27 AD (71; 2.1) 34 HC (68)	Mini-SEA- Emotion Recognition subtest	Language Aphasia Screening Test	–	All patient's groups < HC; svPPA < bvFTD in basic emotion recognition (Mini-SEA) Emotion Recognition significantly correlated with subscales for buccofacial apraxia	–
Marshall et al. (2018a)	10 bvFTD (67; 8.2) 6 RtvFTD (63.8; 6.5) 7 svPPA (65.9; 4.4) 9 nfvPPA (69.6; 4.6) 19 HC (68.8)	Recognition of basic emotional facial expressions in dynamic, naturalistic videos + HR reactivity	Letter fluency (F) Category fluency (Animals) WASI-Vocabulary BPVS GNT	VBM	All patient's groups < HC in emotion identification (no difference between patient's groups) Across the patient's cohort: emotion identification associated with semantic ability (BPVS) bvFTD and nfvPPA: attenuated HR response relative to HC and RtvFTD for all emotions averaged svPPA and RtvFTD: preserved HR responses when viewing facial emotions	Neuranatomical correlates of emotion identification in bvFTD: R dorsal ACC, L OFC, L ACC, R and L anterior insula Neuranatomical correlates of cardiac reactivity index in bvFTD: R dorsal ACC, L OFC; in nfvPPA: R posterior insula
Chen et al. (2018)	17 RSD (62.7; 2.4) 18 LSD (61.3; 3) HC (60.5)	RMET	Similarity test BNT Verbal fluency (Animals) Confrontation naming Single-word comprehension Object knowledge for low-frequency concepts Repetition Surface dyslexia Grammar processing	VBM	Both patient's groups < HC on ToM (RMET), with no difference between them LSD < RSD in naming and word reading	RSD: semantic deficits related to bilateral fusiform gyri and left TP LSD: semantic performance correlated with left fusiform gyrus
Kumfor et al. (2018)	19 bvFTD (62.7; 6.4) 12 LSD (64.9; 5.7) 20 HC (66.3)	Emotion recognition in isolated facial expressions (FAST) and body (context alone) Contextual effects (Emotion recognition in face embedded in body posture context)	SYDBAT- Naming, Comprehension Letter fluency	VBM	bvFTD = LSD < HC in emotion recognition (face and context alone) bvFTD = LSD = HC when faces were presented in a congruent context bvFTD < LSD = HC when faces were presented in an incongruent context bvFTD more likely to label the facial emotion as that portrayed by the context (while SD = HC) Performance in social cognition tasks did not correlate with SYDBAT	Categorization accuracy and abnormal contextual influence correlated with right parahippocampal gyrus/amygdala and left precentral gyrus
Marshall et al. (2018b)	13 bvFTD (66.2; 7.7) 6 RtvFTD (63.8; 6.5) 9 svPPA (66.1; 5.6) 9 nfvPPA (69.6; 4:7) 21 HC (69.1)	Recognition of facial emotional expressions in videos + EMG	Letter fluency (F) Categorical fluency (Animals) WASI-Vocabulary BPVS GNT	VBM	All patient's groups < HC in facial emotion identification accuracy bvFTD and nfvPPA (but not RtvFTD and svPPA) displayed significantly higher EMG reactivity on correct emotion identification trials	Neuranatomical correlates of emotion identification: In svPPA: L superior temporal gyrus, L supplementary motor area, L opercular IFG, L ACC, R fusiform gyrus In nfvPPA: L supplementary motor area, L opercular IFG Neuranatomical correlates of facial EMG reactivity: In svPPA: L and R parahippocampal gyrus

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Table A1 (*continued*)

Study	Sample (mean age; years of disease duration)	Social cognition tasks or questionnaires	Language and semantic processing assessment	Brain measures	Behavioral results	Neuroimaging results
						In nfvPPA: R primary visual cortex, R primary motor cortex, R supplementary motor area
Marshall et al. (2017)	16 bvFTD (65.8; 7.6) 7 svPPA (65.9; 4.4) 9 nfvPPA (69.6; 4.6) 19 HC (68.8)	RSMS-EX (informant version) in relation to IA (measured through a heartbeat counting task)	Letter fluency (F) Category fluency (Animals) WASI-Vocabulary BPVS GNT	VBM	svPPA < HC in IA nfvPPA > other patient's groups in sensitivity to others' emotions (RSMS-EX) bvFTD = svPPA in RSMS-EX Across the patient cohort, IA correlated significantly positively with RMS-EX, but not with BPVS, among other measures	In svPPA, IA significantly positively associated with gray matter volume in right amygdala, right anterior and posterior cingulate cortex and right insula
Gola et al. (2017)	14 bvFTD (59.7) 11 RtvFDT (59.7) 8 nfvPPA (68.4) 9 svPPA (63.9) 44 AD (65.5) 10 PSP (66.2) 34 HC (68.6)	Intentional emotional expression task-Verbal command, Picture imitation TASIT-EET IRI-EC	–	VBM	No patient's group showed impairment to intentionally express emotion on the basis of a verbal command bvFTD and rtvFTD showed impairment on intentional emotion imitation bvFTD, RtvFTD, svPPA, AD < HC in emotion recognition (TASIT-EET) nfvPPA = HC in TASIT-EET bvFTD, RtvFTD, PSP < HC in affective empathy (IRI-EC) nfvPPA, svPPA = HC in IRI-EC	Intentional emotional imitation deficits correlated with a rightward cortical atrophy pattern
Multani et al. (2017)	13 svPPA (64) 11 nfvPPA (68.7) 9 lvPPA (61.6) 32 HC (67)	TASIT-EET	WAB-Auditory word recognition subtest	DTI VBM	All PPA variants < HC on the emotion recognition (TASIT-EET), controlling for WAB auditory single-word comprehension svPPA < lvPPA on TASIT-EET lvPPA > nfvPPA on TASIT-EET (but not significant)	TASIT-EET performance correlated with GM volume in OFC and ATL, and with right uncinate fasciculus, superior longitudinal fasciculus and inferior longitudinal fasciculus integrity TASIT-EET performance was predicted primarily by the right uncinate fasciculus integrity
Shdo et al. (2017)	75 AD (61.3) 58 bvFTD (60.8) 42 svPPA (63.7) 28 PSP (66.9) 28 nfvPPA (66.1) 44 HC (68.7)	RSMS-EX (informant version) IRI-EC (informant version)	–	VBM	All patient's groups (except nfvPPA) < HC in affect sharing (RSMS-EX) bvFTD and svPPA < HC in emotional empathy (IRI-EC) nfvPPA = HC in IRI-EC	Affect sharing (RMS-EX minus IRI-EC) uniquely correlated with volume in R > l medial/lateral temporal lobe regions (including amygdala and insula) Prosocial motivation (IRI-EC minus RMS-EX) correlated with nucleus accumbens, caudate head, and IFG
Hazelton et al. (2016)	23 nfvPPA (68.5; 3.3) 16 lvPPA (67.3; 4.3) 22 HC (67.9)	Emotion Selection Task IRI-PT, EC, PD, FS (informant version) before illness / present time	SYDBAT-Naming, Semantic association, Comprehension, Repetition Letter Fluency	–	At present time: Both PPA variants < HC in emotion recognition (no difference between them), and in cognitive empathy (nfvPPA < HC in IRI-PT and nfvPPA, lvPPA < HC in IRI-FS); No effect of diagnosis in IRI-EC and IRI-PD Compared to pre-morbid functioning: Both PPA variants < IRI-PT and > PD, and nfvPPA < IRI-EC (in lvPPA, a non-significant trend was observed in IRI-EC) In nfvPPA: IRI-PT loss associated with facial emotion recognition and IRI-EC loss associated with carer burden (trend) In lvPPA: IRI-PT loss associated with visuospatial abilities and IRI-EC loss associated with carer burden Correlations between IRI subscales and subtests of SYDBAT did not reached significance	–

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Table A1 (*continued*)

Study	Sample (mean age; years of disease duration)	Social cognition tasks or questionnaires	Language and semantic processing assessment	Brain measures	Behavioral results	Neuroimaging results
Van Langenhove et al. (2016)	30 svPPA (63.6; 4.4) 22 nfvPPA (65.5; 2.3) 21 lvPPA (65.7; 3.5) 33 bvFTD (63.2; 4) 31 AD (61.6; 2.6)	CBI-R-Empathy loss subscale at baseline and 1-year follow-up	–	–	svPPA: most behavior disturbances characteristic of bvFTD (including empathy loss) at baseline and follow-up nfvPPA and lvPPA: No difference in behavioral symptoms at baseline, but at follow-up, empathy loss was significantly more pronounced in nfvPPA lvPPA: Prevalence and course of behavioral symptoms similar to AD	–
Binney et al. (2016a)	21 LsvPPA (61.5; 4.6) 12 RsvPPA (62.9; 3.75) 14 HC (66.6)	UCSF-Famous face naming, Famous face familiarity CATS-Face matching, Affect matching TASIT-EET, SI-M- Sincere, Sarcasm IRI-EC, PT (informant version)	BNT-15-item- Object naming Phonemic fluency Semantic fluency WAB-Speech fluency, Repetition, Sequential commands Dysarthria Rating Apraxia of Speech Rating PPVT-Word Comprehension Sentence/Syntax Comprehension PPT-Words, Pictures	VBM	Both groups: severe naming and single-word comprehension impairments and surface dyslexic errors but deficits significantly more profound in LsvPPA RsvPPA: greater difficulties in famous faces familiarity judgments and in matching facial expression of emotion Both patient's groups: emotion recognition deficits (TASIT-EET), with a near-significant difference with RsvPPA being worse at comprehending sarcasm (TASIT-SI M) Both patient's groups together exhibited diminished cognitive empathy (IRI-PT) with no differences between them (though RsvPPA scored lower and significantly differed from HC) No significant differences were detected on IRI-EC	Exception word reading impairments correlated with volume of a left lateral mid temporal region
Kumfor et al. (2016)	22 LSD (62.2; 4.1) 9 RSD (62.3; 4.3) 33 AD (65.1; 3.1) 25 HC (64.3)	Face and Emotion Processing Battery- Face Perception, Face Matching, Emotion Matching, Emotion Selection CBI	SYDBAT-Naming, Comprehension, Semantic association	Cortical thickness (annually)	At baseline: RSD < HC in the Face tasks (LSD and AD performed normally); Both SD groups < HC = HC in Emotion Matching task; All patient's groups < HC in Emotion Selection task Longitudinal changes: General cognition declined in all patients; Both LSD and RSD declined significantly faster than AD on the Emotion Selection task, and declined more than AD in SYDBAT measures	In SD patients: involvement of the contralateral hemisphere with disease progression LSD: progressive thinning in the right TP RSD: thinning in the OFC and ACC AD: thinning in bilateral posterior regions Emotion recognition (all groups) correlated with cortical thickness of the right fusiform, right TP and right medial OFC
Bejanin et al. (2016)	19 SD: 4RSD, 14LSD, 1bilateral (66.63) 36 Cognitive-HC (64.14), 39 Neuroimaging-HC (68.92)	Cognitive ToM: Visual-verbal false-belief task Affective ToM: RMET	MDRS-Concept subscale Literal fluency (P) Categorical fluency (Animals) Picture naming	VBM Resting state-fMRI (intrinsic connectivity)	Patients < HC in cognitive and affective ToM even when controlling for semantic memory (categorical verbal fluency) No difference between groups in the control condition of the false-belief task No difference between RSD and LSD in cognitive / affective ToM	Affective ToM correlated with left medial TP (amygdala, hippocampus and parahippocampus) Cognitive ToM correlated with medial PFC and parietal regions, as well as the right frontal operculum Decreased functional connectivity in patients, mainly between midline cortical regions and temporal regions, and functional isolation of left medial temporal regions
Cohen et al. (2016)	11 bvFTD (68; 5.3) 7 svPPA (64; 2.2) 6 nfvPPA (68; 5.7) 39 HC (68)	Art emotion test (valence matching task on abstract paintings) Facial emotion matching Ekman faces-adapted	BPVS GNT Polysyllabic word repetition Letter fluency Category fluency	VBM	All patient's groups: deficit of art emotion processing Performance on art emotion valence matching not significantly correlated with facial expression matching All patients with bvFTD, one patient with svPPA and two patients with nfvPPA showed a deficit on the adapted Ekman facial emotion identification test relative to HC norms	Impaired processing of emotion from art was associated with GM volume in right lateral occipital temporal cortex, overlapping the anatomical location of human V5

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Study	Sample (mean age; years of disease duration)	Social cognition tasks or questionnaires	Language and semantic processing assessment	Brain measures	Behavioral results	Neuroimaging results
Woolley et al. (2015)	79 bvFTD (60.7) 25 first-degree relatives of bvFTD (48.2) 18 nfvPPA (67.7) 21 svPPA (62.8) 31 PSP (66.9) 104 AD (61.5) 24 CBS (66.4) 90 HC (69.4)	Disgusting Behaviors TASIT-EET	–	VBM	bvFTD: Disgusting behaviors significantly more frequent than in other diagnostic groups except for svPPA bvFTD, svPPA, AD and PSP < HC in disgust and other emotions recognition (TASIT-EET), while nfvPPA = HC Subjects with disgusting behaviors were significantly more impaired at recognizing disgust and other emotions compared to patients without disgusting behaviors	The presence of disgusting behaviors and impaired recognition of disgust associated with less GM volume bilaterally in the ventral anterior insula (this relationship remained significant even when restricting analysis to bvFTD or svPPA) Impaired recognition of disgust was associated with decreased GM volume in the bilateral ventroanterior and ventral middle regions of the insula
Kamminga et al. (2015)	12 RSD (65; 4,2) 19 bvFTD (60.5; 4,3) 20 HC (65.8)	Face-Emotion Matching Task Emotion Selection Task Ekman 60 task Structured interview-Loss of empathy	Letter fluency (FAS) SYDBAT-Naming, Comprehension	VBM	Both patient's groups: preserved face-perception ability and impaired facial matching bvFTD < HC in Face Emotion Matching (while RSD = HC in this task) bvFTD and RSD < HC in selecting a specific emotion from distractors (Emotion Selection and Ekman 60) RSD: significant greater difficulties with language and prosopagnosia Both patient's groups: comparable levels of reduced empathy	In RSD, emotion processing dysfunction associated with right medial/lateral TP, compared to mainly left temporal, IFG, OFC in bvFTD
Balconi et al. (2015)	16 bvFTD (65.6) 12 nfvPPA (67) 14 AD (72.2) 20 HC (68.6)	Observe and evaluate affective pictures (IAPS) while autonomic parameters (SCR and HR) were recorded	Fluency-Phonemic, Semantic	VBM	All groups correctly scored valence; bvFTD overestimated both positive and negative cues, compared to AD and HC Regarding arousal rating, bvFTD and nfvPPA evidenced smaller differences between high/low arousing stimuli than AD and HC In bvFTD and nfvPPA: no correlation between valence/arousal ratings and autonomic responses, with HR and SCR changes unrelated to emotional categories Alterations of autonomic responses correlated with the severity of behavioral abnormalities	Emotional responsiveness (arousal/HR ratio) associated with atrophy of the left putamen In nfvPPA, a positive correlation was also found between GM volume of putamen and language performance (phonemic and semantic fluency tasks)
Piguet et al. (2015)	20 nfvPPA (68; 2.7) 18 lvPPA (66.3; 3.8) 21 HC (66.3)	Ekman 60	COWAT-Letter Fluency (FAS) SYDBAT- Naming, Repetition, Comprehension, Semantic association	Cortical thickness PiB-PET scan	nfvPPA < HC = lv-PPA in recognizing facial emotional expressions (Ekman 60) Deficits specific for negative emotions 87% of patients were correctly classified using emotion processing, episodic memory, and visuospatial ability as predictor variable (Regression analyses conducted independently from the performance on language tasks)	Distinct performance profiles reflect the different atrophy patterns: In nfvPA, atrophy in left anterior insular cortex may be related to emotion processing In lvPPA, lateral parietal and posterior cingulate atrophy may be associated with episodic memory deficits
Fletcher et al. (2015)	14 bvFTD (66; 8.8) 10 SD (65; 5.2) 12 nfvPPA (68; 4.8) 10 AD (66; 5.3) 26 HC (67)	Affective valence ratings for nonverbal sounds of varying emotional salience Pupillometry	BPVS Sound classification task	–	bvFTD, SD and nfvPPA showed reduced overall pupil reactivity to sound bvFTD, SD and AD showed altered coupling between autonomic (pupillary) responses and behavioral salience coding	–
Downey et al. (2015)	29 bvFTD (64; 7.8) 15 svPPA (65; 6.2) 37 HC (63)	TASIT-EET, Sarcasm	BPVS GNT	DTI- tract-based spatial statistics VBM	bvFTD and svPPA < HC in identifying canonical emotions (TASIT-EET), simple sarcasm and paradoxical sarcasm (with no difference between them) Verbal semantic comprehension ability (BPVS score) was controlled in TASIT analysis	Social cognition deficits associated with DTI alterations Emotion identification associated with anterior thalamic radiation and fornix; sarcasm identification associated with uncinate fasciculus VBM results implicated the right anterior TP

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Table A1 (*continued*)

Study	Sample (mean age; years of disease duration)	Social cognition tasks or questionnaires	Language and semantic processing assessment	Brain measures	Behavioral results	Neuroimaging results
						and OFC in sarcasm detection DTI associations were more consistent and only partly convergent with the VBM correlates
Hutchings et al. (2015)	16 bvFTD (64; 5.1) 15 SD (64; 3.3) 10 AD (66.2; 6) 17 HC (70.7)	FAST Socio-emotional questionnaire (SEQ-self and informant-rating)-Emotion recognition, Empathy	SYDBAT-Naming, Comprehension	VBM	SD and bvFTD < HC and AD on FAST bvFDT and SD patients were rated significantly lower in emotion recognition and empathy dimensions (SEQ) compared to HC and AD bvFTD patients overestimated their overall socio-emotional performance compared to SD, AD and HC SD overestimated their behavior compared to HC AD and HC presented a tendency to underestimate their abilities	bvFTD: informant rated SEQ overall score associated with left lateralized clusters of GM intensity, including the TP, left hippocampus, left amygdala, and left OFC SD: informant rated SEQ overall score significantly related to GM intensity in the left TP and bilateral hippocampi
Irish et al. (2014)	11 LSD (63.4; 5.2) 10 bvFTD (63.6; 4.9) 10 AD (66.8; 4.2) 14 HC (68)	Cartoon task-Physical, ToM IRI-PT, EC (informant version)	Letter fluency (FAS) SYDBAT-Naming, Comprehension	VBM	SD and bvFTD < HC in ToM, even when controlling for semantic comprehension (SYDBAT) IRI did not correlate with ToM bvFTD and SD < HC in IRI-PT and IRI-EC	ToM deficits in svPPA correlated with right fusiform, right inferior temporal gyrus, bilateral TP, bilateral amygdala, left OFC and left insula
Sollberger et al. (2014)	28 bvFTD (62.4) 16 svPPA (61.8) 4 nfvPPA (62) 23 AD (63.3) 12 CBS (66.8) 19 HC (71.3)	IRI-EC (subject-informant discrepancy score)	–	VBM	bvFTD and svPPA less empathic (IRI-EC) and less aware of their deficit (IRI-EC discrepancy score); They overestimated their level of empathic concern relative to informants' reports nfvPPA = HC in IRI-EC and EC discrepancy score	Overestimation of one's EC was predicted by right anterior paralimbic and associative temporal regions, and right posterior insula Underestimation of EC was not predicted by any brain region
Kumfor et al. (2013)	18 bvFTD (63.8; 3.9) 11 SD (62.4; 5.4) 11 nfvPPA (64.8; 2.2) 27 HC (64.3)	Ekman 60 Ekman Caricatures Face Matching Task	SYDBAT-Naming	VBM	bvFTD and SD performed poorer in the recognition of all negative emotions (Ekman 60); These deficits persisted even after increasing stimuli salience (Ekman Caricatures) nfvPPA showed deficits in anger, fear and sadness (disgust preserved); Manipulation in Ekman Caricatures reduced the difficulties	Fear recognition associated with the right amygdala, hippocampus, and ACC Disgust recognition associated with the left insula and left TP Anger recognition was associated with the left middleTsuperior temporal gyrus Sadness recognition was associated with the left subcallosal cingulate
Couto et al. (2013)	12 bvFTD (69.8) 10 nfvPPA (64.9) 18 HC (69.8)	Face recognition Facial emotion recognition RMET	Naming Phonological fluency Semantic fluency	VBM	nfvPPA showed impairments in face recognition, a trend to misrecognize emotions and a significant deficit in ToM (RMET) bvFTD showed deficits in emotion recognition and ToM Loss of executive functions, language, and semantic memory may partially explain deficits in nfvPPA	Face recognition related to right insula and bilateral fusiform (nfvPPA) Emotion deficits associated with fronto-insular cortex (bvFTD), right TP and bilateral insula (nfvPPA) ToM impairments correlated with fronto-insular cotex (bvFTD) and right insula/TP (nfvPPA)
Irish et al (2013)	10 RSD (68; 4.2) 12 LSD (64.9; 5.1) 20 HC (67.7)	Ekman 60 task TASIT-EET IRI-PT, EC, PD, FS (informant version) CBI	SYDBAT-Naming, Comprehension Verbal fluency (FAS)	–	LSD < HC in the recognition of all negative emotions (Ekman 60) and surprise; Preserved recognition of happiness RDS < HC in the recognition of all basic emotions (Ekman 60); and < lSD for the recognition of anger and happiness Deficits were not fully accounted for perceptual processes (facial matching) and semantic processing (naming) In TASIT, both SD groups showed impairments for the recognition of negative emotions and surprise RSD < lSD in affective empathy (IRI-EC) In the combined group, social cognition measures correlated with behavioral changes on the CBI	–

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Table A1 (*continued*)

Study	Sample (mean age; years of disease duration)	Social cognition tasks or questionnaires	Language and semantic processing assessment	Brain measures	Behavioral results	Neuroimaging results
Hsieh et al. (2013)	18 bvFTD (63.7; 3.8) 14 SD (64.3; 4.4) 18 AD (63.4; 4.2) 30 HC	IRI-PT, EC, PD, FS (patient and informant versions) Emotion Selection Task CBI-R	–	–	bvFTD: significant differences between patient and informant ratings for IRI-EC, PT and PD All patient's groups < HC in emotion recognition, with no differences between them SD: significant correlations between empathy loss and disease severity and behavior (CBI)	–
Miller et al. (2012)	17 bvFTD (61; 3.6) 12 LSD (62; 4) 20 AD (65; 3) 36 HC (65)	Ekman 60 Emotion Matching Task Emotion Selection Task	BNT-15 items Word-Picture Matching Task	–	All patient's groups < HC in all face emotion processing tasks (with no differences between them) Impaired performance of SD group in Ekman 60 and Emotion Selection was eliminated when covarying verbal/semantic component (BNT 15 and Word-Picture Matching) but deficit in Emotion Matching remained significant after covarying a perceptual control task (Face Matching)	–
Duval et al. (2012)	15 SD (64.27; 3.93) 36 HC (64.14)	Attribution of intention test False-belief task Eyes test Tom's taste Theory of mind scale: Cognitive subscale, Affective subscale (self-awareness assessment)	Literal fluency (P) Categorical fluency (Animals) Picture naming MDRS-Concept	VBM PET	SD < HC in cognitive ToM; Deficits not explained by a visual semantic disorder or a comprehension deficit (normal scores in the control conditions) SD < HC in both basic and complex emotions (affective ToM) SD patients estimated their affective ToM more negatively than HC but groups did not differed in cognitive ToM Correlations between ToM and language and cognitive tests become non-significant after false discovery rate control	Cognitive ToM impairment associated with left temporal atrophy and hypometabolism, as well as OFC and ACC Affective ToM related to abnormalities in temporal regions and amygdala
Hsieh et al. (2012b)	11 (L > R)SD (63.3) 12 AD (62.9) 20 HC (66.5)	Emotion recognition in unfamiliar musical tunes Ekman 60	Animal Fluency BNT-15 item	VBM	Both patient's groups < HC in recognition of musical emotions (performance significantly worst in SD) SD < HC in in the recognition of positive and negative musical emotions, and < AD at recognizing musical negative emotions SD < HC = AD in facial emotion recognition	Labelling of emotions correlated with right anterior TP, amygdala and insula Musical emotion was also associated with left anterior and inferior TP Object naming correlated with anterior TP and anterior fusiform gyrus
Rohrer et al. (2012)	11 nfvPPA (72.8; 5.3) 5 lvPPA (4.5) 3 progranulin-associated aphasia (62; 4.3) 14 HC (68.2)	Emotional (affective) prosody Ekman 24	Acoustic processing of prosody components Linguistic prosody Warrington synonyms test	VBM	nfvPPA and lvPPA < HC in acoustic, linguistic and affective dimensions of prosody In patients (but not in HC), recognition of vocal emotions was significantly inferior to recognition of facial expressions	Emotional prosody processing (for negative emotions) was associated with a broadly overlapping network of frontal, temporal, limbic and parietal areas
Kumfor et al. (2011)	16 bvFTD (61.5; 3.5) 12 SD (62.4; 4.8) 13 nfvPPA (65.5; 2.5) 37 HC (64.6)	Ekman 60 Ekman Caricatures	BNT-15 item COWAT	–	bvFTD and SD < HC for all negative emotions nfvPPA < HC for sadness, anger and fear, but not disgust at Ekman 60 Performance improved with increased emotion intensity in bvFTD and nfvPPA groups (except for fear in nfvPPA) Intensity of emotion did not change performance in SD In SD, results suggest sufficient word knowledge to comprehend the task to some extent	–

(*continued on next page*)

Table A1 (*continued*)

Study	Sample (mean age; years of disease duration)	Social cognition tasks or questionnaires	Language and semantic processing assessment	Brain measures	Behavioral results	Neuroimaging results
Omar et al. (2011a)	16 bvFTD (64.7; 6.9) 10 (L > R)SD (62.4; 4.6) 21 HC (67)	Recognition of emotions from music, facial expressions (Ekman 60) and nonverbal vocal sounds Benton facial recognition Famous faces	Synonyms comprehension	VBM	bvFTD and SD showed deficits in the recognition of canonical emotions Both patient's groups (as well as HC) scored highest for emotion recognition from faces, followed by voices, and music	All groups: emotions from music correlated with insula, OFC, ACC, medial PFC, TP, parietal cortices, amygdala and mesolimbic system Recognition of emotions from faces correlated with left lateral OFC cortex and bilateral insula Recognition of emotions from voices did not correlated with any brain region
Omar et al. (2011b)	19 fvFTD (66.7) 13 tvFDT: 12 SD (63.5) 22 HC (65.5)	Ekman 24	Object Decision Test Synonyms Test Picture word matching	VBM	Both patient's groups < HC in emotion recognition (Ekman 60), with no differences between them tvFTD < bvFTD and HC in famous faces identification and in language tasks (Synonyms Test and Picture word matching)	For the combined group, performance on famous face identification correlated with right anterior fusiform gyrus volume; Performance on recognition of anger correlated with posterior insula
Eslinger et al. (2011)	12 bvFTD 7 nfvPPA 7 SD 16 HC	IRI-PT, EC, PD, FS (patient and informant versions) Cartoon Predictions Theory of Mind	–	VBM	bvFTD only: Difference between self and caregivers' ratings in total empathy score nfvPPA and SD: no significant discrepancies from their informants	In bvFTD, reduced PT was related to bifrontal and left anterior temporal atrophy, while EC was related to right medial frontal atrophy
Rankin et al. (2009)	20 bvFTD (60) 11 SD (63) 4 nfvPPA (66.3) 27 AD (59.2) 6 CBD (67) 9 PSP (66.3) 13 HC (61.8)	TASIT-EET, Sincere, Simple Sarcasm CATS-Emotional Prosody Discrimination, Name Prosody Discrimination	BNT Phonemic Fluency (FAS) Semantic fluency (Animals)	VBM	bvFTD, svPPA, PSP < HC in emotion recognition (TASIT-EET), while nfvPPA and AD = HC in this task All groups = HC in the TASIT-Sincere condition Only SD < HC on TASIT-Sarcasm condition, while they outperformed HC in their ability to correctly respond to control questions, suggesting adequate word comprehension for the task Patients failing the Sarcasm recognition task also performed worse on dynamic emotion recognition (TASIT-EET), confrontation naming, semantic fluency, and verbal recognition memory, and had more neuropsychiatric disturbances	Simple Sarcasm score (controlling for Sincere score) correlated with the bilateral TP, bilateral parahippocampal gyri, right middle temporal gyrus, right superior frontal gyrus, and caudate
Rankin et al. (2006)	30 FTD (59.5) 26 SD (65.5) 8 nfvPPA (58.1) 38 AD (65.9) 15 CBD (62.9) 6 PSP (65.5) 20 HC (67.9)	IRI-PT, EC (informant version)	–	VBM	FTD and SD patients showed significantly lower EC and PT scores than HC AD, nfvPPA, CBD and PSP groups had normal emotional empathy (IRI-EC), but showed a wider variation of performance in PT	Empathy total score correlated with right TP/fusiform gyrus and right medial IFG In FTD, empathy correlated with right subcallosal gyrus In SD, empathy correlated with right TP In AD, empathy did not correlate with any region of interest
Rankin et al. (2005)	18 FTD (59.78) 19 SD (67.57) 16 AD (75.56) 10 HC (71.96)	IRI-PT, EC, PD, FS	Phonemic fluency (D) Category fluency (Animals)	–	FTD and SD < AD and HC in empathy SD showed disruption of both emotional and cognitive empathy, whereas FTD showed only disruption of cognitive empathy 32% of the variance in PT score was predicted by Category Fluency, and 25% of the variance in FS was accounted for by Phonemic Fluency	–
Rosen et al. (2004)	13 fvFTD (64.6) 15 tvFTD: SD (64.6) 16 HC (64.7)	Facial Emotion Discrimination Facial Emotion Naming Facial Emotion Selection Facial Emotion Matching	Phonemic fluency Semantic fluency BNT-15 Sentence comprehension	–	Neither patient group showed impairment on the identity discrimination subtest Both patient's groups < HC in the recognition of all negative emotions and neutral facial expressions	–

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Table A1 (*continued*)

Study	Sample (mean age; years of disease duration)	Social cognition tasks or questionnaires	Language and semantic processing assessment	Brain measures	Behavioral results	Neuroimaging results
Rosen et al. (2002b)	9 tvFTD (66) 10 Behavioral-HC (60.3), 13 Neuroimaging-HC (66.8)	Facial Emotion Discrimination Facial Emotion Naming Facial Emotion Selection Facial Emotion Matching	BNT-15 Comprehension of syntactical structure Sentence repetition Phonemic fluency (D) Semantic fluency (animals)	MRI-region of interest analysis	fvFTD patients also showed a mild impairment compared to HC in recognizing happy faces tvFTD < HC in facial emotion comprehension across multiple subtests but preserved facial identity discrimination tvFTD showed greater deficits in the recognition of sadness, anger and fear than happiness Results survived when controlling for general cognitive and confrontational naming (BNT) impairment	Negative emotions (in particular sadness) and happiness were associated with right amygdala/OFC Left OFC was associated with anger

ACC: anterior cingulate cortex; AD: Alzheimer's disease; ATL: anterior temporal lobe; BNT: Boston Naming Test; BPVS: British Picture Vocabulary Scale; bvFTD: behavioral variant frontotemporal dementia; CATS: Comprehensive Affect Testing System; CBD: corticobasal degeneration; CBI: Cambridge Behavioral Inventory; CBI-R: Cambridge Behavioral Inventory Revised; CBS: corticobasal syndrome; COWAT: Controlled Oral Word Association Test; DTI: diffusion tensor imaging; EMG: electromyography; FAST: Facial Affect Selection Test; fMRI: functional magnetic resonance imaging; FTD: frontotemporal dementia; fvFTD: frontal variant frontotemporal dementia; GM: gray matter; GNT: Graded Naming Test; HC: healthy controls; HR: heart rate; IA: interoceptive accuracy; IAPS: International Affective Picture System; IFG: Inferior frontal gyrus; IRI: Interpersonal Reactivity Index; IRI-EC: Interpersonal Reactivity Index - Empathic Concern subscale; IRI-FS: Interpersonal Reactivity Index - Fantasy subscale; IRI-PD: Interpersonal Reactivity Index - Personal Distress subscale; IRI-PT: Interpersonal Reactivity Index - Perspective Taking subscale; L: left; LSD: left-hemisphere predominant temporal atrophy - semantic dementia; LsvPPA: left-hemisphere predominant temporal atrophy - semantic variant primary progressive aphasia; lvPPA: logopenic variant primary progressive aphasia; MDRS: Mattis Dementia Rating Scale; Mini-SEA: Mini Social Cognition and Emotional Assessment; MRI: magnetic resonance imaging; nfvPPA: non-fluent variant primary progressive aphasia; OFC: orbitofrontal cortex; PFC: prefrontal cortex; PSP: progressive supranuclear palsy; R: right; RMET: Reading-the-Mind-in-the-Eyes Test; RSD: right-hemisphere predominant temporal atrophy - semantic dementia; RSMS: Revised Self-Monitoring Scale; RSMS-EX: Revised Self-Monitoring Scale - Sensitivity to the Expressive Behavior of Others subscale; RsvPPA: right-hemisphere predominant temporal atrophy - semantic variant primary progressive aphasia; RtvFTD: right temporal variant frontotemporal dementia; SCR: skin conductance response; SD: semantic dementia; svPPA: semantic variant primary progressive aphasia; SYDBAT: Sydney Language Battery; TASIT: The Awareness of Social Inference Test; TASIT-EET: The Awareness of Social Inference Test - Emotion Evaluation subtest; TASIT-SI-M: The Awareness of Social Inference Test - Social Inference - Minimal subtest; ToM: theory of mind; TP: temporal pole; tvFTD: temporal variant frontotemporal dementia; UCSF: University of California San Francisco; VBM: voxel-based morphometry; WAB: Western Aphasia Battery; WASI: Wechsler Abbreviated Scale of Intelligence.

Table A2
Case studies.

Study	Sample (mean age; years of disease duration)	Social cognition tasks or questionnaires	Language and semantic processing assessment	Brain measures	Behavioral results	Neuroimaging results
Henry et al. (2014)	1 RSD: JT, female (67; 5) 32 Neuroimaging-HC	IRI-PT, EC, PD, FS (informant version) 1st and 2nd year since diagnosis	WAB	MRI	Significant decreases in cognitive aspects of empathy (IRI) over time, including PT and FS, and decrease in emotional empathy (EC)	Spreading asymmetric atrophy (right greater than left) over a three-year period With disease progression, atrophy extended to additional right, then left cortical regions, including posterior and inferolateral temporal cortex and the insula; Frontal lobe involvement remained relatively mild The pattern of atrophy at autopsy mirrored that identified with MRI and white matter degeneration (around anterior/inferior temporal cortex)
Lindquist et al. (2014)	3 SD: EG, male (70; 2) FZ, male (64; 3) CP, female (53; 3) 44 HC	A sorting task to assess spontaneous emotion perception and not emotion labeling per se	Domains assessed: Verbal fluency, Visual confrontation naming, Auditory word picture matching, Phonological, morphological and syntactic processing, Comprehension, Semantic access from pictures	MRI	Each patient presented with anomia and semantic memory deficits together with normal intellectual abilities, executive function, and visuospatial ability. No patient showed agnosia or prosopagnosia Patients spontaneously perceived pleasant and unpleasant expressions on faces, but not discrete emotions such as anger, disgust, fear, or sadness	Patients presented relatively focal left TP atrophy
Michel et al. (2013)	1 SD: CM, male (60; 2) 29 Neuroimaging-HC (61.4) 5 ToM assessment-HC (61.2)	A battery of non-verbal ToM tasks (Attribution of Intentions, Knowledge States and False Beliefs to Others) IRI-PT, EC, PD, FS (informant version) before illness / present time	Domains assesses: Verbal fluency, Presemantic Processing, Word Production, Word Comprehension, Nonverbal Semantic ability, Reading Aloud, Writing to Dictation	MRI- Volume- and surface-based analyses PET	CM showed a totally spared performance in his ability to attribute mental states (intentions, knowledge, and beliefs) to others IRI score revealed significant changes on the PD subscale	CM presented with massive atrophy of the left TP with the right temporal relatively unaffected
Calabria et al. (2009)	1 SD: CMR, female (67; 1.5)	IRI-PT, EC, PD, FS (informant version) before illness / present time Ekman 60-standard, modified	Domains assessed: Naming, Reading, Writing, comprehension, Picture naming	MRI	Lower IRI-PT and FS than before the illness onset, but preserved affective empathy Impairment in the recognition of all basic emotions (Ekman 60-standard version) In the Ekman 60-modified version (picture-picture matching task), CMR only correctly matched all faces depicting happy emotions	Left temporal lobe atrophy
Perry et al. (2001)	3 RtvFTD: A, male (52) C, male (74) D, male (73) 1 LtvFTD: B, male (65) 10 Behavioral-HC 12 Neuroimaging-HC (66.8)	Facial affect discrimination, Facial affect naming, Emotional prosody discrimination, Prosodic affect naming IRI-PT, EC, PD, FS (informant version) Facial expression (Facial Action Coding System)	Verbal fluency (FAS) California Card Sorting Test Naming Pyramids and Palm Trees Test	MRI	LsvPPA – Case B: severe loss of semantic memory but normal emotional processing; no significant empathic change; normal facial movements in expressing positive emotion; intact social interaction RsvPPA – Case A: impairment in naming both facial emotional expressions and emotional prosody, marked loss of empathy; frozen facial expression; abnormal social interaction	All subjects except case B had predominant atrophy in the right temporal lobe

HC: healthy controls; IRI: Interpersonal Reactivity Index; IRI-EC: Interpersonal Reactivity Index - Empathic Concern subscale; IRI-FS: Interpersonal Reactivity Index - Fantasy subscale; IRI-PD: Interpersonal Reactivity Index - Personal Distress subscale; IRI-PT: Interpersonal Reactivity Index - Perspective Taking subscale; LtvFTD: left temporal variant frontotemporal dementia; MRI: magnetic resonance imaging; PET: positron emission tomography; RSD: right-hemisphere predominant temporal atrophy - semantic dementia; RtvFTD: right temporal variant frontotemporal dementia; SD: semantic dementia; ToM: theory of mind; TP: temporal pole; WAB: Western Aphasia Battery.

Table A3
Diagnostic guidelines used to classify PPA variants in the reviewed articles.

Diagnostic guideline	PPA variant		
	nfvPPA	svPPA / SD	lvPPA
Gorno-Tempini et al. (2011)	17	26	4
Gorno-Tempini et al. (2004)	3	1	1
Mckhann et al. (2001)	1	4	none
Neary et al. (1998)	3	13	none
Brun and Passant (1996)	none	1	none

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