





# Empathy In Neurodegenerative Diseases: A Systematic Review

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**Introduction:** Empathy, in its affective and cognitive components, is a crucial interpersonal ability. It is broadly studied in the field of psychopathology, whereas its study in the neurodegenerative diseases is relatively recent. Existing literature, though, focused on a reduced subset of considered diseases, which often found a compromise in empathy abilities. Organized knowledge about a more comprehensive set of diseases is lacking.

**Method:** The present PRISMA systematic review was aimed at collecting the current available literature concerning empathic alterations in adult patients affected by neurodegenerative diseases. It considered the different empathy components, evaluated existing patterns, the impact on patients' lives, and treatment considerations.

**Results:** Overall, the 32 retrieved studies describe a spread deterioration of empathic abilities in patients, with each disease displaying its own pattern of empathy functioning. Literature in this field is fragmented and of heterogeneous quality, and further studies are warranted to increase evidence of many preliminary results.

**Discussion:** In conclusion, we highlight the crucial importance of acknowledging empathy deficits in these diseases, showing their repercussion on both patients' and caregivers' quality of life, the establishment of a functional doctor-patient relationship, and the development of efficacious psychological intervention. These clinical approaches can be enriched by the knowledge of the spared abilities of patients affected by neurodegenerative diseases.

**Keywords:** neurodegenerative diseases, empathy, mentalizing, doctor-patient relationship, psychological intervention, quality of life

## Plain Language Summary

Empathy is a complex construct that can be studied in its affective and cognitive perspectives. These two components seem to have distinct neural correlates. Although the focus of scientific literature on this phenomenon has drastically increased in the last years, few systematic essays have offered a general overview about this construct in neurological diseases involving the central as well as the peripheral nervous system. Our integrative effort considered published literature in scientific databases in the last 30 years, aiming to examine articles that evaluated empathy dimensions in neurological patients. In detail, we underlined the compromised and spared empathic functions for each disorder. Moreover, we inspected the neural substrates compromised in these patients. Since empathy is crucial in both medical and psychological therapeutic relations, the main objective of our systematic review is to provide neurologists and clinical psychologists with an accurate perspective of the peculiarly compromised and/or spared functions in these patients. Our purpose is to provide those taking care of these patients with information useful in building a better working alliance and, in general, a better understanding of the peculiar psychological profile of these patients.

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## Introduction

### Rationale

Empathy is broadly studied in the field of psychopathology and brain lesions, whereas its study in the neurodegenerative disorders is relatively recent. Neurodegenerative disorders are characterized by progressive loss of selectively vulnerable populations of neurons, with the consequent alteration of physical and cognitive functions. Nonetheless, empathy deficits are often perceived more detrimental to quality of life than physical symptoms<sup>1</sup> and affect caregivers' quality of life as well.<sup>2</sup> In the last years, these studies have been collected in literature reviews,<sup>3–8</sup> systematic reviews,<sup>9–11</sup> and meta-analyses.<sup>1,12–17</sup> Existing literature, though, focused either on specific empathy components or a reduced subset of considered diseases.

### Empathy

Empathy is a multifaceted psychological construct that reflects the cognitive and emotional reactions of one individual to the observed and inferred experiences of another.<sup>18,19</sup>

Starting in the 1980s<sup>20,21</sup> and 1990s,<sup>22,23</sup> researchers begun the scientific investigation of empathy, through the development of validated instruments and the assessments of clinical populations. Since then, empathy has been confirmed as a crucial component of personal and clinical relationships, but the construct defied the researchers' effort of finding a common definition,<sup>22</sup> consequently hindering its measurement. A recent review,<sup>23</sup> indeed, reports the presence of a plethora of instruments aiming to measure empathy as a whole or in its different aspects, with each instrument referring to a different theoretical construct. While most developed measurement tools consist in questionnaires, recent studies are exploring further approaches in measuring empathy, for instance by assessing interpersonal physiological activity.<sup>24</sup>

Among the most solid models of empathy, Decety and Jackson<sup>18</sup> propose a general distinction between two main components. The first, affective empathy, refers to automatic and implicit processes such as mimicry and emotional contagion. The second, mentalizing or cognitive empathy, regards the recognition and understating of others' states and is itself composed of an affective and a cognitive component. This conceptualization is supported by broad neural evidence finding distinct areas throughout the Central Nervous System that underlie the different facets of empathy. Shamay-Tsoory<sup>25</sup> proposed an elegant and comprehensive neuroanatomical model integrating the neuronal and

functional components of empathy. According to this model, regions underlying the functions of affective empathy are the inferior frontal gyrus (IFG), inferior parietal lobule, anterior cingulate cortex (aCC), and anterior insula.<sup>25</sup> Conversely, cognitive empathy relies on the medial prefrontal cortex (mPFC), the superior temporal sulcus, the temporoparietal junction, and the temporal poles.<sup>25</sup> Further evidence toward Decety's and Jackson's distinction was recently reported by Sessa et al<sup>26</sup> who found that separate EEG event-related potentials were associated alternatively to affective vs cognitive empathy stimuli.

### Objective And Research Question

This work is set forth to systematically review the current available literature concerning empathic alterations in adult patients affected by neurodegenerative diseases, considering the different empathy components, and evaluate existing patterns, impact on patients' lives, and treatment considerations. Overall, the aim of the study is to provide a valuable guide for physicians and clinicians treating these patients, as well as a basis for future studies.

## Methods

### Search Strategy

Our search strategy was developed in accordance with PRISMA guidelines.<sup>27</sup> A systematic search of online databases using key phrases was conducted to identify cross-sectional studies published from January 1, 1988 to July 31, 2019. The choice of diseases to be included in the search terms was based on the manual by Angelini and Battistin.<sup>28</sup> Neurodegenerative diseases were selected based on two reasons, the first one being their high frequency in population. The second one being their potential impact, despite their lower frequency, on caregivers or physicians care (i.e., Alzheimer disease, frontotemporal dementia, Lewy bodies disease, Parkinson disease, prion disease, Huntington disease, chorea minor, ataxias, amyotrophic lateral sclerosis, primary lateral sclerosis, hereditary spastic paraparesis, spinal and bulbar muscular atrophy, and myotonic dystrophy). To the best of our knowledge, existing reviews focus only on the most common neurodegenerative diseases while systematic knowledge on the less common neurodegenerative diseases is lacking. Since, as we expected, fewer articles would be retrieved for less common diseases, we decided to consider a wide time-span in order to maximize the number of search results. Thirteen independent literature searches

were performed in Scopus, PubMed, and PsycINFO online databases, each using the word “empathy” in logical conjunction (“AND”) with each disease name. The complete list of disease keywords was: Alzheimer, Frontotemporal, Lewy, Parkinson, Prion, Huntington, Chorea Minor, Ataxia, Amyotrophic Lateral Sclerosis, Primary Lateral Sclerosis, Hereditary Spastic Paraparesis, Spinal and Bulbar Muscular Atrophy, and Myotonic dystrophy. Search areas for Scopus included the “title/abstract/keywords” for the neurological diseases set and the word Empathy. Last search was performed on August 1, 2019. Furthermore, relevant studies not resulting from the bibliographic search were included when found in the reference list of each retrieved article, as well as in the “cited by” section each article, in each database.

## Screening And Eligibility

Abstracts were reviewed for eligibility and only original research articles, written in English and published in international peer-reviewed journals, were considered. All eligible articles underwent a second in-depth inspection to check for the following inclusion criteria: assessing adult patients, empathy assessed through quantitative measures, performing a comparison with a healthy control group and being a cross-sectional study. Criteria are listed in Table 1.

In the case of multiple studies analyzing the same dataset with the same methodology, since including both articles might result in an overestimation of the results (i.e., duplication bias<sup>29</sup>), only the oldest publication was retained in the qualitative synthesis.

The whole search procedure, and the number of articles for each stage, is summarized in a PRISMA flow diagram (Figure 1). For all selection choices, a criterion of inclusiveness was preferred to a quality one, in order to report an exhaustive state of the art of the literature.

**Table 1** Summary Of Eligibility And Inclusion Criteria

Eligibility Criteria
From January 1, 1988 to July 31, 2019
Original research articles
Written in English
Published in international peer-reviewed journals
Inclusion criteria
Assessing adult patients
Empathy assessed through quantitative measures
Comparison with a healthy control group
Cross-sectional study

## Data Extraction

The following relevant information was extracted by one author (E.P.) from the retrieved articles: (a) type and number of participants; (b) type of empathy; (c) methods used; and (d) main results.

Given the paucity of retrieved studies for some diseases, no risk of bias assessment in individual studies was performed.

## Results

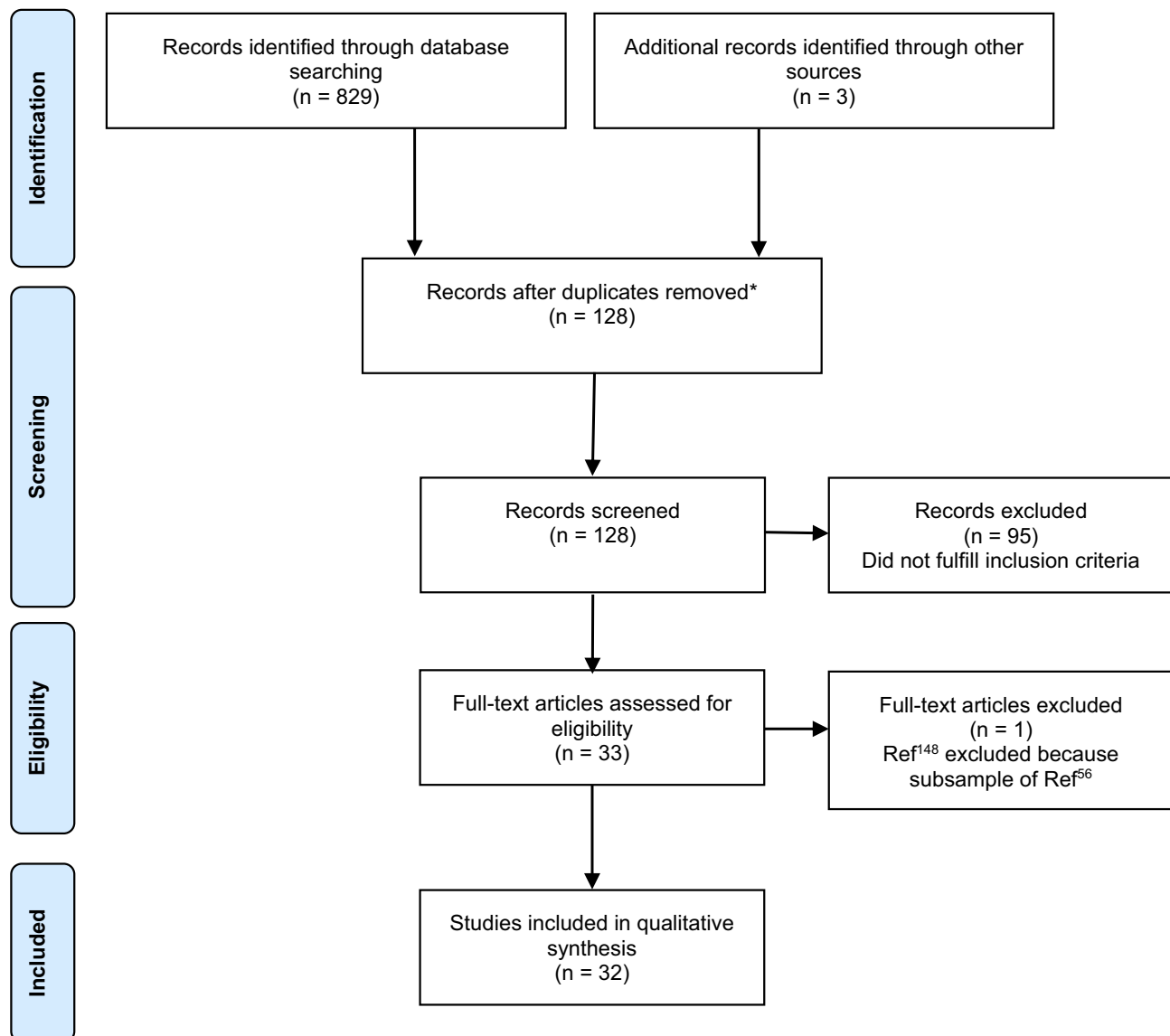
The number of retrieved articles for each disease is shown in Table 2. The total number of analyzed articles was 32. Table 3 reports the complete article list and the results summary. It should be noted that since five articles investigated more than one disease, they were retrieved from their respective literature searches but have been qualitatively analyzed only once.

## Primary Dementias

### Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of dementia with an approximate range of incidence of 500 to 7000–8000 per 100,000 person-years in people aged 65 or more.<sup>30</sup> AD is caused by an accumulation of amyloid plaques in neurons with a consequent widespread loss of gray matter (GM) and characterized by progressive cognitive decline with remarkably impaired episodic memory due to degeneration of medial temporal lobes.<sup>31</sup> Brain imaging in patients with AD shows predominant left-sided GM atrophy<sup>32</sup> and decreased metabolic activity especially in posterior cingulate cortex.<sup>33</sup>

In patients with AD, various studies reported the affective component of empathy as preserved while the cognitive one was impaired, in questionnaires rated by caregivers.<sup>34–37</sup> This dissociation has been detected also when patients self-rate their own empathy.<sup>38</sup> In contrast, some authors find no decrement in empathy as reported by caregivers.<sup>39</sup> Caregiver-rated questionnaires are the standard assessment approach in the presence of patients' frank cognitive impairment.<sup>40,41</sup> Visual recognition of emotional facial expressions, a process necessary in affective mentalizing, is generally preserved in AD patients, with the exception of fearful and ambiguous expressions;<sup>34,35</sup> in another face recognition task, using fMRI, left-lateralized decrease in neuronal activity was observed in patients with AD compared to healthy controls.<sup>42</sup> This peculiar pattern in mentalizing tasks is compatible with structural lesions present in patients with AD<sup>32</sup> that overlap areas considered as neural substrate of cognitive empathy.<sup>19,43</sup>



\*The following five articles were counted only once in the flow diagram because investigated more than one disease. Refs<sup>34,35,37,39</sup> investigated both Alzheimer's disease and frontotemporal dementia. Ref<sup>44</sup> investigated both Alzheimer's disease and Parkinson's disease.

**Figure 1** Flow diagram for qualitative systematic review of empathy functioning in neurodegenerative diseases.

In summary, both caregivers and patients with AD perceive affective empathy as spared, while deficits are reported for cognitive empathy. Surprisingly, the ability to recognize emotional facial expressions is not completely damaged. Neuroimaging data seem to support these conclusions. Eventually, caregivers' psychological distress might arise when they fail to acknowledge the subtle empathic deficits of their relatives with AD.<sup>44</sup>

### Frontotemporal Dementia

Frontotemporal dementia (FTD) is a group of heterogeneous dementias characterized by a loss in behavioral control (behavioral variant FTD, bvFTD) and/or loss in language abilities (semantic dementia, SD; progressive non-fluent aphasia, PNFA), associated with general degeneration in frontal and anterior temporal lobes.<sup>45</sup> FTD is less common than AD, with an incidence ranging 1.3–16.7 cases for 100,000 person-years

**Table 2** Summary Of The Number Of Articles Retrieved For Each Source Of Information, For Each Disease

	Database	Scopus	PubMed	PsycINFO	External Sources	Total	Used
Disease							
Alzheimer's disease		221	19	22	0	262	8
Frontotemporal dementia		192	71	57	1	321	14
Dementia of Lewy bodies		14	2	2	0	18	0
Parkinson's disease		71	12	10	0	93	2
Prion disease		1	0	0	0	1	0
Huntington's disease		24	11	8	0	43	6
Chorea minor		0	0	0	0	0	0
Ataxias		11	1	1	0	13	0
Amyotrophic lateral sclerosis		50	12	2	0	64	3
Primary lateral sclerosis		7	0	0	0	7	0
Hereditary spastic paraparesis		0	0	0	0	0	0
Spinal and bulbar muscular atrophy		1	1	0	1	3	2
Myotonic dystrophy		2	1	0	1	4	2
Total		594	130	102	3	829	37

as the age of onset increases, and the behavioral variant is the predominant presentation.<sup>46</sup> Specifically, in patients with bvFTD degeneration of paralimbic brain areas including mPFC, aCC and frontoinsula cortices are prominent.<sup>47,48</sup> Functional imaging presents frontal hypoperfusion.<sup>49</sup>

In patients with bvFTD, typical core symptoms are behavioral egocentrism and interpersonal difficulties which are reflected by their disrupted empathy and emotions.<sup>50</sup> Most studies report that both cognitive and affective components of empathy were rated lower in patients than in controls.<sup>37,51-53</sup> In contrast, a research on 18 patients with bvFTD found impairment only in cognitive empathy.<sup>39</sup>

Affective empathy assessed in patients with bvFTD through the electromyographical (EMG) reactivity for facial muscles implicated in negative emotional reactions (i.e., frowning) was not different from controls. Instead, patients displayed an augmented EMG reactivity in facial muscles implicated in positive emotions (i.e., smiling) irrespective of the presented facial emotional expression.<sup>52</sup> Patients with bvFTD scored low on visual and verbal tasks of vignettes depicting social situations, measuring the cognitive and the affective components of mentalizing.<sup>51,54,55</sup> More prominent deficits appeared in affective mentalizing.<sup>56,57</sup> Verbal abilities covaried with verbally presented mentalizing tasks indicating that deficits in mentalizing might be partly dependent on the verbal difficulties in some patients with bvFTD.<sup>51</sup> Moreover, patients with bvFTD could not identify and discriminate violations of social norms.<sup>51,55</sup> In tasks presenting faces with emotional expression, a measure of affective mentalizing, patients with bvFTD have been found consistently

impaired in selecting the appropriate emotional category for the presented face.<sup>52,55,58</sup> They struggled in deciphering ambiguous emotions on a videotape but correctly inferred well-defined positive or negative emotions.<sup>34</sup> In the context of empathy for pain, Baez et al<sup>55,59</sup> presented images of people inflicting pain to others which were rated by patients as having lower levels of intentionality compared to the ratings given by healthy controls. Patients with bvFTD were also less aroused, on a self-rating scale, by images of realistic situations with negative valence, while neutral and positive valence images were as arousing as controls.<sup>60</sup>

In the second manifestation of FTD, SD, patients are characterized by anterior temporal atrophy mostly localized in the left hemisphere<sup>61</sup> with consequent reduced metabolism.<sup>62</sup>

The overall view on empathy in SD shows inconsistencies. Rankin et al<sup>39</sup> found that both cognitive and affective empathy were perceived as impaired by caregivers, while Eslinger et al reported no deficits.<sup>53</sup> A group of patients with SD, who had right hemispheric lesions, presented poorer performance in a facial matching task for emotional expression compared to healthy controls.<sup>58</sup>

Other studies not reporting the FTD subtypes found an overall decrement in caregiver-perceived empathy of patients, with greater impairment of affective mentalizing.<sup>54,63</sup>

Lastly, patients with PNFA present disruption of large-scale neural networks centered in left inferior frontal and anterior superior temporal regions<sup>64,65</sup> and left frontal hypometabolism.<sup>66</sup> The retrieved evidence does not support empathy deficits for patients with PNFA.<sup>53</sup>

**Table 3** Review Results Sorted By Disease

References	Participants	Type Of Empathy	Methods		Results (“<” Lower Than Controls; “=” Equals To Controls; “>” Greater Than Controls)			
			Empathy evaluation	Cognitive deficits	Affective empathy	Cognitive empathy	Affective mentalizing	Cognitive mentalizing
<b>AD only</b>								
Sturm et al, 2013 <sup>36</sup>	64 AD, 62 MCI and 111 HC	Affective empathy	IRI other-rated	AD yes; MCI no	<	NA	NA	NA
Nash et al, 2007 <sup>38</sup>	20 AD and 20 HC	Cognitive and affective empathy	IRI self-rated	Yes	=	<	NA	NA
Lee et al, 2013 <sup>42</sup>	12 AD, all females, and 12 HC	Affective mentalizing	Facial emotion recognition	Yes	NA	NA	=	NA
<b>AD and FTD</b>								
Fernandez-Duque et al, 2010 <sup>34</sup>	8 AD, 9 bvFTD and 10 HC	Cognitive and affective empathy	Videotape for inference on thoughts and feelings, IRI other-rated	Yes	< (only for ambivalent video); IRI: bvFTD < AD	< (only for ambivalent video); IRI: bvFTD < AD	NA	NA
Narme et al, 2013 <sup>35</sup>	13 AD, 13 FTLD (bvFTD and SD) and 26 HC	Cognitive and affective empathy. Cognitive and affective mentalizing	IRI other-rated, Ekman 60, FPT, Yoni task	Yes	FTLD < AD < HC	FTLD < AD < HC	Ekman 60 (FTLD < AD; AD = HC); FPT (FTLD < HC); Yoni (FTLD & AD < HC)	FPT (FTLD & AD < HC); Yoni (FTLD & AD = HC)
Dermody et al, 2016 <sup>37</sup>	25 AD, 24 bvFTD and 22 HC	Cognitive and affective empathy. Affective mentalizing	Ekman 60, IRI other-rated	Yes	AD =; bvFTD <	AD <; bvFTD <	AD =; bvFTD <	NA
Rankin et al, 2005 <sup>39</sup>	16 AD, 37 FTLD (18 bvFTD and 19 SD) and 10 HC	Cognitive and affective empathy	IRI other-rated	Yes	AD =; bvFTD =; SD <	AD =; bvFTD <; SD <	NA	NA
<b>AD and PD</b>								
Martinez et al, 2018 <sup>44</sup>	25 AD, 17 PD and 42 HC	Cognitive and affective empathy. Affective mentalizing	EET of TASIT, IRI other-rated	Yes	NA	NA	<	NA
<b>FTD only</b>								

Lough et al, 2006 <sup>51</sup>	18 bvFTD and 13 HC	Cognitive and affective empathy. Affective mentalizing	Four mentalizing tasks, facial emotion recognition, IRI other-rated	Yes	<	<	<	<	<	NA
Hua et al, 2018 <sup>52</sup>	26 bvFTD and 25 HC	Cognitive and affective empathy. Emotional contagion. Affective mentalizing	Emotion recognition task, IRI other-rated for patients and controls	Yes	<	<	<	<	<	NA
Eslinger et al, 2011 <sup>53</sup>	12 bvFTD, 7 PNFA, 7 SD and 16 HC	Cognitive and affective empathy	IRI	Not reported	Self-rating =; Other-rating bvFTD <; PNFA =; SD =	Self-rating =; Other-rating bvFTD <; PNFA =; SD =	NA	NA	NA	NA
Eslinger et al, 2007 <sup>54</sup>	26 FTD (12 SOC/ EXEC and 14 APH) and 17 HC	Cognitive and affective empathy	GCPT, Happé, empathy questionnaire (self- and other-rated)	Yes	Self-rating =; Other-rating <; Other-rating OSC/EXEC < APH	Self-rating =; Other-rating <	NA	NA	NA	NA
Baez et al, 2014 <sup>55</sup>	37 bvFTD and 30 HC	Cognitive and affective empathy. Affective mentalizing	EPT, EET of TASIT, RMET	Yes	<	<	<	<	<	NA
Cerami et al, 2014 <sup>56</sup>	18 bvFTD and 36 HC	Cognitive and affective mentalizing	SET	Yes	NA	NA	NA	<	<	<
Caminiti et al, 2015 <sup>57</sup>	12 bvFTD and 30 HC	Cognitive and affective mentalizing	SET	Yes	NA	NA	NA	<	<	<
Kamminga et al, 2015 <sup>58</sup>	19 bvFTD, 12 right-damaged SD and 20 HC	Affective mentalizing	Three tasks on facial emotion recognition	Yes	NA	NA	NA	<	<	NA
Baez et al, 2016 <sup>59</sup>	26 bvFTD and 23 HC	Cognitive and affective empathy	EPT	Yes	<	<	<	NA	NA	NA
Oliver et al, 2015 <sup>60</sup>	24 bvFTD and 24 HC	Cognitive and affective empathy	MET	Yes	<	<	<	NA	NA	NA
<b>PD only</b>										

(Continued)

Table 3 (Continued).

References	Participants	Type Of Empathy	Methods		Results (“<” Lower Than Controls; “=” Equals To Controls; “>” Greater Than Controls)				
			Empathy evaluation	Cognitive deficits	Affective empathy	Cognitive empathy	Affective mentalizing	Cognitive mentalizing	
Narme et al, 2013 <sup>63</sup>	23 non-demented PD and 46 HC	Cognitive and affective empathy. Cognitive and affective mentalizing	IRI other-rated, Ekman 60, FPT, Yoni task	Yes	<	<	<	<	
<b>HD only</b>									
Trinkler et al, 2013 <sup>82</sup>	13 HD and 13 HC	Cognitive and affective empathy. Affective mentalizing	Facial emotion recognition (Ekman and Lundqvist), facial emotion expression (mimic), IRI and BEES self-rated	Yes	=	<	=	NA	
Adjerroud et al, 2016 <sup>83</sup>	23 manifest HD, 16 preclinical HD and 39 HC	Cognitive and affective empathy. Cognitive and affective mentalizing	Yoni test, self-rated IRI and BES	Manifest HD = Yes Preclinical HD = No	Manifest =; Preclinical =	Manifest <; Preclinical =	Manifest =; Preclinical =	Manifest <; Preclinical =	
Maurage et al, 2016 <sup>84</sup>	19 manifest HD, 17 preclinical HD and 36 HC	Cognitive and affective empathy	EQ self-rated	Yes	Manifest =; Preclinical =	Manifest <; Preclinical =	Manifest <; Preclinical =	NA	
Eddy et al, 2015 <sup>85</sup>	20 preclinical HD and 26 HC	Cognitive and affective empathy. Affective mentalizing	FPT, RMET, IRI	No	=	<	<	NA	
Baez et al, 2015 <sup>86</sup>	18 manifest HD, 19 relatives w/out genetic testing and 36 HC	Cognitive and affective empathy. Affective mentalizing	EPT, EET of TASIT, ad-hoc emotion recognition	Manifest HD = Yes Relatives = No	Manifest =; relatives =	Manifest <; relatives =	Manifest =; relatives =	NA	
Trinkler et al, 2017 <sup>87</sup>	28 HD and 24 HC	Emotional contagion, affective mentalizing	Facial emotion recognition (Ekman and Lundqvist)	Yes	<	<	NA	NA	
<b>ALS only</b>									



Cerami et al, 2014 <sup>95</sup>	20 non-demented ALS (4 cognitively and 2 behaviorally impaired), 56 HC	Cognitive and affective mentalizing	SET	80% no; 20% yes	NA	<	<	=
van der Hulst et al, 2015 <sup>96</sup>	33 non-demented ALS and 26 HC	Cognitive and affective empathy. Cognitive and affective mentalizing	Cognitive–Affective Judgement of Preference Test (similar to Yoni), IRI self- or other-rated	Yes for verbal tests, no for spatial tests	=	=	<	=
Watermeyer et al, 2015 <sup>97</sup>	55 non-FTD-demented ALS and 49 HC	Cognitive and affective empathy. Affective mentalizing	RMET, TASIT, Happé, IRI	Yes, but normal IQ	IRI =	IRI =; Happé <	=	NA
<b>SBMA only</b>								
Di Rosa et al, 2015 <sup>102</sup>	20 SBMA and 18 HC	Cognitive empathy and affective mentalizing	FPT, RMET	No	NA	<	=	NA
Marcato et al, 2018 <sup>103</sup>	64 SBMA and 78 HC	Affective empathy	Story with affective valence	No	>	NA	NA	NA
<b>DMI only</b>								
Labaryu et al, 2018 <sup>123</sup>	38 DMI and 38 HC	Cognitive and affective empathy. Affective mentalizing	POFA, FPT, TECA self-rated	No	=	=	<	NA
Serra et al, 2016 <sup>124</sup>	20 DMI and 18 HC	Cognitive empathy and affective mentalizing	RMET, modified Happé	No	NA	<	<	NA

**Abbreviations:** BEES: Balanced Emotional Empathy Scale;<sup>137</sup> BES: Basic Empathy Scale;<sup>138</sup> EPT: Empathy for Pain Task;<sup>139</sup> EQ: Empathy Quotient Questionnaire;<sup>140</sup> FPT: Faux-Pas Test;<sup>141</sup> GCPT: Guilford's Cartoon Predictions Test;<sup>42</sup> IRI: Interpersonal Reactivity Index;<sup>43</sup> MET: Multifaceted Empathy Test;<sup>144</sup> POFA: pictures of facial affect;<sup>45</sup> RMET: Reading the Mind in the Eyes Test;<sup>46</sup> SET: Story-based Empathy Task;<sup>36</sup> TASIT: The Awareness of Social Inference Test;<sup>47</sup> TECA: The Test of Cognitive and Affective Empathy.<sup>148</sup>

In summary, core deficit in patients with bvFTD is both affective and cognitive empathy. In particular, patients cannot discriminate between harmful versus non-harmful intentions and lack the capacity to respond with the appropriate facial expression to the emotions of other people, probably because they are unable to correctly identify the perceived emotion. Moreover, for patients with bvFTD, it is difficult to anticipate people's behavior in social context, especially if the context itself is ambiguous. Whilst patients are quite unaware of their deficits, these are well recognized by caregivers. Deficits similar to bvFTD seem present in patients with SD, although our knowledge is less thorough due to the limited amount of research performed so far. Finally, the only study retrieved on patients with PNFA does not indicate empathy deficits.

## Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disease after AD, with an incidence of 160 per 100,000 person-years people aged 65 years or older.<sup>67</sup> PD is caused by a loss of dopaminergic neurons in the pars compacta of the substantia nigra,<sup>68</sup> with hallmark motor manifestations being bradykinesia, rigidity, and rest tremor.<sup>69</sup> Non-motor symptoms are present as well, with cognitive deficits in executive functioning, memory, and neuropsychiatric symptoms that can lead to overt dementia in 70% of the cases.<sup>70–72</sup> Neuroimaging indicates a widespread GM atrophy in non-demented patients with PD, especially in right prefrontal cortex and bilateral temporal lobes.<sup>72</sup> In functional brain imaging, significant perfusion decrements were limited to the frontal lobe area in the same population.<sup>73</sup> When demented patients with PD are considered, GM atrophy spreads also to subcortical structures<sup>72</sup> and hypoperfusion to temporal and parietal areas.<sup>73</sup> The distinction between demented and non-demented patients is important because the two eligible studies resulting from the bibliographic search considered only patients suffering from PD without overt dementia.

Although empathy deficits are not a hallmark of patients with PD, according to Narme et al,<sup>63</sup> both cognitive and affective empathy are perceived as low in non-demented patients with PD by their caregivers. The assessment of cognitive empathy elicited from verbal stimuli resulted in a diminished accuracy in explaining faux pas, with overall mentalizing impairments. The poor level of stimuli comprehension caused by patients' cognitive alterations exaggerated the degree of the assessed empathic impairment.<sup>63</sup>

Similarly, the recognition for the visual presentation of emotional facial stimuli was diminished in patients with PD relatively to controls.<sup>44,63</sup> In this case, the performance might have been affected by patients' difficulty in processing facial stimuli.<sup>63</sup> Interestingly, caregivers who were less aware of patient's empathy difficulties displayed increased level of depression and burden.<sup>44</sup> Empathy deficits cannot be generalized as most studies were conducted on non-demented patients, who account for only about 30% of the PD population.

To sum up, patients with PD present deficits of both affective and cognitive empathy with brain atrophy and hypoperfusion that seem severe enough to make patients fail in empathic tasks of faux pas interpretation and facial emotion recognition, although not so detrimental as to give overt dementia. Areas important for affective and cognitive empathy<sup>25,43</sup> are those impaired in PD.<sup>72,73</sup> Although these deficits are not a hallmark of non-demented patients with PD, they are severe enough to be perceived by caregivers.

## Huntington's Disease

Huntington's disease (HD) is caused by an expansion of the CAG trinucleotide repeat in the *huntingtin* gene, exiting in choreiform movements, rigidity, cognitive impairments, and behavioral disturbances.<sup>74</sup> Epidemiology indicates an incidence spanning 0.05–0.8 cases per 100,000 person-years across all ages.<sup>75</sup> The hallmark structural changes in the brain of patients with HD occur in basal ganglia since the caudate nucleus decreases in volume.<sup>76,77</sup> More recent findings show that the neurodegenerative process of HD seems to impact also cortical structures brain-wise<sup>78,79</sup> and in particular reduces GM volume in pCC and sensorimotor cortex.<sup>80</sup> Glucose metabolism is reduced not only in striatum but is detected also in frontal and temporal cortices.<sup>81</sup>

Contrary to primary dementias, patients with HD usually present a degree of cognitive impairment ranging from null to mild. Empathy assessment can thus be performed through self-report questionnaires. These measures typically report no difference between patients and control groups,<sup>82–84</sup> with the exception of one study<sup>85</sup> that shows a decrement in both affective and cognitive empathy in 20 preclinical patients with HD. In another study, the affective component resulted spared when the patients were asked how bad they felt for a person in physical pain.<sup>86</sup> The mild cognitive impairment affecting patients with HD might cause difficulties in discriminating social emotional stimuli removed from the context. Indeed, in emotional face discrimination tasks, patients with manifest or

preclinical HD made more errors than controls indicating lower affective mentalizing.<sup>82,85–87</sup> Interestingly, though, this deficit vanished when the face was presented in a richer environment with contextual cues (i.e., a videotape).<sup>61</sup> The core deficit of HD patients appears to be in the domain of cognitive empathy, and especially cognitive mentalizing. In fact, performance dropped in tasks where the objective was to grasp the presence of embarrassing events or the intentionality of a painful action.<sup>85,86</sup> These results indicate a lack of understanding for accidental embarrassing or painful scenarios. Mentalizing deficits hold also with simpler stimuli for patients with manifest HD, while for patients with preclinical HD impairments are present in second-order mentalizing processes only.<sup>83</sup> Finally, Trinkler et al<sup>87</sup> measured facial EMG activity during passive view of emotional faces. Healthy controls automatically modulated EMG activity in the different facial muscles depending on the facial expression presented, while patients did not.

In conclusion, the structural and functional neural abnormalities of patients with HD<sup>76–81</sup> not only are reflected in motor and cognitive symptoms but extend to the interpersonal and empathic domains. Specifically, impairments in cognitive empathy and in the most automatic part of affective empathy might be a reflection of the neural areas which are commonly involved in those functions.<sup>19,43,88</sup>

In brief, in patients with HD, the affective component of empathy seems relatively spared. The core deficit seems to be in cognitive mentalizing. The deficits might be mitigated if patients are supported with sufficient contextual cues and a richer social environment.

## Neuromuscular Diseases

### Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) has an incidence of 2.16 cases per 100,000 person-years.<sup>89</sup> Etiology is largely unknown<sup>90</sup> and degeneration of upper and lower motor neurons in ALS pathology results in symptoms such as weakness, muscle atrophy, slurred speech, and dysphagia.<sup>90</sup> Extra-motor manifestation of cognitive impairment lays on a continuum, from 35–40% showing no deficits whatsoever to 50% of the patients with ALS showing mild cognitive impairment, and a 10–15% reaching criteria for diagnosis of FTD.<sup>91</sup> Cognitive deficits are associated with mild-to-severe psychological symptoms, as well as suicidal ideation.<sup>92</sup> Structural neuroanatomical investigations detected GM reduction in motor areas, in left IFG and in left superior temporal gyrus.<sup>93</sup> Heterogeneity of cognitive impairments is

reflected by decreased metabolism in the frontal areas extending bilaterally to the parietal regions for patients with cognitive impairments, while for patients without cognitive impairments, metabolism was lower in the left superior frontal gyrus.<sup>94</sup> Research on empathy commonly studies patients with ALS without comorbid dementia, although about 30–35% of the sampled patients suffer from cognitive or behavioral impairments. Affective empathy and cognitive mentalizing seem relatively preserved in patients with ALS<sup>95–97</sup> with only a subsample of van der Hulst et al<sup>96</sup> showing deficits, and to which patients are unaware of. Lack of awareness that becomes evident in the comparison between self-report questionnaires and caregivers' reports.<sup>96</sup> Another common finding is a marked deficit in affective mentalizing assessed through inference of mental characteristics of fictitious characters.<sup>95–97</sup> But in this case, patients seem aware of the deficit according to van der Hulst et al.<sup>96</sup> In a different task, showing faces and interaction of real people, Watermeyer et al<sup>97</sup> found no deficits in patients with ALS, indicating spared affective and cognitive mentalizing.

In summary, the drive to share other people's feelings and to resonate with them (i.e., affective empathy) seems spared in patients with ALS. Patients show predominantly affective and cognitive mentalizing deficits that might be a consequence of the neural structures typically involved in this disease<sup>93,94</sup> and that are classically linked to empathy functioning in healthy individuals.<sup>43</sup> Although impairment in cognitive empathy seems pervasive, according to the reviewed studies, it mostly derives from a subset of patients. Specifically, van der Hulst et al<sup>96</sup> observed that 61% of the participating patients were free from cognitive empathy deficits whatsoever. Similarly, the other two studies retrieved indicate that only 5–18% of the patients with ALS have severe deficits compared to controls.<sup>95,97</sup> Deficits in cognitive mentalizing disappear when stimuli are more ecological. Interestingly patients were aware of their affective mentalizing deficits.

### Spinal And Bulbar Muscular Atrophy

Spinal and bulbar muscular atrophy (SBMA), also known as Kennedy's disease, is a rare genetic disease with an incidence of 0.19 cases per 100,000 person-years in the male population.<sup>98</sup> It has classically been considered as a lower motor neuron disease, but now it is better described as a multisystem disease.<sup>99</sup> Common clinical manifestations are heterogeneous and manifest through muscle weakness and endocrine dysfunctions<sup>100</sup> due to androgen receptor insensitivity caused by genetic mutation.<sup>101</sup> Patients with

SBMA display null<sup>102,103</sup> to mild<sup>104–106</sup> cognitive deficits. Neuroimaging studies indicate cerebral involvement in patients with SBMA who show a subtle reduction of GM and white matter in brainstem, primary motor cortex, and frontal areas.<sup>107,108</sup> Accordingly, reduced metabolic activity is present in frontal areas.<sup>109</sup>

Recent scientific developments showed interest in the empathic abilities of patients with SBMA. Performance for affective mentalizing, in a facial emotion recognition task, resulted spared.<sup>102</sup> In a further task, employing a verbal assessment of cognitive mentalizing, patients' performance dropped compared to controls.<sup>102</sup> A surprising result was recently found by Marcato et al.<sup>103</sup> The authors reported a better performance than healthy controls in a prose memory task with emotional/affective valence, in a large sample of patients suffering from SBMA and without signs of cognitive impairment. The result that cognitive mentalizing is impaired in a context of relative preservation of cognitive functions has been hypothesized to derive from the specific pattern of subtle frontal lobe impairment. While classical neuropsychological tests are not able to detect the slight changes in frontal cognitive functions, cognitive mentalizing deficits could be detected with more fine-grained tests<sup>110</sup> thanks to the association between cognitive empathy and executive functions.<sup>111</sup> It was hypothesized that the better performance in the affective prose memory test derived from a possible protective role of androgen receptors deficit for the emotional aspects. Research shows that a single testosterone administration in females impairs their capacity to infer emotion and mental states of others.<sup>112</sup> Indeed, testosterone has a role in mediating sexual dimorphism and several behaviors and attitudes,<sup>113,114</sup> and in males, it is one of the most common androgens. Baron-Cohen<sup>115</sup> formalized this concept in his Empathizing-Systemizing theory, based on the observation that women show on average a stronger drive to empathize than men.

In conclusion, the deficit of androgen receptors might lead patients with SBMA to a surprisingly enhanced, or at least spared, ability to connect with others via more affective routes. Conversely, the subtle metabolic and structural alterations in frontal cortical areas might be a possible cause for the inability of patients with SMBA to infer the intentions of others. This ability, indeed, highly depends on the correct functioning of frontal brain areas.<sup>25,43</sup>

## Myotonic Dystrophy Type 1

Myotonic dystrophy type 1 (DM1) is the most common adult-onset muscular dystrophy with an incidence ranging 28.9–44.6 per 100,000 person-years.<sup>116</sup> DM1 is caused by an autosomal-dominant GTC-repeat expansion<sup>117</sup> and is a multisystem disease with symptoms ranging from muscle weakness, cardiovascular dysfunctions, and endocrine abnormalities, up to cognitive deficits.<sup>118</sup> Patients with DM1 do not display a unique cognitive phenotype, rather it lays on a continuum ranging from no deficits to specific clusters of dysfunctions,<sup>119</sup> probably because of the high variability in the neural structures involved. For example, Romeo et al<sup>120</sup> found two patterns of brain involvement: a diffuse white matter decrease in temporal and insular areas, and a focal to diffuse white matter decrease in fronto-parietal areas. About half of the participants had no white matter atrophy at the time of investigation. Similarly, some authors point to deficits in functions subserved by fronto-temporal areas such as language and executive functions,<sup>121</sup> while others reported deficits in cognitive flexibility and visuoconstructive ability subserved by fronto-parietal areas.<sup>122</sup>

A group of patients with DM1 with normal IQ level was tested in their affective empathy as well as their affective and cognitive parts of mentalizing.<sup>123</sup> Authors found that self-reported empathy was comparable to that of healthy controls (both cognitive and affective), as was the performance on a verbal cognitive mentalizing task. A contrasting result emerged from the work by Serra et al.<sup>124</sup> The authors investigated cognitive empathy in a group of 20 patients suffering from DM1, with normal IQ and no cognitive impairment. Patients underperformed controls in a verbal cognitive mentalizing task, also performing poorly in a facial emotion recognition task. Their brains showed abnormal disconnections within temporal and temporo-occipital regions,<sup>124</sup> areas classically deputed to mentalizing.<sup>43</sup>

To conclude, patients with DM1 presented self-reported empathy comparable to that of controls. Some deficits emerged in cognitive empathy, but there is no consensus about which subcomponent of mentalizing is more impaired. Further studies are needed for a cohesive picture about the empathy specificities of DM1 patients and to generalize their relations to the neural structures involved.

## Discussion

### Summary Of Main Findings

This study represents the most comprehensive systematic review on empathy alterations in neurodegenerative

disorders. While other literature review efforts were recently published, this systematic review provides a more inclusive list of considered diseases and makes explicit distinction between different empathy components.<sup>18</sup>

Overall, the retrieved studies describe a spread deterioration of empathic abilities in neurological patients. In general, each disease displays its own pattern of empathy functioning. Affective empathy seems the most variable component. Patients with either AD, HD, ALS, or DM1 show a preservation of this domain; on the contrary, it is clearly impaired in those who suffer from FTD or PD, while in patients with SBMA, it seems surprisingly enhanced. Regarding cognitive empathy, there is a general impairment in all diseases, with patients suffering from HD, ALS, or DM1 showing only minor deficits. While not all studies make explicit distinctions between empathy subcomponents, available evidence shows that affective mentalizing is preserved in patients with SBMA, slightly impaired in those with AD, HD, or ALS, and clearly impaired in those who suffer from FTD, PD, or DM1. Cognitive mentalizing is unimpaired in patients with ALS, minor deficits are found in those with AD or SBMA, while the function is markedly impaired in those who suffer from FTD, PD, or HD. In accordance with the literature taken into consideration, compromised and preserved components of empathy turned out to be substantially consistent with the neurological impairment peculiar for each disorder.

As highlighted by the literature on the measurement of empathy,<sup>23</sup> it is interesting to note that this systematic review confirms the great variability in instruments used, as can be seen in Table 3. Its limiting consequences will be debated in the Limitations section. Although our search included papers published in the last 30 years, the oldest article retrieved was published in 2005. The relative recency of this literature is comparable to broader trends in patient care. Today's consensus<sup>125</sup> is that a positive doctor–patient relationship is a cornerstone of efficacious medical intervention. A good relationship is associated with patient compliance with treatments, perception of care and, ultimately, clinical outcome.<sup>126</sup> Research in this field, though, has mostly focused on the *doctor's* empathy, showing that physicians presenting higher levels of empathy are able to promote a more efficacious doctor–patient relationship.<sup>127</sup> An efficacious relationship, though, requires the active involvement of both the doctor and the patient<sup>128</sup> and is strongly influenced by the patients' characteristics as well:<sup>129</sup> a particularly crucial matter in

the case of neurodegenerative diseases where these functions are often compromised.

Although, to the best of our knowledge, there is currently no publication investigating the influence of the patient's empathy in the doctor–patient relationship, our results lead to the reasonable hypothesis that the broad spectrum of empathy alterations in neurodegenerative disorders may be an obstacle to efficacious clinical relationships. The knowledge of the peculiar alteration of each disease could prove of great importance to clinicians, who may tailor their communication strategies in a person-centered manner, according to the capacity of each patient to develop trust towards the medical team, and consequently increase the chances of patients' compliance with medical procedures.<sup>126</sup>

The European Academy of Neurology guidelines encourage a multidisciplinary team composed also of psychologists to take care of patients and caregivers, with the aim of improving their quality of life, psychological health and coping with other distressful feelings (e.g., loneliness).<sup>130–132</sup> Also regarding psychological interventions, clinicians' communication can be enriched by the knowledge of which abilities and resources are spared in a given patient. For instance, patients with preserved affective empathy may benefit from experiential treatments or strategies appealing to patient's feelings and emotions,<sup>133</sup> eventually informed by emerging interpersonal physiology techniques.<sup>134</sup> On the contrary, techniques promoting mentalizing abilities<sup>135</sup> might be more effective in patients with spared cognitive empathy. For example, in the case of AD where psychological intervention represents the first-line approach for most individuals' neuropsychiatric symptoms,<sup>136</sup> knowing that these patients are characterized by the preservation of affective empathy and a clear deficit in cognitive empathy may help in the development and delivery of efficacious treatments. In a recent study,<sup>2</sup> an explicitly tailored mind–body intervention proved particularly efficacious in improving anxiety and quality of life in patients with ALS, probably thanks to their spared competence in the affective domains of empathy.

## Limitations

Primarily, limitations of this review pertain to the limited number of studies performed in this area. As can be seen in Table 2, eligible studies ranged from 2 to 14 for each disease. Given that this interest in neurological patient empathy seems to be a new trend, it is somewhat expected that there are few studies in the literature, yet evidence for most selected disorders cannot be considered conclusive.

There are also limitations with the individual studies reviewed. First, most studies were based on small samples. While this is a common limitation of studies on rare diseases, in most cases, the group-comparison analyses were probably underpowered. Second, empathy was evaluated through a broad range of measures and approaches and then by referring, in turn, to multiple empathy models. This variability in measurements adds to the individual variability in empathic abilities of the patients considered. Thus, it limits the possibility of direct comparisons between the studies, and our cohesive picture of patients' deficits and residual components.

## Conclusions

In conclusion, the research on empathy alterations in neurodegenerative diseases is recent, heterogeneous, and describes a broad variability of deficits across different pathologies. Overall, the results highlight the importance of this field of study in helping patients and caregivers to cope with diseases and for the development of ad-hoc psychological strategies. Further studies should focus on potential positive alterations as in the case of SBMA.

## Abbreviations

aCC, anterior cingulate cortex; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; BEES, Balanced Emotional Empathy Scale; BES, Basic Empathy Scale; bvFTD, behavioral variant FTD; DM1, myotonic dystrophy type 1; EMG, electromyography; EPT, Empathy for Pain Task; EQ, Empathy Quotient questionnaire; fMRI, functional magnetic resonance imaging; IFG, inferior frontal gyrus; FPT, Faux-Pas Test; FTD, frontotemporal dementia; GCPT, Guilford's Cartoon Predictions Test; GM, grey matter; HD, Huntington's disease; IRI, Interpersonal Reactivity Index; MET, Multifaceted Empathy Test; mPFC, medial prefrontal cortex; PD, Parkinson's disease; PNFA, progressive non-fluent aphasia; POFA, pictures of facial affect; RMET, Reading the Mind in the Eyes Test; SBMA, spinal and bulbar muscular atrophy; SD, semantic dementia; SET, Story-based Empathy Task; TASIT, The Awareness of Social Inference Test; TECA, The Test of Cognitive and Affective Empathy.

## Data Availability

All data relevant to the study are included in the article.

## Author Contributions

AP and SM conceptualized the idea. AP and EP designed the article. EP acquired and analyzed the data. EP and JRK

wrote the main manuscript. AP, EP, and JRK interpreted the results. AP, JRK, and SM critically revised the manuscript for important intellectual content. All authors approved the final version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved.

## Disclosure

The authors report no conflicts of interest in this work.

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