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Yliranta, Aino; Jehkonen, Mervi : Limb and face apraxias in frontotemporal dementia : A systematic scoping review.

1. INTRODUCTION

Frontotemporal dementia (FTD) refers to a family of neurodegenerative syndromes characterised by early behavioural and cognitive alterations. FTD is among the most common early-onset dementias, along with Alzheimer's disease and vascular dementia (Vieira et al., 2013).

The current clinical criteria for FTD distinguish four clinical variants (Gorno-Tempini et al., 2011; Rascovsky et al., 2011). The behavioural variant of FTD (bvFTD) exhibits prominent socio-emotional and dysexecutive changes, while the three linguistic variants present with primary progressive aphasia (PPA). In the nonfluent or agrammatic variant of PPA (nfvPPA), speech fluency and grammar degrade first. The semantic variant of PPA (svPPA) begins with a multimodal impairment of conceptual understanding, while the logopenic variant of PPA (lvPPA) starts with short-term memory deficit and phonological speech errors (Gorno-Tempini et al., 2011).

One-third of clinical cases are familial, and the majority of these are caused by mutations in the *chromosome 9 open reading frame 72* (*C9orf72*), *progranulin* (*GRN*) and *microtubule-associated protein tau* (*MAPT*) genes (Greaves & Rohrer, 2019). The underlying molecular pathologies locate FTD on a wider spectrum of frontotemporal lobar degeneration (FTLD) syndromes that include corticobasal degeneration and progressive supranuclear palsy (Seelaar et al., 2011). Alzheimer's type beta amyloid pathology is occasionally found in the behavioural, nonfluent and semantic variants and appears in a majority of logopenic cases (Bergeron et al., 2018; Meeter, Kaat, Rohrer, & van Swieten, 2017). LvPPA is therefore sometimes classified as an atypical linguistic variant of Alzheimer's disease (Rogalski et al., 2016).

The variants are challenging to diagnose clinically because in over 90% of FTD patients, behavioural and linguistic symptoms co-occur (Harris et al., 2016). Furthermore, all variants share cognitive features, such as executive dysfunction or word finding difficulties, with Alzheimer's disease. Although neuropsychological profiling is an essential part of diagnostic decision making, the traditional neuropsychological tests of episodic memory and executive functions only moderately differentiate between FTD and Alzheimer's disease (Hornberger, Piguet, Graham, Nestor, & Hodges, 2010; Ramanan et al., 2017).

Apraxias are common early findings in neurodegenerative disorders. They are defined as disorders of performing and understanding skilled actions and movement independent of sensory, cognitive or

elementary motor deficits (Cubelli, 2017; Osiurak & Rossetti, 2017) and manifest themselves as the gradual loss of, for instance, tool use ability or comprehension of social gestures. Apraxias may appear independently in various body parts, but the most commonly investigated are those involving the upper limbs and face. Alzheimer's disease patients show defective execution of hand movements and action-related knowledge from early disease stages (for a review, see Lesourd et al., 2013). Limb apraxia is considered the hallmark of corticobasal degeneration and appears in mild forms in combination with face apraxia in progressive supranuclear palsy (Zadikoff & Lang, 2005).

The process models of apraxia assume separate, interacting systems for conceptual understanding of objects and actions and for producing those actions (Osiurak & Le Gall, 2012). Understanding perceived actions and object function depends on the conceptual system that comprises semantic knowledge of actions, gestures and objects; mechanical knowledge about objects; and sensorimotor knowledge about the manipulation of objects (Buxbaum & Saffran, 2002; Goldenberg & Hagmann, 1998). During clinical assessment, the patient is asked to evaluate the meaning or quality of gestures, to match tools and actions by function or semantic content and to select and use appropriate tools for the mechanical task at hand. Tool tasks may require manipulation in isolation (i.e., single tool use) or with its relevant object (i.e., real tool use). The tasks may involve multiple steps, and serial actions are sometimes investigated with picture sequencing tasks. Mechanical knowledge is tested through tasks requiring technical reasoning (mechanical problem solving, novel tool use and alternative tool selection).

The production system translates the conceptual representations into motor commands. This system involves knowledge of body topography in self and others (Buxbaum, Giovannetti, & Libon, 2000; Goldenberg & Hagmann, 1997) and the visuospatial abilities needed to evoke and execute actions (Stamenova, Roy, & Black, 2014). Production praxis is assessed by observing how fluently and precisely the patient executes gestures, movements, facial expressions or limb positions. The task is performed either on verbal command or on imitation, and the patient is asked to demonstrate meaningful and meaningless gestures as well as to pantomime the use of imaginary tools. Pantomimes are considered to be sensitive tasks necessitating semantic and sensorimotor knowledge in addition to movement production ability (Jax, Rosa-Leyra, & Buxbaum, 2014).

Face apraxia serves as an umbrella term for the inability to voluntarily control facial expressions, movements or instrumental actions (Pizzamiglio, Caltagirone, Mammucari, Ekman, & Friesen, 1987). Apraxia in the lower face (mouth, tongue and throat) is specifically referred to as buccofacial or nonverbal oral apraxia to distinguish it from apraxia of speech (Bizzozero et al., 2000). Apraxia of

speech solely disrupts speech production (Whiteside, Dyson, Cowell, & Varley, 2015) and belongs to the diagnostic features of nfvPPA (Gorno-Tempini et al., 2011). The exact neural sites underlying face apraxia are unclear.

Functional imaging data from healthy adults specify limb praxis networks for tool use and for intransitive gesture imitation (Ishibashi, Pobric, Saito, & Lambon Ralph, 2016; Lesourd et al., 2018; Reynaud, Lesourd, Navarro, & Osiurak, 2016). The two networks share left-sided activation peaks in the inferior and superior parietal lobe, intraparietal sulcus and precentral gyrus as well as bilateral peaks in the middle/inferior frontal gyri. The tool network additionally involves bilateral posterior temporo-occipital structures and premotor cortices (Ishibashi et al., 2016; Reynaud et al., 2016), while the imitation network specifically recruits superior/premotor aspects of the frontal cortex, insula and basal ganglia (Lesourd et al., 2018). Posterior portions of the left middle and inferior temporal gyri and lateral occipital areas participate in the processing of contextual and familiar tool knowledge (Ishibashi et al., 2016; Reynaud et al., 2016).

As for pantomiming, review evidence from healthy brains suggests a left-distributed network with most reliable activations in inferior and superior parietal lobes, intraparietal sulcus, inferior temporal gyrus, premotor cortex and inferior and middle frontal gyri (Niessen, Fink, & Weiss, 2014). The documented posterior temporo-occipital activations are scarce, although lesions in this region are reported to disrupt pantomiming gestures (Buxbaum, Shapiro, & Coslett, 2014; Hoeren et al., 2014). In brief, the production praxis relies on the bilateral dorso-dorsal stream involving superior fronto-parietal and the respective subcortical structures (Binkofski & Buxbaum, 2013). Conceptual knowledge and action understanding relate to the more lateral dorso-ventral left-sided structures.

Although it has been suggested that apraxias are associated with nfvPPA (Snowden et al., 2011) and *GRN* mutation carriership (Devenney & Hodges, 2014), we lack a comprehensive picture of the frequencies and apraxia types that may characterise FTD variants. The patterns of early neural damage in the FTD variants partly overlap the praxis networks (Meeter et al., 2017). The structural and functional imaging data on bvFTD reveal changes in multiple frontal sites (orbital, dorsolateral and medial), insula and anterior cingulate, anterior temporal lobe, basal ganglia and, in some forms, the parietal lobe (Whitwell & Josephs, 2012). We therefore expect early impairment in imitation and pantomiming for this variant. The prominent pathology in the left inferior/dorsolateral frontal and insular structures typical of nfvPPA should result in a production deficit with a motor emphasis (Meeter et al., 2017). SvPPA shows early asymmetric anterior and inferior temporal lobe pathology later proceeding to the posterior temporal lobe (Meeter et al., 2017). The praxis deficit should restrict

itself to semantic/functional impairment but not appear very early in the disease. LvPPA exhibits left temporo-parietal junction atrophy (Meeter et al., 2017), a passage of the dorso-ventral stream previously suggested to participate in sensorimotor processing (Ishibashi et al., 2016). Thus, pantomiming, intransitive gesture production and tool-related action are expected to suffer.

We systematically reviewed the literature on limb and face apraxia findings to scope the existing knowledge of the following: (1) how frequent (prevalent) apraxias are in FTD, (2) whether the variants show distinct apraxia profiles that may enable clinical differentiation between the variants and from Alzheimer's disease and (3) how apraxias correlate to imaging findings in FTD.

2. METHODS

We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study. No part of our study procedures or analyses were pre-registered prior to the research being conducted.

We searched the literature for all study types addressing face and limb apraxias in FTD variants. The search was conducted in the Ovid Medline, PsycINFO and Scopus databases on 21 May 2019. We used the search terms *frontotemporal dementia*, *frontotemporal lobar degeneration*, *primary progressive aphasia*, *nonfluent variant*, *semantic variant* and *logopenic variant* combined with *apraxia* (for the detailed search strategy, see the Supplement) without language limitations. The following criteria were established before data analysis: To enhance the comparability of FTD diagnoses across studies, the publishing year range was set from 1998, when the first modern consensus criteria were established by Neary et al., to the present. We included all prospective and retrospective study types and case series with five or more participants. Studies were included if they reported a systematic assessment of limb or face apraxia and results on either deficit frequencies or group comparisons. The reference lists of the included full texts were searched for relevant records. We assessed the quality of case-control studies with the Newcastle-Ottawa Scale (Wells et al., n.d.) and cross-sectional studies with the AXIS Scale (Downes, Brennan, Williams, & Dean, 2016).

From the included articles, we extracted the following data: patient's diagnostic, genetic or pathologic status; age at examination for clinical samples; age at onset for genetic and pathologic samples; disease stage and duration at examination; praxis assessment methods; apraxia frequencies and group comparison results; and associations between apraxia and imaging findings. We contacted authors

for missing frequency data. We merged data from separate reports by the same authors (assuming they involved the same subjects) if the reports were published at proximate time points and the same assessment methods were applied. In these cases, weighted means and standard deviations were calculated for patient age, disease severity scores and disease duration.

3. RESULTS

The search resulted in 817 publications, of which 487 nonduplicates were screened based on title and abstract. Of the screened articles, 136 full texts were assessed for eligibility, and 10 additional reports were detected from reference lists. The reasons for and number of exclusions are presented in the flow chart (Figure 1). Finally, of the 46 articles obtained for data extraction, three were excluded because the diagnostic criteria were inaccurate or older than the 1998 consensus criteria. The quality scores for the articles are found in the Supplement.

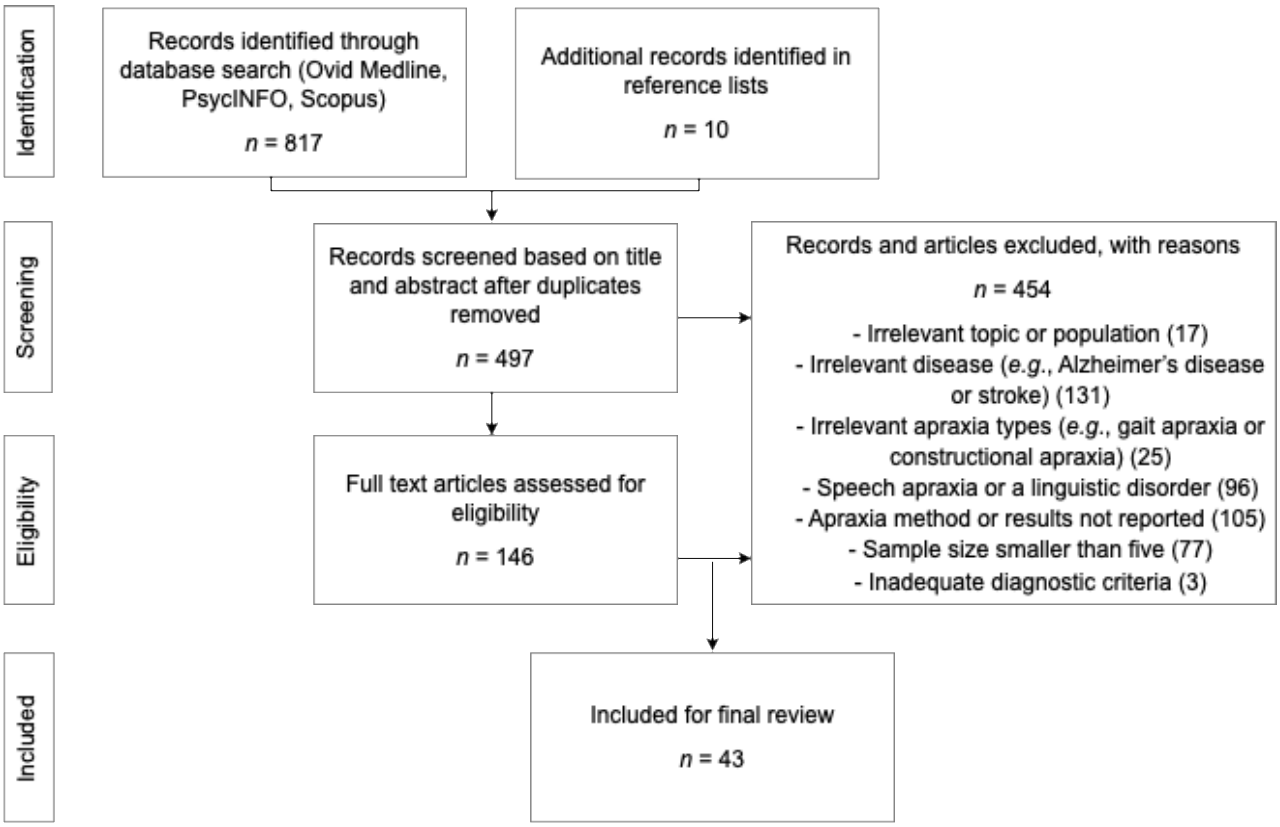

Figure 1. Flow chart of the literature search

3.1 Sample characteristics and assessment strategies

Several of the 43 articles included in the analysis were based on overlapping patient samples. We inferred from author lists and publishing years that the articles were based on 27 independent studies. Eighteen of these studies addressed clinical FTD variants (see Table 1 for details), and nine studies involved either genetically or proteinopathologically defined samples (Table 2). One of the genetic studies included presymptomatic mutation carriers (Bertrand et al., 2018). All clinical diagnoses conformed to the diagnostic principles published by Neary et al. (1998) or more recently by Gorno-Tempini et al. (2004, 2011), Mesulam et al. (2001, 2003) or Rascovsky et al. (2011). The diagnoses were adequately ensured, as specified in Supplement Tables 1 and 2. However, the representativeness of the cases and control participants was less accurately described.

Mean age at examination in the samples of clinical variants ranged from 61 to 73 years. The bvFTD groups were generally found at the lower end and the nfvPPA groups at the higher end of this range. The mean age at examination in the presymptomatic cohort was 42 years, and the mean age at onset in the genetic/pathologic samples was 60 years.

Disease severity was mild in most samples as measured by the Mini-Mental State Examination, Frontal Assessment Battery or Clinical Dementia Rating scale. However, two lvPPA groups and one svPPA group exhibited moderate disease severity (Hodges, Bozeat, Lambon Ralph, Patterson, & Spatt, 2000; Pawlowski et al., 2019; Rohrer, Ridgway, et al., 2010). Disease duration at examination averaged between 3.1 and 3.6 years across clinical variants.

In 10 studies, the praxis data were collected prospectively as a pat of a clinical neurological status examination or a neuropsychological screening (Croisile, Astier, & Beaumont, 2003; Floris et al., 2015; Gorno-Tempini et al., 2004; LeBer et al., 2007, 2008; Pickering-Brown et al., 2008; Rohrer, Paviour et al., 2010; Rohrer, Ridgway, et al., 2010; Schaeverbeke et al., 2018; Seelaar et al., 2011; van Langenhove et al., 2013). Retrospective patient record analyses were used in six studies (Ahmed, Baker, Thompson, Husain, & Butler, 2016; Chare et al., 2014; Mahoney et al., 2012; Rohrer et al., 2011; Shea, Ha, & Chu, 2015; Snowden et al., 2015), and multi-item praxis batteries in the remaining 11 studies. Descriptions of apraxia assessment methods and results were incomplete in most cross-sectional studies (Supplement Table 2).

3.2 Apraxia in the behavioural variant

For bvFTD, multi-item praxis batteries yielded limb apraxia frequencies of 70–95% (Cossini, Tabernero, & Politis, 2018; Gómez & Politis, 2011; Pawlowski et al., 2019; Politis, Rubinstein, & Tabernero, 2016). Remarkably lower frequencies were found in retrospective patient record analyses (10% and 23% by Ahmed et al. [2016] and Chare et al. [2014], respectively) and on neuropsychological screening (24% by LeBer et al. [2008]). Figure 2a shows the frequencies of bvFTD limb apraxia according to assessment strategy.

3.2.1 Limb apraxia in bvFTD

Imitation of hand and finger postures was compromised among bvFTD patients (Gómez, Politis, & Rubinstein, 2010; Johnen et al., 2015; Johnen, Brandstetter, et al., 2016; Johnen, Frommeyer, et al., 2016; Johnen, Reul, Wiendl, Meuth, & Duning, 2018; Politis et al., 2016). Tool pantomimes were affected in 52–88% of patients when assessed with multiple test items and visual stimuli (i.e., photographs of tools; Gómez et al., 2010; Politis et al., 2016; Reul, Lohmann, Wiendl, Duning, & Johnen, 2017). Half of the patients were impaired in gesture production on verbal command (Gómez et al., 2010; Politis et al., 2016), although in one study, the difference between the patient and healthy control group remained nonsignificant (Johnen et al., 2015).

A small minority of patients showed deficits in actual tool use, while 21–50% of patients failed to match tools correctly with objects or functions (Gómez et al., 2010; LeBer et al., 2008; Politis et al., 2016). Gesture recognition and matching was impaired in up to half of patients (Gómez et al., 2010; Politis et al., 2016).

3.2.2 Face apraxia in bvFTD

Face apraxia was assessed with three different batteries and repeatedly reported as a distinctive impairment in bvFTD (Johnen et al., 2015; Johnen, Frommeyer, et al., 2016; Johnen et al., 2018; Pawlowski et al., 2019; Siri, Benaglio, Frigerio, Binetti, & Cappa, 2001), whether assessed with imitation or facial gesture production tasks. Facial expressions with emotional content were particularly challenging for these patients to imitate (Johnen, Frommeyer, et al., 2016). As an exception, the patient record analysis by Chare et al. (2014) suggested face apraxia to be less common than limb apraxia (frequency of 8% vs. 23%).

Table 1. Limb and face apraxia findings in the clinical variants of FTD

Study	No. of subjects	Age, mean (*SD*)	Disease stage; score, mean (*SD*); duration, years (*SD*)	Praxis assessment method and/or domain	Prevalence of apraxia
I Behavioral variant					
Ahmed et al., 2016	20	62 (8)	duration 2.6 (2.2)	patient record analysis (tool pantomime, hand imitation, multistep pantomime)	10 %
Chare et al., 2014	66	61 (9)	not reported	patient record analysis (limb)	23 %
				patient record analysis (face)	8 %
Cossini et al., 2018; Politis et al., 2016	22-24	66 [1]	duration 4.6 (0.8)	BECA all domains	88-95 %
				tool pantomime (visual)	88 %
				gesture imitation (meaningful)	79 %
				gesture matching	54 %
				gesture production (verbal)	50 %
				function naming	50 %
				gesture imitation (meaningless)	46 %
				gesture recognition	33 %
				tool use	33 %
				tool-object matching	21 %
Gómez et al., 2010; Gómez & Politis, 2011	24-40	64 (9)	MMSE 26 (3)	BECA	84-90 %
				tool pantomime (visual)	84 %
				gesture imitation (meaningful)	70 %
				gesture production (verbal)	55 %
				gesture matching	48 %
				function naming	48 %
				gesture imitation (meaningless)	40 %
				tool use	28 %
				tool-object matching	26 %
				gesture recognition	25 %
				evaluation of function	3 %

Johnen et al., 2015; Johnen, Brandstetter, et al., 2016; Pawlowski et al., 2019; Reul et al., 2017	18-43	65 [1]	MMSE 25 (4) [1] FAB 12 (4) [1] duration 2.5 (1.4) [1]	CAS total score limb pantomime and imitation face pantomime and imitation	70 % 26 % 52 %
				IAT (limb imitation)	not reported
				MI (production of meaningful gestures on verbal command, limb imitation)	not reported
Johnen et al., 2018; Johnen, Frommeyer, et al., 2016	24-31	64 (8) [1]	MMSE 25 (4) [1] FAB 12 (4) [1] duration 2.5 (1.6) [1]	DATE (hand and finger imitation, tool pantomime, face imitation, oral emblems, pseudoword imitation)	not reported
Le Ber et al., 2008	22 GRN+	62 (7)	duration 3.3 (2.3)	meaningful gesture production and imitation tool use	23 % 5 %
Siri et al., 2001	14	70 (7)	MMSE 20 (6) duration 6.0 (5.0)	Ideomotor apraxia test by De Renzi (imitation of hand and finger movements and positions)	not reported
				Oral apraxia test by De Renzi (production of oral emblems)	not reported
II Nonfluent variant					
Adeli et al., 2013; Botha et al., 2014; Josephs et al., 2013	9-21	69 [1]	MMSE 27 [1] FAB 14 duration 2.8 [1]	WAB (meaningful gestures, pantomime of tool use, complex pantomimes; limb and face)	not reported
				oral emblems	78 %
Ahmed et al., 2016	7	67 (8)	duration 2.6 (2.1)	patient record analysis (tool pantomime, hand imitation, multistep pantomime)	57 %
Chare et al., 2014	16	70 (8)	duration 6 (2)	patient record analysis (limb) patient record analysis (face)	24 % 24 %
Croisile et al., 2003	9	73 (8)	MMSE 24 (4)	meaningful gestures, imitation of serial gestures	not reported

Gorno-Tempini et al., 2004	11	68 (8)	MMSE 26 (3) duration 4.4 (2.5)	neuropsychological screening (tool pantomime, meaningful gestures, buccofacial emblems)	not reported
Harris et al., 2018	12	71 (7)	duration 4.0 (2.0)	Manchester praxis screen (oral actions, facial gestures and pantomimes; limb gestures and pantomimes)	not reported
Johnen et al., 2018	14	68 (11)	MMSE 24 (5) FAB 10 (4) duration 2.0 (0.8)	DATE (hand and finger imitation, tool pantomime, face imitation, oral emblems, pseudoword imitation)	not reported
Pawlowski et al., 2019	15	70	MMSE 22 (5) FAB 11 (4) duration 1.8 (1.0)	CAS total score limb imitation and pantomime face imitation and pantomime	83 % 58 % 67 %
Rohrer, Paviour, et al., 2010; Rohrer, Ridgway, et al., 2010	14	72 (7) [1]	MMSE 24 (6) [1] FAB 10 (4) [1] duration 5.4 (2.1) [1]	The Queen Square Screening Test for Cognitive Deficits (limb)	40-75 %
Rohrer et al., 2010a, 2010b	16-24	70 (7) [1]	duration 5.3 (1.9) [1] MMSE 21 (7)	ABA-2 limb (pantomime of tool use, meaningful gestures) ABA-2 orofacial (meaningful and meaningless gestures)	40-44 % 69 %
Schaeverbeke et al., 2018	12	66	MMSE 25 (4) duration 4.2 (1.4)	neurological status examination (limb)	0 %
Tetzloff et al., 2018	11	69	FAB 13 duration 1.8	WAB (meaningful gestures, pantomime of tool use, complex pantomimes; limb)	not reported
III Semantic variant					
Ahmed et al., 2016	6	68 (8)	duration 1.6 (0.8)	patient record analysis (tool pantomime, hand imitation, multistep pantomime)	0 %

Baumard et al., 2016, 2018, 2019; Lesourd et al., 2016, 2017	13-16	67 (8) [1]	MMSE 23 (5) [1] FAB 13 (2) [1]	tool use tool-object selection and use mechanical problem solving functional/contextual matching pantomime of tool use recognition of tool use	63-69 % 46-63 % 13-31 % 69-75 % 69 % 23 %
Botha et al., 2014	5	65 (7)	duration 5.9 (5.1)	WAB (limb pantomime and gestures) oral emblems	not reported 40 %
Chare et al., 2014	31	65 (7)	duration 8 (3)	patient record analysis (limb) patient record analysis (face)	0 % 3 %
Gorno-Tempini et al., 2004	10	63 (6)	MMSE 23 (7) duration 4.0 (1.2)	neuropscyhological screening (tool pantomime, meaningful gestures, buccofacial emblems)	not reported
Harris et al., 2018	8	67 (3)	duration 3.6 (1.2)	Manchester praxis screen (oral actions, facial gestures and pantomimes; limb gestures and pantomimes)	not reported
Hodges et al., 2000	9	not reported	MMSE 16 (7)	gesture production and imitation, mechanical problem solving, tool use semantic matching of tools	not reported 89 %
Johnen et al., 2018	21	67 (9)	MMSE 22 (5) FAB 11 (3) duration 2.8 (1.9)	DATE (hand and finger imitation, tool pantomime, face imitation, oral emblems, pseudoword imitation)	not reported
Pawlowski et al., 2019	13	65	MMSE 23 (5) FAB 12 (3) duration 2.2 (1.0)	CAS total score limb imitation and pantomime face imitation and pantomime	80 % 90 % 70 %
Rohrer, Ridgway, et al. 2010	9	62 (9)	MMSE 23 (5) FAB 14 (2) duration 5.3 (1.2)	The Queen Square Screening Test for Cognitive Deficits (limb)	0 %
Schaeverbeke et al., 2018	5	63 (9)	MMSE 27 (3) duration 3.5 (4.3)	neurological status examination (limb)	0 %

IV Logopenic variant					
Ahmed et al., 2016	12	69 (9)	duration 2.2 (0.9)	patient record analysis (tool pantomime, hand imitation, multistep pantomime)	67 %
Adeli et al., 2013; Botha et al., 2014	26-41	66 (9) [1]	duration 3.2 (1.3) [1] MMSE 22 (6)	WAB (meaningful gestures, pantomime of tool use, complex pantomimes; limb and face)	not reported
				oral emblems	41 %
Chare et al., 2014	22	66 (8)	duration 9 (3)	patient record analysis (limb)	36 %
				patient record analysis (face)	0 %
Gorno-Tempini et al., 2004	10	72 (9)	MMSE 22 (5) duration 4.5 (0.8)	neuropscyhological screening (tool pantomime, meaningful gestures, buccofacial emblems)	not reported
Harris et al., 2018	13	70 (6)	duration 3.8 (2.2)	Manchester praxis screen (oral actions, facial gestures and pantomimes; limb gestures and pantomimes)	not reported
Pawlowski et al., 2019	13	65	MMSE 13 (6) FAB 9 (5) duration 1.8 (1.2)	CAS (pantomime of tool use, hand and finger imitation, face imitation)	not reported
Rohrer, Ridgway, et al., 2010	9	64 (7)	MMSE 16 (2) FAB 8 (2) duration 4.2 (0.9)	The Queen Square Screening Test for Cognitive Deficits (limb)	100 %
Teichmann et al., 2013	19	66 (9)	MMSE 21 (4) FAB 11 (3) duration 3.2 (0.6)	Mathieux-Laurent scale (meaningful gestures on verbal command, pantomimes, imitation of meaningless gestures)	53 %
V Mixed sample of clinical variants					
Shea et al., 2015	9 FTD	79	duration 3.0 (1.0)	patient record analysis	0 %

[1] = combined *M* and *SD* from several reports; ABA = Apraxia Battery for Adults; BECA = Batería de Evaluación Cognitiva de Apraxias; CAS = Cologne Apraxia Screen; DATE = Dementia Apraxia Test; FAB = Frontal Assessment Battery; IAT = Ideomotor Apraxia Test; MI = Münster Apraxia Items; MMSE = Mini Mental State Examination, WAB = Western Aphasia Battery.

Table 2. Apraxia findings in samples of genetic mutations and pathologic types of FTD

Study	No. of subjects	Age at onset, mean (*SD*)	Disease stage; score, mean (*SD*); duration, years (*SD*)	Praxis assessment method and/or domain	Prevalence of apraxia
Bertrand et al., 2018	41 *C9orf72*+ 39 *C9orf72*-	not available not available	presymptomatic	Batterie d'Evaluation des Praxies (finger imitation, imitation of meaningless gestures, production of meaningful gestures, pantomime of tool use)	37 % 10 %
Floris et al., 2015	9 *C9orf72*+ (FTD) 27 *C9orf72*- (FTD+PPA)	58[1] 67[1]	not reported	status examination (imitation of meaningful and meaningless limb gestures)	11 % 11 %
Le Ber et al., 2007	13 *PGRN*	60 (9)	duration 4.5 (1.8)	status examination (limb)	54 %
Le Ber et al., 2008	5 *GRN*+ (PPA)	60 (7)	duration 2.8 (1.9)	meaningful gesture production and imitation tool use	20 % 0 %
Mahoney et al., 2012	16 *C9orf72* (13 bvFTD, 3 FTD-MND, 1 nfvPPA)	55 (7)	not reported	patient record analysis (limb) patient record analysis (face)	57 % 19 %
Pickering-Brown et al., 2008	14 *PGRN* 17 *MAPT*	59 (5) 53 (6)	not reported	status examination (limb)	35 % 0 %
Rohrer et al., 2011	5 FUS	42 (9)	MMSE 25 (6)	patient record analysis (limb)	20 %
Seelaar et al., 2011	19 FTLD-TDP (6 GRN) 10 *MAPT*	57 (9) 50 (6)	duration 2.4 (1.6) duration 2.3 (1.3)	status examination (limb)	21 % 0 %
Snowden et al., 2015	15 *MAPT* 17 *GRN* 42 *C9orf72*	53 (6) 59 (6) 58 (8)	duration 6 (6) duration 3 (2) duration 3 (3)	patient record analysis (object knowledge / gestural praxis)	80% / 10% 7% / 33% 16% / 3%
van Langenhove et al., 2013	8 *MAPT* 27 *GRN* 26 *C9orf72* 69 no mutation, familial 145 no mutation, sporadic	57 (4) 60 (7) 55 (8) 63 (10) 64 (11)	not reported	status examination (limb)	0 % 19 % 0 % 4 % 6 %

[1] = median age; MMSE = Mini Mental State Examination.

3.2.3 Comparison with Alzheimer's disease

Based on patient records, only 10% of bvFTD patients exhibited limb apraxia as opposed to 69% of Alzheimer's disease patients (Ahmed et al., 2016). In more extensive studies, bvFTD groups outperformed Alzheimer's disease groups, particularly for hand and finger imitations (Gómez et al., 2010; Johnen et al., 2018; Pawlowski et al., 2019), although in three reports, this result did not reach statistical significance (Johnen et al., 2015; Johnen, Brandstetter, et al., 2016; Johnen, Frommeyer, et al., 2016). One study reported comparable group means (Siri et al., 2001).

Although bvFTD and Alzheimer's disease did not coherently differ in limb praxis, the severity of face apraxia enabled some researchers (Johnen, Frommeyer, et al., 2016; Johnen et al., 2018; Pawlowski et al., 2019; Reul et al., 2017) to discriminate the two diseases by subtracting face scale scores from limb scores. Alzheimer's disease patients obtained negative differences due to more severe limb apraxia than face apraxia, while in bvFTD, the score difference approached or exceeded zero. The determined subtraction cut-off showed a discrimination sensitivity of 74% and specificity of 93% (Johnen, Frommeyer, et al., 2016). In the same vein, oral apraxia was one of the four best discriminating neuropsychological features in the study by Siri et al. (2001).

3.3 Apraxia in the nonfluent variant

3.3.1 Limb apraxia in nfvPPA

Limb apraxia frequencies in nfvPPA varied mostly between 40% and 58% (Ahmed et al., 2016; Chare et al., 2014; Pawlowski et al., 2019; Rohrer, Paviour, et al., 2010; Rohrer, Ridgway, et al., 2010; Rohrer, Rossor, & Warren, 2010a, 2010b), with the exception of 0% in the 2018 study by Schaeverbeke et al. (Figure 2b). The impairment was generally more obvious than in bvFTD (Ahmed et al., 2016; Johnen et al., 2018) and comparable to that in lvPPA (Adeli, Whitwell, Duffy, Strand, & Josephs, 2013; Ahmed et al., 2016). Bimanual and serial pantomimes appeared to be more challenging than simple pantomimes and limb imitation (Adeli et al., 2013; Johnen et al., 2018).

NfvPPA differed from other clinical groups in two aspects. First, limb apraxia was less often accompanied by left parietal dysfunction (dysgraphia, dyslexia and dyscalculia) in nfvPPA (14%) compared to amnestic Alzheimer's disease (35%) and lvPPA (75%; Ahmed et al., 2016). Second, face apraxia predicted more severe limb apraxia in other variants of PPA but not in the nonfluent variant (Botha et al., 2014).

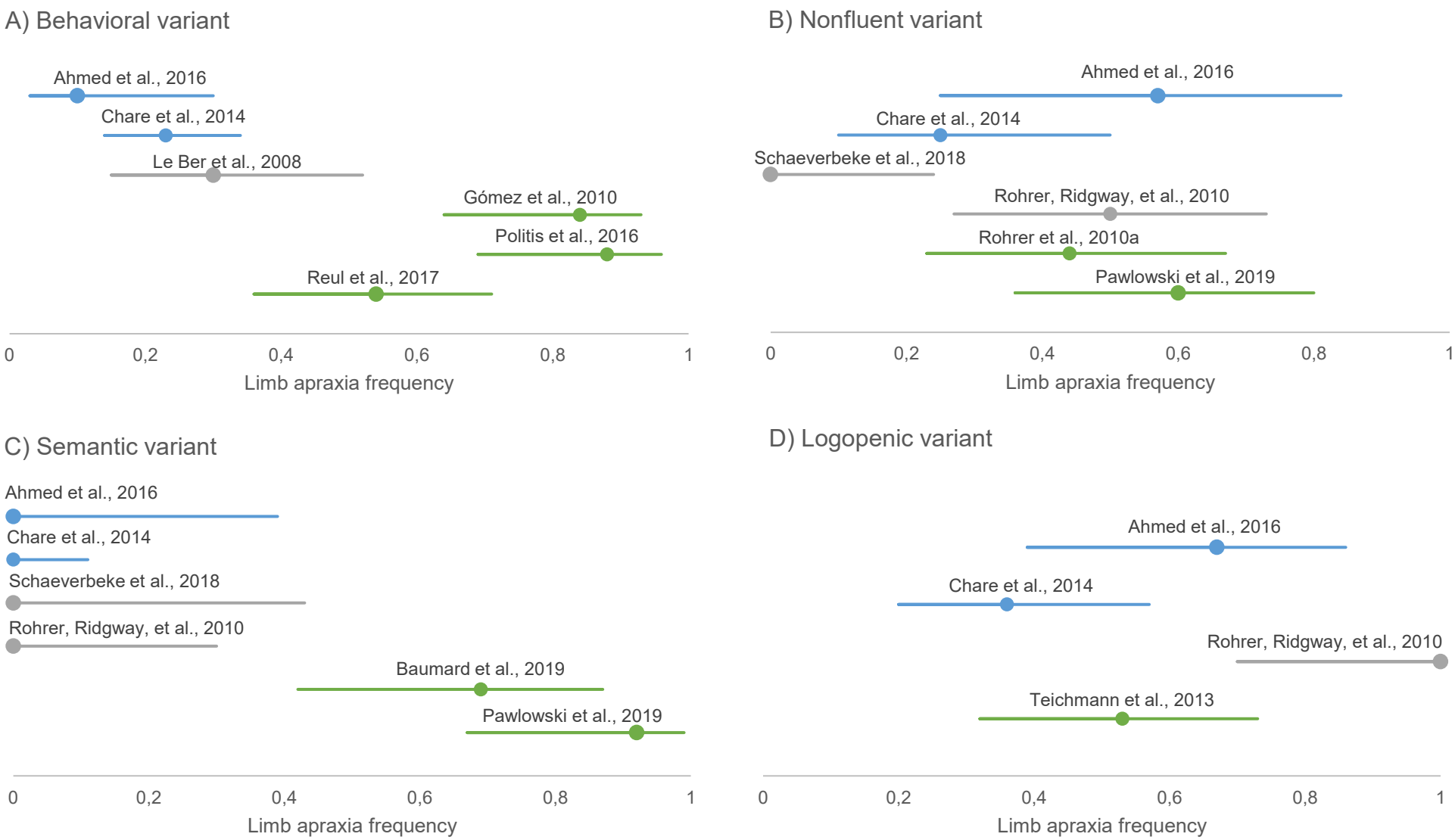

Figure 2. The influence of assessment strategy on apraxia prevalence in clinical variants FTD. Blue indicates retrospective data collection. Grey indicates neurological status examination and brief screening procedures. Green indicates multi-item apraxia batteries. The error bars indicate the 95 % confidence interval.

3.3.2 Face apraxia in nfvPPA

Face apraxia occurred with frequencies of 24% (Chare et al., 2014), 69% (Rohrer, Rossor, & Warren, 2010a) and 78% (Botha et al., 2014). It was reported mild at onset of the disease (Botha et al., 2014), and its severity was found to correlate with disease duration (Rohrer, Rossor, & Warren, 2010a). Face apraxia was more common in nfvPPA than in other variants of FTD (Botha et al., 2014; Chare et al., 2014), which enabled differentiating nfvPPA from the otherlinguistic variants and from Alzheimer's disease (Harris, Saxon, Jones, Snowden, & Thompson, 2018). NfvPPA patients generally scored lower than other groups for oral gesture production, face pantomime and expression imitation tasks (Adeli et al., 2013; Harris et al., 2018; Johnen et al., 2018).

3.4 Apraxia in the semantic variant

Patient record analyses and neurological status examinations yielded 0% apraxia frequencies for svPPA (Ahmed et al., 2016; Chare et al., 2014; Rohrer, Ridgway, et al., 2010; Schaeverbeke et al., 2018). Multi-item batteries revealed production deficits in 69–90% of patients and conceptual deficits in 23–89% of patients (Figure 2c; Baumard et al., 2016, 2018, 2019; Pawlowski et al., 2019).

3.4.1 Limb apraxia in svPPA

The most challenging tasks for svPPA patients were tool and action matching requiring semantic or functional understanding (Baumard et al., 2016, 2018, 2019; Hodges et al., 2000; Lesourd et al., 2016, 2017). Use of single tools and tool-object pairs seemed better preserved than executing tool pantomimes (Baumard et al., 2019; Lesourd et al., 2017). This applied even to tools for which the patients had lost contextual and functional knowledge. This finding is in line with a hypothesis that the mechanical properties of tools and objects enable inferring their usage despite the loss of semantic knowledge (Baumard et al., 2019). Accordingly, performance in mechanical problem solving equalled that of healthy controls (Baumard et al., 2016, 2018). The preserved technical reasoning could explain the intactness of daily instrumental functioning in semantic dementia even in a progressed stage. As Baumard et al. (2019) noted, personal experiences of tool use may also compensate for lost explicit memory representations.

Impairments in conceptual association tasks were more common and severe than in Alzheimer's disease (Baumard et al., 2016, 2018, 2019; Hodges et al., 2000; Lesourd et al., 2016, 2017). The svPPA group outperformed the Alzheimer's disease group for mechanical problem solving and recognition of tool manipulation (Baumard et al., 2016, 2018, 2019; Hodges et al., 2000; Lesourd et

al., 2016, 2017). Tool use tasks did not differentiate svPPA from Alzheimer's disease, although the first group tended to commit more content errors (i.e., unrecognisable movements or perplexity) and the latter more spatiotemporal errors (i.e., recognisable but distorted movements; Baumard et al., 2019).

Imitation of simple meaningful gestures was reported as mainly intact in a small cohort of moderate-stage patients, while production of the same gestures on verbal command was severely impaired (Hodges et al., 2000). In another cohort of mild-stage patients, bimanual limb imitation and object pantomimes were both severely defective (Johnen et al., 2018).

3.4.2 Face apraxia in svPPA

Face praxis appeared to be less impaired in svPPA than in other FTD variants (Botha et al., 2014; Harris et al., 2018; Johnen et al., 2018). In one study, producing oral emblems on verbal command seemed more impaired than imitating facial expressions or repeating pseudowords (a task measuring apraxia of speech; Johnen et al., 2018). Intact repetition of syllables and nonwords reliably differentiated svPPA from nfvPPA (Harris et al., 2018; Johnen et al., 2018).

3.5 Apraxia in the logopenic variant

3.5.1 Limb apraxia in lvPPA

Limb apraxia appeared in lvPPA with a frequency, severity and profile comparable to Alzheimer's disease, and it often co-occurred with parietal symptoms (Ahmed et al., 2016; Harris et al., 2018; Pawlowski et al., 2019; Rohrer, Ridgway, et al., 2010). Two case note analyses reported limb apraxia frequencies of 36% (Chare et al., 2014) and 67% (Ahmed et al., 2016), the highest of all FTD variants, and a more comprehensive apraxia scale reported a frequency of 53% (Teichmann et al., 2013; Figure 2d). The neurological status examination procedure by Rohrer, Ridgway, et al. (2010) revealed apraxia in all patients. Although the frequencies among lvPPA seemed highest of all FTD variants, group score comparisons did not differentiate between the groups, possibly because scores for several task types, face and limb were reported as a sum score (Adeli et al., 2013; Botha et al., 2014; Gorno-Tempini et al., 2004; Harris et al., 2018; Pawlowski et al., 2019).

3.5.2 Face apraxia in lvPPA

Face apraxia was reported to be either absent (Chare et al., 2014) or mild (Botha et al., 2014). It was less severe than limb apraxia (Pawlowski et al., 2019), and it was less frequent as compared with nfvPPA (Adeli et al., 2013; Botha et al., 2014).

3.6 Genetic and pathological samples

The highest limb apraxia frequencies were found in *GRN* carriers (LeBer et al., 2007, 2008; Pickering-Brown et al., 2008; Snowden et al., 2015; van Langenhove et al., 2013). On average, *GRN* carriers were older than *MAPT* or *C9orf72* carriers (weighted mean ages across all samples were 60, 53 and 57 years, respectively) and overrepresented among apraxic individuals compared to other genotype patients, as shown in Figure 3. Their clinical diagnoses were bvFTD in approximately 60% of cases and nfvPPA in a little less than 40% of cases (LeBer et al., 2007, 2008; Pickering-Brown et al., 2008; Snowden et al., 2015; van Langenhove et al., 2013). Two *GRN* carriers developed progressive limb apraxia as a solitary symptom (Pickering-Brown et al., 2008).

Productive limb apraxia was found in just one *MAPT* carrier (Pickering-Brown et al., 2008; Seelaar et al., 2011; Snowden et al., 2015; van Langenhove et al., 2013), while object knowledge (a domain related to conceptual praxis) was defective in 80% of carriers in one sample (Snowden et al., 2015). Their clinical diagnoses were bvFTD or a combination of bvFTD and svPPA (Pickering-Brown et al., 2008; Seelaar et al., 2011; Snowden et al., 2015; van Langenhove et al., 2013).

The *C9orf72* carriers exhibited mainly low limb apraxia frequencies, with the exception of 57% of patients in one sample (Mahoney et al., 2012). In a cohort of asymptomatic relatives of demented patients, *C9* carriership was associated with significantly lower scores in gesture production (Bertrand et al., 2018). Face apraxia was reported to be rarer than limb apraxia in one study (Mahoney et al., 2012). The *C9* carriers were diagnosed with bvFTD in approximately 80% of cases and with either nfvPPA or svPPA in the remaining cases (Floris et al., 2015; Mahoney et al., 2012; Snowden et al., 2015; van Langenhove et al., 2013).

One-fifth of patients with FUS and FTLD-TDP pathology showed limb apraxia (Rohrer et al., 2011; Seelaar et al., 2011). All of these patients were clinically diagnosed as bvFTD with or without motor neuron disease.

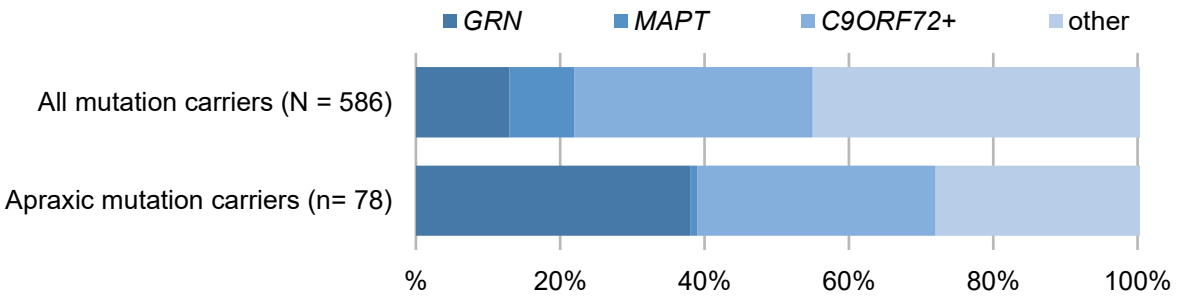

Figure 3. Proportions of GRN, MAPT and C9orf72 among all gene mutation carriers and among apraxic mutation carriers

3.7 Imaging findings related to apraxia

The imaging correlates of limb and face apraxia were examined in five studies. Limb apraxia was related to similar cortical atrophy loci in bvFTD and Alzheimer's disease (Johnen, Brandstetter, et al., 2016). Limb imitation was correlated with volume reductions in left inferior parietal lobe and bilaterally in superior and medial parietal lobes. Object pantomime was associated with a right hemisphere cluster stretching from the inferior parietal lobe (including angular gyrus) to posterior middle temporal gyrus and middle occipital gyrus (Johnen, Brandstetter, et al., 2016).

Among the linguistic variants, one study reported that limb apraxia was correlated with left inferior parietal lobe atrophy in nfvPPA (Rohrer, Rossor, & Warren, 2010a), while other studies found correlations with superior frontal and subcortical abnormalities in nfvPPA and lvPPA (Adeli et al., 2013; Tetzloff et al., 2018). Praxis performance and its decline were related to the degeneration of premotor and motor cortices either in the left hemisphere (Adeli et al., 2013) or bilaterally and with reduced metabolism in the supplementary motor area (Tetzloff et al., 2018). In nfvPPA, the respective subcortical structures included the motor white matter, middle cingulum, internal capsule, cerebral peduncle, occipital white matter and brainstem (Tetzloff et al., 2018). All of these studies used a mixture of transitive and intransitive pantomimes.

Bertrand et al. (2018) did not find any correlations between limb praxis and grey or white matter loss among their presymptomatic participants, possibly due to the small variation in praxis scores. Alzheimer-type pathology of the CSF (i.e., decreased beta-amyloid level and increased tau level) was associated with poorer limb praxis performance in all FTD variants (Pawlowski et al., 2019; Teichmann et al., 2013).

Oral apraxia was related to atrophy in the medial and lateral prefrontal cortices bilaterally (Botha et al., 2014) and in the left middle frontal gyrus, premotor and supplementary motor areas (Rohrer et

al., 2010a). These findings accord with the observation that bvFTD patients with distinctive face apraxia showed greater bilateral atrophy in medial frontopolar areas than Alzheimer's disease patients, whose face praxis was mainly intact (Johnen, Brandstetter, et al., 2016).

4. DISCUSSION

Our review is the first work to systematically address limb and face apraxia literature in FTD. Our search resulted in a reasonable amount of published papers, and the analysed data enabled us to conclude that apraxias are indeed common within the first four years of the disease and that each of the clinical variants exhibits a specific pattern of apraxia-related features. These patterns are visualised in Figure 4 based on the frequency and group comparison data analysed above and by Lesourd et al. (2013). The radar chart presents the suggested profiles of the clinical variants of FTD and Alzheimer's disease as the relations of preserved and impaired domains. The domains correspond to the tasks that seem to differentiate best between the diseases: bimanual limb imitation, limb gestures on verbal command, tool pantomime, speech praxis (i.e., word or syllable repetition), face

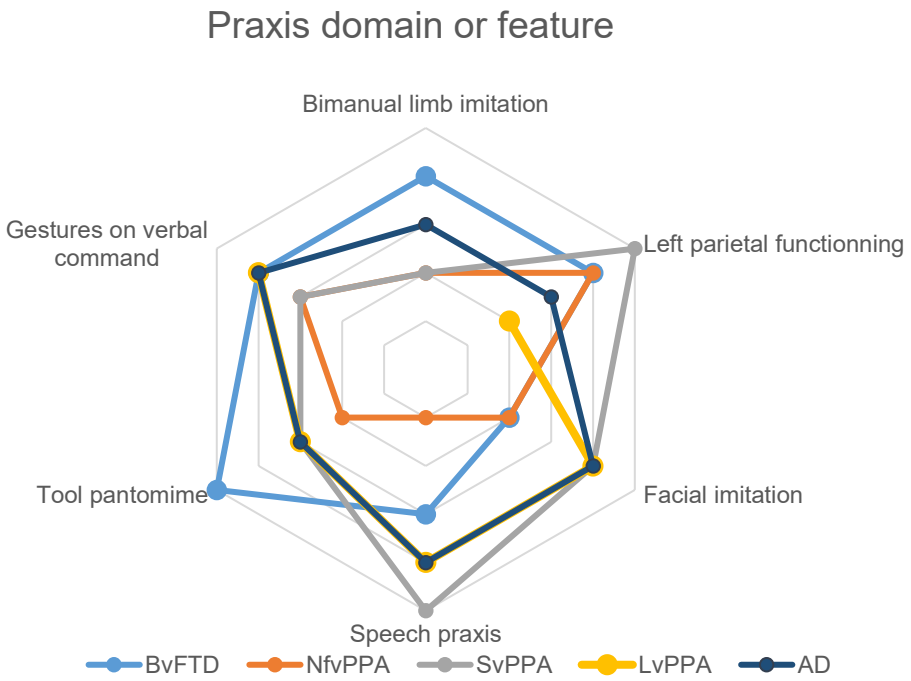

Figure 4. Preserved and impaired features of praxis in clinical variants FTD and Alzheimer's disease. The outermost circle represents preserved abilities and the inner circles denote progressive impairment in the ability. AD = Alzheimer's disease.

imitation and the intactness of left parietal functions (e.g., reading and writing). NfvPPA, for instance, exhibits relatively spared parietal functioning, despite demonstrating the widest range of praxic impairments. We discuss the profiles in detail in Sections 4.2–4.5.

4.1 The influence of assessment strategy

Retrospective patient record analyses, neurological status examinations and brief screening procedures generally yielded lower apraxia frequencies than multi-item apraxia batteries in bvFTD and svPPA. Some neurological status procedures and screening methods developed for Alzheimer's disease and stroke populations may capture the obvious limb apraxia seen in nfvPPA and lvPPA but ignore the more subtle production errors of bvFTD (Ahmed et al., 2016; LeBer et al., 2008; Rohrer, Ridgway, et al., 2010). Face apraxia and conceptual understanding of actions and tools are rarely assessed thoroughly enough to detect the specific impairments of bvFTD and svPPA. This notion does not mean we should replace screening methods with lengthy detailed procedures, however. Some of the multi-item batteries revealed apraxia frequencies of up to 95% of the sample (Baumard et al., 2016; Gómez et al., 2010; Johnen et al., 2015; Johnen, Frommeyer, et al., 2016; Politis et al., 2016), partly irrespective of the diagnosis. These high impairment rates highlight the abnormality of praxis in early FTD but do not allow for clinical differentiation between diseases. A concise assessment may suffice as long as it covers the diverse domains of apraxias susceptible to degradation in FTD.

Another common assessment pitfall is that if patients fail to produce a gesture on verbal command, they are asked to imitate the gesture to obtain the points. This strategy is applied in Western Aphasia Battery, Apraxia Battery for Adults and Manchester praxis screen, and possibly in many status procedures, which readily obscures any deficits of action understanding in svPPA patients. Performances in different modalities and task types should be scored and reported separately. The same applies to scores for each body part. Several authors reported a sum score of face and limb performances, which is unfortunate considering the diagnostic value of the differences across these domains.

4.2 Detecting the behavioural variant

According to the first consensus criteria, early severe apraxia was an exclusion symptom for the diagnosis of bvFTD (Englund et al., 1994). However, the data above show that both face and limb apraxia seem to appear within the first years of the disease.

Face apraxia proved to be the cardinal deficit in bvFTD as measured by three different batteries (Johnen et al., 2015; Johnen, Frommeyer, et al., 2016; Siri et al., 2001). Impaired imitation of facial expressions and production of oral gestures differentiated bvFTD from Alzheimer's patients – whose face praxis remains mainly intact – with 84% overall accuracy. Put into perspective, this hit rate is comparable to CSF biomarker accuracy (i.e., the tau/beta-amyloid ratio; Meeter et al., 2017).

Specifically challenging for patients to imitate were faces with emotional loading, such as anger and disgust (Johnen, Frommeyer, et al., 2016). The authors speculate an association between imitative praxis and social cognition through a failure in internal simulation of others' reactions (Johnen, Frommeyer, et al., 2016) and decreased interoceptive awareness (Johnen & Bertoux, 2019). Correlations between praxis tasks and social cognition do exist, as measured by emotion recognition, faux pas and false belief tasks (Johnen et al., 2018; Politis et al., 2016), but the association does not restrict itself to facial imitation.

Politis et al. (2016) reported moderate to strong correlations between social cognition and limb imitation, gesture discrimination, tool tasks, function naming and pantomiming on visual stimuli. Furthermore, emotion recognition impairment has been found in Alzheimer's disease patients from the mild disease stage onwards (Gola et al., 2017), although these did not exhibit face apraxia (Johnen et al., 2015, 2018; Johnen, Brandstetter, et al., 2016; Johnen, Frommeyer, et al., 2016). Thus, while both social cognition and voluntary action necessitate accurate interoception, the relationship with facial imitation does not seem specific.

Politis et al. (2016) also reported a more specific association between gesture production on verbal command and a false belief task. The finding comes close to Goldenberg's (2017; see also Finkel, Hogrefe, Frey, Goldenberg, & Randerath, 2018) proposition of the communicative nature of pantomime gestures. According to the hypothesis, the purpose of a pantomime is to convey symbolic information, and left anterior fronto-temporal lesions specifically weaken the symbolic quality of these gestures (Finkel et al., 2018). A failure to understandably communicate a message would thereby in part contribute to gestural apraxia.

Besides their pronounced face apraxia, bvFTD patients showed impaired limb imitation compared to test norms and healthy controls (Cossini et al., 2018; Gómez & Politis, 2011; Gómez, Politis, & Rubinstein, 2010; Johnen et al., 2015, 2018; Pawlowski et al., 2019; Politis et al., 2016; Reul et al., 2017). The severity of the defect was either comparable to (Johnen et al., 2015; Johnen, Frommeyer, et al., 2016; Siri et al., 2001) or milder than (Gómez & Politis, 2011; Johnen et al., 2018; Pawlowski et al., 2019) in Alzheimer's disease. Visual stimuli (photographs or examiner's model) and limb

postures involving both hands seem to reveal apraxia in bvFTD with more sensitivity than verbally given or unimanual tasks (Ahmed et al., 2016; Chare et al., 2104; Gómez & Politis, 2011; Johnen et al., 2015; Pawlowski et al., 2019; Politis et al., 2016).

Conceptual apraxia, in turn, may manifest itself as the disease progresses. Tool use or tool pantomime deficits were not obvious within the first three years (Ahmed et al., 2016; Johnen et al., 2015, 2018; LeBer et al., 2008), but severe impairment of understanding of object function and gesture meaning were detected at closer to five years (Cossini et al., 2018; Gómez & Politis, 2011; Gómez et al., 2010; Politis et al., 2016). The strong correlation between conceptual impairment and Clinical Dementia Rating scale score (Gómez et al., 2010) supports this interpretation.

4.3 Detecting the nonfluent variant

NfvPPA exhibited the widest range of defects, including those for limb, face and oral actions. The production apraxia in this variant was severe and near or at the level of lvPPA and Alzheimer's disease (Adeli et al., 2013; Ahmed et al., 2016; Botha et al., 2014; Chare et al., 2014; Johnen et al., 2018; Pawlowski et al., 2019). A peculiar finding was that it rarely co-occurred with signs of left parietal dysfunction (dysgraphia, dyslexia and dyscalculia; Ahmed et al., 2016). In this respect, nfvPPA differs from lvPPA and Alzheimer's disease.

Face apraxia was present in a majority of nfvPPA patients and took mild forms at onset (Botha et al., 2014; Rohrer et al., 2010a). Face apraxia discriminates nfvPPA from the other linguistic variants and Alzheimer's disease (Harris et al., 2018). Defective repetition of syllables and words (apraxia of speech) is a specific feature of this variant and supports differentiation from the behavioural variant, other linguistic variants and Alzheimer's disease (Harris et al., 2018; Johnen et al., 2018).

Another peculiarity was that limb and face apraxia seemed unrelated in nfvPPA. In the other linguistic variants, the presence of nonverbal oral apraxia was associated with slightly more severe limb apraxia. In nfvPPA, limb performance was equal whether or not the patient exhibited oral apraxia (Botha et al., 2014). While nfvPPA shows oral apraxia quite early the deficit may in the more posterior variants signal the spreading of neural pathology to medial and premotor frontal areas. These features suggest a strong fronto-subcortical contribution to limb apraxia in this variant, which is discussed further in Section 4.7.

4.4 Detecting the semantic variant

As expected, svPPA shows impairment in tasks comprising semantic and functional understanding of objects and actions (Baumard et al., 2016, 2018, 2019; Gorno-Tempini et al., 2004; Hodges et al., 2000; Lesourd et al., 2016, 2017). Pantomiming tool use and producing oral gestures on verbal command rely on the left ventro-dorsal stream (Binkofski & Buxbaum, 2013; Niessen et al., 2014), which deteriorates with progression of the disease (Meeter et al., 2017). Compared to healthy controls and Alzheimer's disease patients, svPPA patients exhibited more content errors in tool tasks (e.g., confusion with tool use or unintelligible pantomime movements), but their ability to solve mechanical problems seemed to remain intact (Baumard et al., 2019; Hodges et al., 2000).

SvPPA patients outperformed bvFTD and nfvPPA patients in face and word imitation (Harris et al., 2018; Johnen et al., 2018) and succeeded at simple limb imitation better than lvPPA or Alzheimer's disease patients (Ahmed et al., 2016; Rohrer, Ridgway, et al., 2010). Bimanual items require detailed visual analysis of hand and finger positions that seem to exceed these patients' executive capacity (Johnen et al., 2018).

4.5 Detecting the logopenic variant

LvPPA exhibited an apraxia profile similar to Alzheimer's disease: intact facial and oral praxis combined with severely affected productive limb praxis and parietal dysfunction (Ahmed et al., 2016; Pawlowski et al., 2019; Teichmann et al., 2013). This was expected since two-thirds of lvPPA patients exhibit Alzheimer's neuropathology (Mesulam et al., 2014). This profile should assist in discriminating lvPPA from other FTD variants (Adeli et al., 2013; Ahmed et al., 2016; Pawlowski et al., 2019). Differentiating lvPPA from Alzheimer's disease based on praxis results alone does not appear to be plausible at present. However, a potential discriminator might come from the finding that the neural pathology in lvPPA commonly restricts itself to the left hemisphere (Teichmann et al., 2013). Hypothetically, this could imply an advantage in visually demanding tasks such as bimanual imitations.

4.6 Gene mutations and protein pathology

GRN carriers frequently exhibit apraxia, as suggested earlier (Devenney & Hodges, 2014). The data, albeit limited to retrospective patient record analyses and status examinations, suggest that *GRN* carriers exhibit deficits in the production of limb movements but not in object knowledge or tool use (LeBer et al., 2008; Snowden et al., 2015). This mutation is associated with early degeneration of

fronto-temporo-parietal cortices and long association tracts (Meeter et al., 2017; Sudre et al., 2017) that are central to apraxia, as discussed in Section 4.7.

For *C9orf72*, we found a wide range of limb apraxia frequencies. A noteworthy finding came from the only study applying a standardised apraxia battery; one-third of asymptomatic *C9* mutation carriers showed subtle limb apraxia almost 20 years before the estimated onset of the disease (Bertrand et al., 2018). The authors speculated that the finding may represent a developmental alteration, since apraxia has rarely been found in *C9* diseases. The most common clinical phenotype of *C9* is bvFTD (van Mossevelde, Engelborghs, van der Zee, & van Broeckhoven, 2018), and as our results suggest, the rarity of apraxia in bvFTD may be an artefact of assessment strategy. It is thus tempting to support the interpretation that Bertrand et al.'s (2018) early findings were preclinical signs of the disease. Cortical hypoperfusion has been documented in the inferior parietal lobe in another cohort of presymptomatic *C9* carriers (Mutsaerts et al., 2019), albeit not earlier than 10 years prior to the expected onset. For the rest of the genetic and proteinopathologic variants, more detailed data are needed.

4.7 Imaging correlates in FTD

Limb apraxia in bvFTD is associated with cortical atrophy in bilateral parietal regions and in right ventral structures, similar to Alzheimer's disease (Johnen, Frommeyer, et al., 2016). In comparison with the imitation and pantomime networks described in Section 1, frontal correlates are absent, and the right hemisphere contribution is pronounced.

Pantomime-related atrophy in bvFTD and in Alzheimer's disease was limited to posterior middle temporal gyrus of the right hemisphere (Johnen, Frommeyer, et al., 2016), adding to previous left-sided evidence (Niessen et al., 2014). To account for the role of the right hemisphere, Johnen, Frommeyer, et al. (2016) underline the necessity of visual attention and visuospatial ability for limb actions dependent on right hemisphere integrity. Visual dysfunction does explain impairment in tasks such as bimanual imitation, gesture recognition and gesture discrimination (Rousseaux, Rénier, Anicet, Pasquier, & Mackowiak-Cordoliani, 2012; Stamenova et al., 2014) but the effect on tool pantomimes is not as obvious (Stamenova et al., 2014). Hermsdörfer, Li, Randerath, Roby-Brami and Goldenberg (2013) found that right-sided stroke lesions slowed tool use and pantomiming due to imprecise movement directions and tool grip. They interpreted the fluency of tool pantomimes to suffer from the general disturbance of spatial processing. Indeed, successful tool pantomimes and bucco-facial imitation share a component loading with an allocentric visuospatial task in right-sided lesions (Ubben et al., 2019). All three tasks require processing of the spatial features of an object, and

failure in them correlates with right temporo-occipital and parahippocampal lesions (Ubben et al., 2019).

The right hemisphere may also function as a compensator. Apraxic patients may become dependent on visual guidance to aim their movements (Jax et al., 2014), which emphasises the importance of right hemisphere integrity. At the neural level, the damaged left-sided praxis network recruits homologous right-sided regions. This was evidenced by the finding that stronger interhemispheric connectivity is related to better performance in pantomiming tool use after stroke (Watson, Gotts, Martin, & Buxbaum, 2019).

Although the pantomime and imitation networks in healthy brains involve multiple frontal sites (Lesourd et al., 2018; Niessen et al., 2014), limb apraxia in bvFTD and in Alzheimer's disease was seen to rely exclusively on posterior lobes. Interestingly, apraxia in nfvPPA was most reliably related to grey matter loss in the frontal lobe, including premotor and motor cortices. NfvPPA in general showed more frontal and subcortical than parietal contribution to limb apraxia, inferring from the lack of parietal dysfunction and the worsening performance along with fronto-subcortical degeneration (Tetzloff et al., 2018). This anatomical combination underlies limb apraxia in movement disorders (Hamilton, Haaland, Adair, & Brandt, 2003; Huey et al., 2009) that often feature nfvPPA, especially in *GRN* carriers (van Mossevelde et al., 2018). Subcortical damage alone seems to cause mild postural dysfunction (Hanna-Pladdy, Heilman, & Foundas, 2001), but damage to premotor and supplementary cortices severely distorts bimanual movements (Halsband et al., 2001).

Oral face apraxia was associated with atrophy in lateral and medial aspects of middle and superior frontal gyri bilaterally. Based on stroke studies, damage in either hemisphere is expected, but lesion location has been undefined thus far (Bizzozero et al., 2000). Medial frontal atrophy may also be responsible for the imitative face apraxia seen in bvFTD but not in Alzheimer's disease (Johnen, Frommeyer, et al., 2016).

Finally, Alzheimer's disease CSF pathology was related to increased limb apraxia severity and frequency in all FTD variants (Pawlowksi et al., 2018). In Teichmann et al.'s (2013) sample, lvPPA patients with Alzheimer's disease CSF pathology did not differ from those without CSF pathology in terms of grey matter volume. Instead, they exhibited less perfusion in the left temporo-parietal junction, which has previously been shown to deposit neurofibrillary tangles in lvPPA (Mesulam et al., 2014) and is located on the ventro-dorsal stream (Binkofski & Buxbaum, 2013). The exact role of this locus for apraxia is yet to be clarified.

5. LIMITATIONS

The descriptions outlined here are based on a very heterogenous set of data considering the variety of assessment strategies, measurement methods and reporting styles – a problem also faced in previous apraxia reviews (Lesourd et al., 2013; Zadikoff & Lang, 2005). A number of papers reported the results as sum scores without specifying the subscores for limb and face or different task types. For the same reason, exact frequencies were impossible to define. While frequencies are not the optimal values for comparing group performances, only a small minority of the reports presented data in more detail, as apraxia was not the target outcome in most studies. A quantitative meta-analysis was not the primary goal of this work and may not even have been reliably conducted for the reasons mentioned above.

Although the differences in apraxia profiles between clinical variants seemed consistent, they were examined at the group level and will presumably be less obvious in individual patients. These apraxias were documented, on average, within four years from onset, while subtle alterations in praxis have been found in presymptomatic individuals with FTD-related gene mutations. The questions of how and when exactly apraxias start to debilitate their carriers' lives and how they progress may be answered by longitudinal studies and case series.

6. CONCLUSIONS

A systematic assessment of apraxia seems to support the clinical discrimination of neurodegenerative diseases. However, we should apply more multifaceted assessment methods than those developed for stroke populations. Gradual diffuse degeneration of brain tissue results in different forms of apraxia compared to a sudden injury. In the bilateral degeneration seen in bvFTD and in Alzheimer's disease, imitation tasks and visual stimuli are essential, as the right hemisphere dysfunction results in the degradation of visual ability and in the failure of interhemispheric compensation. Face apraxia frequently co-occurs with limb apraxia in diseases that involve marked (medial) frontal atrophy. Diseases with pronounced subcortical pathology (i.e., movement disorders and nfvPPA) specifically seem to affect the productive aspects of limb praxis, whereas the dorso-ventral damage characteristic of svPPA, lvPPA and Alzheimer's disease should be tested with tasks related to pantomimes, single

tool use, functional knowledge and mechanical problem solving. Importantly, items for verbal and visual modalities as well as for different body parts need to be scored and reported separately.

We call for a concise assessment battery or a combination of brief batteries that covers all of these domains and demonstrates validity among dementia populations. The Dementia Apraxia Test by Johnen, Frommeyer, et al. (2016) includes multiple items of bimanual and facial imitation that enable differentiating between certain FTD variants and Alzheimer's disease. For a more detailed testing of pantomiming ability and the laterality of limb apraxia, the brief screen version from the Test of Upper Limb Apraxia by Vanbellingen et al. (2011) may be useful. The conceptual apraxia batteries previously applied among dementia populations enable a comprehensive assessment of the diverse conceptual aspects of praxis, but we need a selective, less time-consuming set of items for clinical routine.

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APPENDIX

Supplementary material

This document includes detailed literature search strategies for each database and data on the quality assesesment of the articles included in the review.

Search strategy in Ovid Medline & PsycINFO

#	Searches	Results
1	Front* Dement*.mp.	10328
2	behav* variant*.mp.	2088
3	primar* progres* apha*.mp.	1968
4	progres* non* apha*.mp.	469
5	agrammatic* variant*.mp.	184
6	semant* dement*.mp.	3298
7	semant* variant*.mp.	457
8	logopen* variant*.mp.	318
9	non* variant*.mp.	2261
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	15211
11	aprax*.mp.	8248
12	front* lob* deg*.mp.	4166
13	10 or 12	17507
14	11 and 13	395
15	limit 14 to yr="1998 -Current"	369

Search strategy in Scopus

TITLE-ABS-KEY("front* dement*" OR "front* lob* deg*" OR "behav* variant*" OR "primar* progres* apha*" OR "progres* non* apha*" OR "agrammatic* variant*" OR "non* variant*" OR "semant* variant*" OR "semant* dement*" OR "logopen* variant*") AND TITLE-ABS-KEY(aprax*) AND PUBYEAR > 1997

448 document results

Supplement table 1. Case-control studies evaluated with the Newcastle-Ottawa Scale (Wells et al., 2013)

Criterion	Adeli et al., 2013	Ahmed et al., 2016	Baumard et al., 2016	Baumard et al,. 2018	Baumard et al., 2019	Bertrand et al., 2017	Botha et al., 2014	Cossini et al., 2018	Croisile et al., 2003	Gómez et al., 2010	Gorno-Tempini et al.	Harris et al., 2018	Hodges et al., 2000	Johnen et al., 2015	Johnen et al., 2016a	Johnen et al., 2016b	Johnen et al., 2018	Josephs et al., 2013	Lesourd et al., 2016	Lesourd et al., 2017	Pawlowski et al., 2018	Reul et al., 2017	Rohrer et al., 2010a	Rohrer et al., 2010b	Rohrer et al., 2010d	Shea et al., 2015	Siri et al., 2001	Teichmann et al., 2013	Tetzloff et al., 2018
Selection																													
Is the case definition adequate?	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Representativeness of the cases	+	?	+	?	?	?	?	?	?	?	+	+	?	?	?	?	?	+	?	?	+	+	+	?	?	?	?	?	?
Selection of controls	+	+	+	+	+	+	+	?	+	?	-	+	?	+	+	+	+	+	?	?	+	+	?	?	?	+	+	+	+
Definition of controls	+	+	+	+	+	+	+	?	+	?	+	+	+	+	+	+	+	+	-	-	+	+	+	?	?	+	+	+	+
Comparability																													
Comparability of cases and controls on the basis of the design or analysis (0-2 factors)	++	-	++	+	++	++	++	-	-	-	++	++	++	+	++	+	+	+	++	++	-	++	++	++	++	++	-	-	++
Exposure																													
Ascertainment of exposure	+	+	+	+	+	+	+	+	+	?	+	+	+	+	+	+	+	+	?	?	+	+	+	+	+	+	+	+	+
Same method of ascertainment for cases and controls	+	+	+	+	+	+	+	-	-	+	-	+	?	-	-	-	-	+	-	-	+	+	+	-	-	+	+	+	+
Same non-response rate for both groups	+	-	-	+	?	+	+	?	+	+	-	-	+	+	+	+	+	+	-	+	+	?	+	+	+	+	+	+	+
Total score	9	4	8	7	7	8	8	2	5	3	6	8	6	6	7	6	6	8	3	4	7	8	8	5	5	8	6	6	8

'Controls' = healthy individuals or patients with other diseases; 'exposure' = a neurodegenerative disease; + = the study fulfills the criterion; - the study does not fulfill the criterion; ? = the report does not enable evaluation of the criterion.

Supplement table 2. Case-control studies evaluated with the Newcastle-Ottawa Scale (Wells et al., 2013)

Criterion	Chare et al, 2014	Floris et al., 2015	Gómez et al,. 2011	Le Ber et al., 2007	Le Ber et al., 2008	Mahoney et al., 2012	Pickering-Brown et al	Politis et al., 2016	Rohrer et al., 2010c	Schaeverbeke et al.	Seelaar et al., 2011	Snowden et al., 2015	van Langenhove et al.
1. Were the aims/objectives of the study clear?	1	1	1	1	1	1	1	1	1	1	1	1	1
2. Was the study design appropriate for the stated aim(s)?	1	1	1	1	1	1	1	1	1	1	1	1	1
3. Was the sample size justified?	1	1	1	1	1	1	1	1	?	1	1	1	1
4. Was the target/reference population clearly defined? (Is it clear who the research was about?)	1	1	1	1	1	1	1	1	1	1	1	1	1
5. Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?	1	1	1	?	?	?	1	?	1	?	1	1	1
6. Was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation?	1	1	1	1	1	1	1	?	?	1	?	1	1
7. Were measures undertaken to address and categorise non-responders?	0	0	0	0	0	0	0	0	0	0	0	0	0
8. Were the risk factor and outcome variables measured appropriate to the aims of the study?	1	1	1	1	?	?	?	1	1	?	?	?	?
9. Were the risk factor and outcome variables measured correctly using instruments/ measurements that had been trialled, piloted or published previously?	?	?	1	?	?	?	?	1	1	?	?	?	?
10. Is it clear what was used to determined statistical significance and/or precision estimates? (eg, p values, CIs)	1	0	0	0	1	1	0	0	1	1	1	1	1
11. Were the methods (including statistical methods) sufficiently described to enable them to be repeated?	1	1	1	0	0	0	0	1	1	0	0	0	0
12. Were the basic data adequately described?	1	1	1	1	1	0	0	1	1	1	1	1	0
13. Does the response rate raise concerns about non-response bias?	0	?	1	?	0	1	?	1	1	1	1	0	1
14. If appropriate, was information about non-responders described?	0	0	n.a.	0	0	1	0	0	n.a.	n.a.	n.a.	0	n.a.
15. Were the results internally consistent?	1	1	1	1	1	1	0	1	1	1	1	1	1
16. Were the results for the analyses described in the methods, presented?	1	1	n.a.	n.a.	n.a.	1	n.a.	1	1	1	1	1	1
17. Were the authors' discussions and conclusions justified by the results?	1	1	1	1	1	1	0	1	1	n.a.	n.a.	0	1

18. Were the limitations of the study discussed?	1	0	0	0	0	1	1	0	0	1	1	1	0
19. Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?	1	?	1	1	1	1	1	1	1	1	1	1	1
20. Was ethical approval or consent of participants attained?	1	1	?	1	1	1	1	1	1	1	1	1	1
Total score	16	13	14	11	11	14	9	14	15	13	13	13	13

Methods and results evaluated for praxis assessment. 1 = the study fulfills the criterion; 0 = the study does not fulfill the criterion; ? = the report does not enable evaluation of the criterion; n.a. = not applicable.