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Primary progressive aphasia: ReADing the clinical GRANularity

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Abstract

Primary progressive aphasia remains a diagnostic challenge despite (or even because of) the increasing availability of ancillary tests and biomarkers. We present a 67-year-old man with apparently sporadic logopenic aphasia and positive Alzheimer biomarkers who was subsequently found also to have a pathogenic mutation in the progranulin gene. This was signalled by early atypical features (mild expressive agrammatism and behavioural change, rapid clinical deterioration) around the core logopenic aphasia syndrome. Each of the canonical progressive aphasia syndromes has a 'halo' of less typical variants that may herald alternative or additional pathologies. The accurate diagnosis of primary progressive aphasia depends on careful clinical analysis to direct investigations appropriately.

Introduction

The 'language-led dementias' or primary progressive aphasias (PPA) continue to present substantial diagnostic challenges despite their increasing recognition by neurologists.[1] These disorders are much less common than Alzheimer's disease, and are clinically complex and pathologically heterogeneous. Although there is now considerable interest in identifying biomarkers of PPA, its diagnosis continues to rely on careful clinical characterisation. The current diagnostic evaluation of PPA has been shaped by the 2011 consensus diagnostic criteria[2], which enshrine three major canonical variant syndromes, each with clinical and neuroanatomical features that typically dominate the presentation (Table 1). The nonfluent/agrammatic variant (nfvPPA) is led by impaired speech production with articulatory errors and/or agrammatism, often associated with predominantly left anterior peri-Sylvian atrophy. The semantic variant (svPPA) is led by impaired vocabulary and word knowledge due to a broader problem with semantic memory, reliably associated with predominant left anterior-mesial and inferior temporal lobe atrophy. The logopenic variant (lvPPA) is led by word finding pauses, anomia and impaired verbal short term memory, often associated with left temporo-parietal atrophy. Whereas nfvPPA and svPPA are usually underpinned by non-Alzheimer pathologies in the frontotemporal lobar degeneration spectrum, lvPPA is due to Alzheimer pathology in most cases.[1] Indeed, lvPPA is often regarded as the 'language variant' of Alzheimer's disease. Overall, and in sharp contrast to the behavioural variant presentation of frontotemporal dementia, most cases of PPA are sporadic and a genetic basis is uncommon.

However, clinical experience and published case series[3-5] suggest that there are significant exceptions to this standard formulation (Table 2). In up to perhaps a third of cases, PPA may present atypically, with fragmentary or mixed features or associated extra-linguistic symptoms that are not classifiable under the current consensus criteria or suggest an overlap syndrome. From a clinical perspective, it is important to identify such cases as they raise distinct implications for prognosis and management and are more likely to signal a genetic cause, in particular a progranulin gene (*GRN*) mutation.[5,6]

Here we describe a case of logopenic variant PPA exemplifying these principles.

Case report

A 67-year-old retired police community support officer presented with an 18-month history of gradually evolving difficulties with speech. His conversation was marred by word finding hesitations, contextually inappropriate word substitutions (e.g., 'soap' for 'shop') and mispronunciations. His emails contained spelling errors and word omissions. He had no difficulty understanding spoken or textual messages. There were no concerns with his episodic or topographical memory nor any difficulty using tools or household appliances. His family reported that he continued to drive safely and they did not feel there had been any clear change in his personality or behaviour.

His past medical history included a skull fracture resulting from an accident while playing football many years before (without neurological sequelae), hypertension, dyslipidaemia and mild coronary artery disease. His mother had died with a diagnosis of Alzheimer's disease aged 78, having reportedly developed the illness in her late sixties. His father had died aged 73 with a myocardial infarction but no prior cognitive concerns and his three younger brothers and two children were well.

On examination, his propositional speech was interrupted by word-finding pauses but non-effortful. He made phonological (e.g., 'drek' for 'deck') and jargonistic (e.g., 'hampergene' for 'champagne') errors. There were no misarticulations or other features of speech apraxia. He showed marked anomia and impaired sentence repetition (e.g., 'Eddy boy refroots fute' for 'Every good boy deserves fruit') despite intact repetition of single words and short phrases. His written sentences contained grammatical errors (e.g., 'Small boy also hit me as well - don't know he knew judo.') He had some difficulty following more complex multi-stage commands despite intact single word comprehension. Spelling and arithmetical skills were also impaired; however he performed well on tests of visual perception and limb and orofacial praxis. The general neurological examination was normal. He seemed mildly disinhibited (for example, he embraced the clinic nurse on being introduced to her); however, his family felt he had always been a demonstrative person.

We made a clinical diagnosis of lvPPA and arranged several initial investigations. Neuropsychological assessment (Table S1 in Supplementary Material online) identified prominent anomia, impaired grammar comprehension and dyscalculia with relatively

preserved visuospatial skills, corroborating the bedside impression of dominant parietal and temporal lobe dysfunction. Volumetric brain MRI (Figure 1) showed asymmetric, predominantly left-sided temporo-parietal atrophy, with minimal cerebrovascular burden. A lumbar puncture identified a CSF profile of reduced amyloid-$\beta_{1\text{-}42}$ (311 pg/mL; local normal range 627–1322) with raised total tau (1,073 pg/mL; 146–595) and phosphorylated tau (124 pg/mL; 24–68) concentrations, supporting underlying Alzheimer pathology.

He was given trials of donepezil and memantine. However, over the next two years his language skills declined markedly. His speech became increasingly disorganised and essentially unintelligible and comprehension of even simple messages posed difficulties. He also showed increasing behavioural rigidity but continued to live independently, to drive and to manage his house successfully. We considered the rapidity and severity of his aphasia, the associated expressive agrammatism and early behavioural changes to be somewhat atypical for lvPPA due to Alzheimer's disease. Genetic screening identified a novel heterozygous (NM_002087.2 c.548del p.(Gly183Alafs*73) *GRN* mutation. This mutation was not present in >200,000 healthy control samples and considered highly likely to be pathogenic.

He was subsequently lost to follow up and died six years after the onset of symptoms.

Discussion

This case teaches several key lessons for the diagnosis, management and nosology of PPA.

First and foremost, it shows that accurate diagnosis depends on a detailed characterisation of clinical features in the individual patient, including identification of features that may not conform to a particular, canonical PPA subtype[1,2] (see Figure 2). In this case, the constellation of impaired word finding and naming, length-dependent impairment of sentence repetition (phonological working memory), phonological errors and preserved word comprehension without speech apraxia met current consensus diagnostic criteria for a diagnosis of lvPPA. MR scan of brain corroborated this. However, the presence of early expressive agrammatism and behavioural changes (which are not part of the canonical lvPPA syndrome) signalled a need for diagnostic vigilance.

Secondly, disease evolution is an integral element of the diagnosis as well as care planning in PPA. Cross-sectional 'snapshots' of a dynamic neurodegenerative process such as PPA

inevitably give an incomplete picture of the illness. Neurodegenerative syndromes tend to converge insidiously as they evolve. However, in this case, 'mixed' features of more than one syndrome (besides lvPPA, elements of nfvPPA and behavioural variant frontotemporal dementia) developed early. Moreover, the disintegration of his language skills and overall disease progression were more rapid than is typically the case in lvPPA.[5] Together, these features raised the possibility of an alternative (or additional), non-Alzheimer pathology.

Thirdly, this case demonstrates both the potential value of laboratory biomarkers in the diagnosis of PPA and the need for discretion in their deployment. The profile of CSF neurodegeneration markers here gave clear support for underlying Alzheimer's disease - the pre-eminent pathological substrate of lvPPA and the only entity within the PPA spectrum for which pathophysiologically relevant, symptomatic pharmacotherapy (acetylcholinesterase inhibitors) is available. However, in patients with lvPPA who lack Alzheimer biomarkers (perhaps 10–20% of lvPPA cases overall) *GRN* mutations are the leading diagnostic consideration.[3,7] *GRN* mutations are the major genetic cause of PPA and most often give rise to lvPPA, albeit frequently with subtle, additional atypical features, particularly agrammatism.[8] *GRN* mutations are associated with early development of executive and social cognitive as well as language deficits and tend to pursue an aggressive course.[3] On MR brain imaging, atrophy may be strikingly asymmetric and extend widely within the left cerebral hemisphere, albeit variably between patients.[7] Moreover, *GRN* mutations may (as in this case) occur without a known family history of frontotemporal dementia and in conjunction with positive Alzheimer biomarkers.[3] Recognising a genetic basis for PPA is clinically imperative: it may have far-reaching implications for other family members and informs genetic counselling. In retrospect, the diagnosis of relatively early onset Alzheimer's disease in this patient's mother was probably relevant and may signal an unrecognised frontotemporal dementia syndrome.

Finally, this case highlights a fundamental issue in the syndromic categorisation of PPA. Ultimately, all such categorisations are arbitrary. The very 'atypicality' of *GRN*-associated PPA is a hallmark of the underlying molecular lesion. The mixed clinical phenotype reflects pathogenic protein spread in dorsal and/or ventral pathways of the language network from a cortical hub in the temporo-parietal junction.[7] Improved definition of entities such as *GRN*-associated PPA that do not conform to a single cardinal syndrome may motivate a revision

of the current consensus criteria for PPA that lays greater emphasis on molecular and physiological biomarkers. Indeed, several such entities are recognised within the PPA spectrum and genetic causes are over-represented within this atypical spectrum (Table 1). In the present case, however, only recognition of initially subtle, non-canonical phenotypic features led to the disclosure of a second, genetic pathology. Even in an age of increasingly sophisticated biomarkers, the granular bedside analysis of these diverse syndromes is likely to remain paramount in guiding the accurate diagnosis of PPA. Here, re**AD**ing the clinical **GRAN**ularity of PPA uncovered both Alzheimer's disease (**AD**) and a pro**GRAN**ulin mutation.

Table 1. Current consensus criteria for primary progressive aphasia (after Gorno-Tempini et al., *Neurology* 2011; **76**(11): 1006-14)

Level diagnosis	**nfvPPA**	**svPPA**	**lvPPA**
Clinical	*At least one of:*	*Both of:*	
Core features	Agrammatism in language production	Impaired confrontation naming	Impaired single-word retrieval in spontaneous speech and naming
	Effortful, halting speech with inconsistent speech sound errors and distortions (speech apraxia)	Impaired single-word comprehension	Impaired repetition of sentences and phrases
Other features	*At least two of:*	*At least three of:*	*At least three of:*
	Impaired comprehension of syntactically complex sentences	Impaired object knowledge, particularly for low-frequency or low-familiarity items	Speech (phonologic) errors in spontaneous speech and naming
	Spared single-word comprehension	Surface dyslexia or dysgraphia	Spared single-word comprehension and object knowledge
	Spared object knowledge	Spared repetition	Spared motor speech
		Spared speech production (grammar and motor speech)	Absence of frank agrammatism
Imaging-supported	*At least one of:*	*At least one of:*	*At least one of:*
	Predominant left posterior fronto-insular atrophy on MRI	Predominant anterior temporal lobe atrophy	Predominant left posterior peri-sylvian or parietal atrophy on MRI
	Predominant left posterior fronto-insular hypoperfusion/metabolism on SPECT /PET	Predominant anterior temporal hypoperfusion/metabolism on SPECT /PET	Predominant left posterior peri-sylvian or parietal hypoperfusion/ metabolism on SPECT/PET
Pathologically definite	*At least one of:*	*At least one of:*	*At least one of:*
	Histological evidence of specific neurodegenerative pathology	Histological evidence of specific neurodegenerative pathology	Histological evidence of specific neurodegenerative pathology
	Known pathogenic mutation	Known pathogenic mutation	Known pathogenic mutation

The current consensus proposes clinical, neuroimaging-supported and pathologically definite criteria for the clinical and research diagnosis of the major syndromes of primary progressive aphasia. An imaging supported or pathologically definite diagnosis rests on a clinical diagnosis of the relevant progressive aphasia syndrome. A clinical diagnosis of any of these syndromes rests on meeting all three of the following inclusion criteria: most prominent clinical feature is language decline, language deficits are the principal cause of impaired daily living, aphasia is the most prominent deficit at symptom onset. The diagnosis of primary progressive aphasia is *excluded* by any of the following: pattern of deficits is better accounted for by another neurological or medical disorder, pattern of deficits is better accounted for by a psychiatric diagnosis, prominent initial episodic memory or visuoperceptual deficits, prominent initial behavioural disturbance. lvPPA, logopenic variant of primary progressive aphasia; nfvPPA, nonfluent/agrammatic variant of primary progressive aphasia; svPPA, semantic variant of primary progressive aphasia.

Table 2. Some diagnostic features and associations of typical and atypical primary progressive aphasia

Syndrome	Leading clinical features	Associated clinical features	MR brain scan atrophy profile	Key laboratory investigations	Histopathology / genetics
Typical					
nfvPPA	Effortful apraxic speech, binary reversals, expressive agrammatism	Orofacial > limb apraxia, executive dysfunction, parkinsonism, falls, gaze palsy, dystonic / 'alien' limb	L anterior peri-Sylvian, subcortical	Genetics (younger patient, family history of young onset dementia)	Most tauopathies (PSP, CBD, Pick's disease), some AD in older patients; rarely MND, *GRN, C9orf72, TBK1*, others
svPPA	Anomia, impaired single word comprehension, surface dyslexia	Visual / other sensory agnosia, abnormal socio-emotional behaviours	L > R antero-mesial / inferior temporal lobe	None	TDP-43 type C; rarely AD, others
lvPPA	Word-finding pauses / anomia, impaired phrase > word repetition, phonological errors	Reduced digit span, acalculia, apraxia, impaired episodic memory	L temporo-parietal junction	CSF (AD biomarkers)	AD; rarely CBD, *GRN*
Atypical					
Progressive pure anomia	Relatively isolated anomia	None or minor	L > R anterior temporal lobe	None	?TDP-43
Progressive dynamic aphasia	Impoverished spontaneous conversational speech with paucity of other verbal deficits	May have executive dysfunction, parkinsonism, falls, gaze palsy	L fronto-subcortical	None	PSP, CBD
'svPPA-plus'	Anomia, impaired single word comprehension	May have prominent acalculia, MND features, very prominent early disinhibition /musicophilia / other behaviours*	L > R antero-mesial / inferior temporal lobe	Genetics	CBD, Pick's disease, MND, *MAPT, TBK1*
'lvPPA-plus'	Anomia, impaired phrase > word repetition, early jargon	Expressive agrammatism, severe word comprehension deficit, early behavioural change, may have rapid course, parkinsonism*	L > R hemispheric (may be striking)	CSF (AD biomarkers), genetics	AD, *GRN,* CBD
Other 'mixed'	Anomia, expressive agrammatism, impaired single word comprehension	Variable*	L anterior peri-Sylvian, anterior temporal lobe	CSF (AD biomarkers), genetics	AD, *GRN,* others

Data based on references [1,3,4,5,6,7,9,10]. Some examples of atypical PPA syndromes are included here, however the list is not exhaustive. *Additional phenotypic features vary with underlying pathology; AD, Alzheimer's disease; *C9orf72,* pathogenic mutation in chromosome 9 open reading frame 72; CBD, corticobasal degeneration; *GRN,* pathogenic mutation in progranulin gene; L, left; lvPPA, logopenic variant of primary progressive aphasia; *MAPT*, pathogenic mutation in microtubule associated protein tau gene; MND, motor neuron disease; nfvPPA, nonfluent/agrammatic variant of primary progressive aphasia; PSP, progressive supranuclear palsy; R, right; svPPA, semantic variant of primary progressive aphasia; *TBK1,* pathogenic mutation in TANK Binding Kinase 1 gene; TDP-43, TAR DNA-binding protein

Key points

- Logopenic aphasia—progressive word finding difficulty with reduced phonological memory, preserved articulation and word comprehension—is usually an Alzheimer's disease variant.
- A significant minority of cases are due to progranulin gene mutations, which may be signalled by additional features such as agrammatism.
- Genetic causes should be considered in atypical progressive aphasia syndromes, even when apparently sporadic.
- Clinical vigilance is essential when assessing logopenic and other progressive aphasia syndromes, to direct investigations appropriately.

Further reading

Marshall CR, Hardy CJD, Volkmer A, Russell LL, Bond RL, Fletcher PD, et al. Primary progressive aphasia: a clinical approach. J Neurol 2018; 265: 1474-90.

Rohrer JD, Ridgway GR, Crutch SJ, Hailstone J, Goll JC, Clarkson MJ, et al. Progressive logopenic/phonological aphasia: erosion of the language network. Neuroimage 2010; 49: 984-93. doi: 10.1016/j.neuroimage.2009.08.002.

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Ethics statements

Patient consent for publication

Consent for publication was obtained from the patient's next of kin.

Footnotes

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Contributors: AC and JDW conceptualised the study. CRM and NVH acquired and analysed clinical and neuropsychology data. AC, JDW, and CJDH performed literature review, acquired and analysed clinical and neuropsychology data, and drafted the manuscript. JDW, JDR, and HH edited and critically revised the manuscript for important intellectual content. All authors gave final approval of the submitted manuscript.

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Competing interest: The authors declare no competing interests.

Move table 1 currently in the supplementary material to feature in a box within the paper

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Figure legends

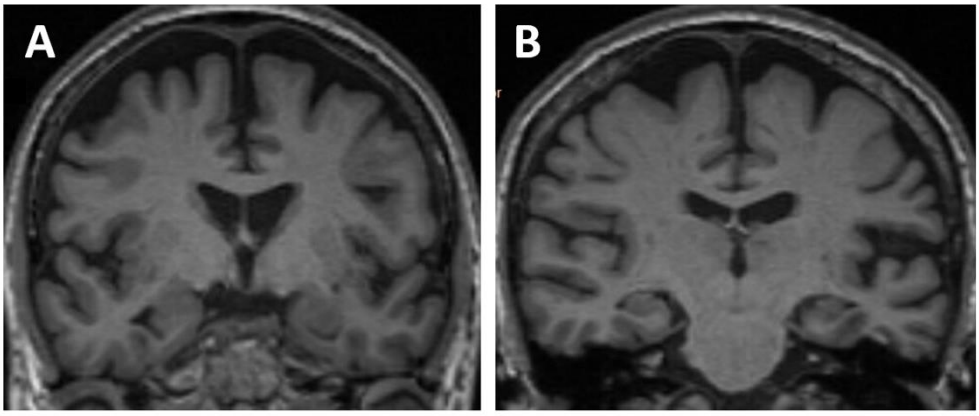

Figure 1. Neuroanatomical findings in this case
Representative coronal T1-weighted brain MRI sections through the anterior (A), mid (B) and posterior (B) temporal lobes are shown, with the left hemisphere projected on the right. There is asymmetric, predominantly left-sided widening of the Sylvian fissures and atrophy of adjacent cortices, more marked posteriorly and involving the inferior parietal lobe, in addition to mild bilateral hippocampal atrophy.

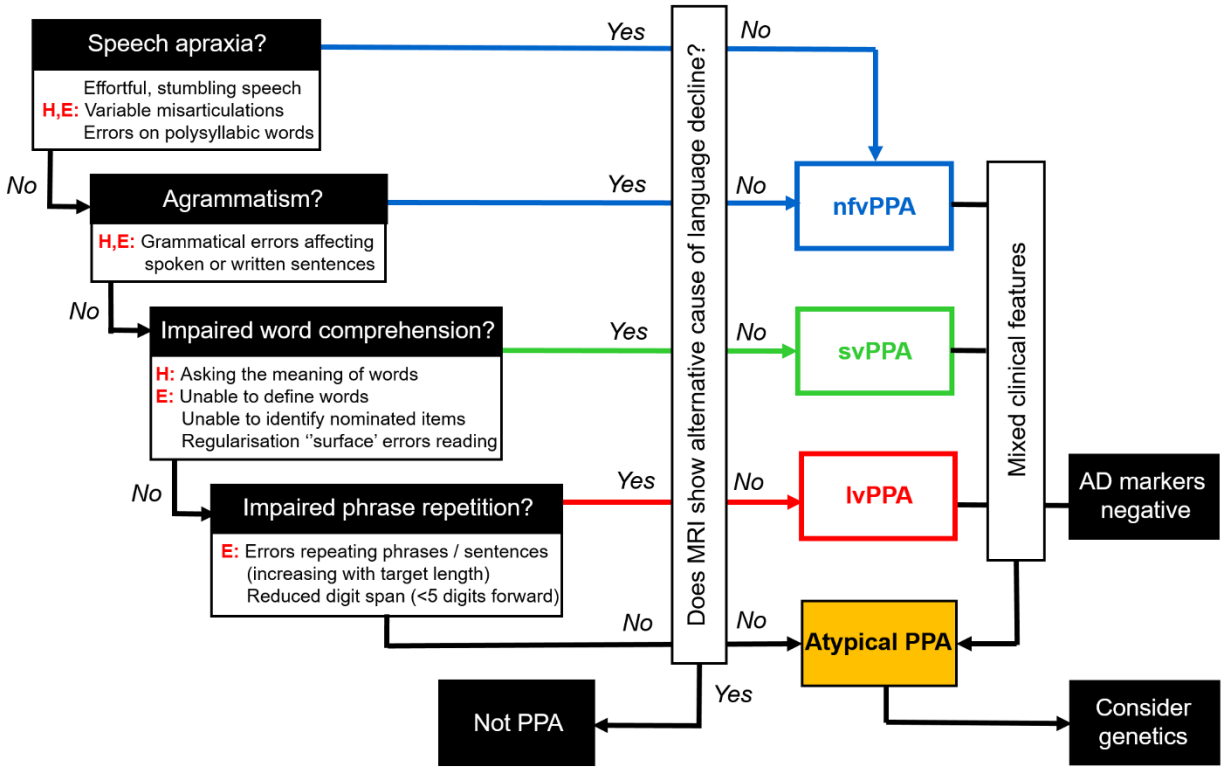

Figure 2. A roadmap for bedside diagnosis of primary progressive aphasia
The Figure outlines a clinical approach to assessing a patient who presents with progressive speech and/or language decline as their leading complaint. In this situation, primary progressive aphasia (PPA) is the main diagnostic consideration; on the left of the figure, we list the sequence of key clinical questions and features on cognitive history (**H**) and/or examination (**E**) that we have found most useful to establish the syndromic diagnosis. Speech production impairment (speech apraxia and/or agrammatism) points to a syndromic diagnosis of nonfluent/agrammatic variant primary progressive aphasia (**nfvPPA**); impaired single word comprehension to the semantic variant, **svPPA**; and impaired repetition of heard phrases and sentences disproportionate to any difficulty repeating single words (reduced phonological memory) to the logopenic variant, **lvPPA**. Note that this formulation does not include a number of clinical features that, while often found in PPA, are less useful in differentiating syndromes (for example, anomia is prominent in both svPPA and lvPPA). Brain imaging (ideally, MRI) is always required in suspected PPA, both to corroborate the syndromic diagnosis and to rule out rare non-degenerative mimics (**Not PPA**). A significant minority of cases of PPA will not conform to a single canonical syndrome (**Atypical PPA**), either because core features are lacking (e.g., in 'progressive pure anomia' and dynamic aphasia) or because mixed linguistic or prominent extra-linguistic (e.g., behavioural) features are present (see Table 1). If available, neuropsychometry (not indicated on the Figure) is very helpful in fully characterising and quantifying the cognitive profile. In lvPPA, ancillary diagnostic investigations (CSF or brain amyloid PET) show biomarkers suggestive of underlying Alzheimer's disease (**AD**) in most cases; in lvPPA cases with negative AD markers and in cases of mixed PPA, genetic screening should be considered, particularly in younger patients and/or where there is a family history of younger onset dementia (see text) [adapted from Marshall CR et al., *J Neurol* 2018; 265:1474-90. doi: 10.1007/s00415-018-8762-6, under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/].

SUPPLEMENTARY MATERIAL: Primary progressive aphasia: ReADing the clinical GRANularity by A Chokesuwattanaskul et al.

Table S1. Summary of neuropsychological findings in this case

Test	Score	Normative scores
Mini-Mental State Examination	**26/30**[a]	N/A
Verbal IQ[b]	**76**	N/A
Performance IQ[b]	92	
Language		
NART	20/50	Full IQ 94
Graded Naming Test	**11/30**	**1-5**
Synonyms comprehension - concrete	19/25	25
Synonyms comprehension - abstract	20/25	25-50
Test of Reception of Grammar	**14/20**	**1-5**
Graded Difficulty Spelling Test	13/30	16
Verbal working memory		
WMS-R Digit Span Forwards	**4/12 (max span: 4)**	**5**
WMS-R Digit Span Backwards	6/12 (max span: 4)	60
Repetition of single words[c]	10/10	N/A
Repetition of sentences	**5/10**[d]	N/A
Episodic memory		
RMT faces	24/25	75
RMT words	23/25	25
AMIPB Story immediate recall	**13**	**<10**
AMIPB Story delayed recall	**9**	**<10**
AMIPB Figure immediate recall	53/76	50-75
AIMPB Figure delayed recall	50/76	50-75
Executive functions		
Phonological fluency (letter S)	12	31
Category fluency (animal)	21	75-90
Stroop Colour Word	**59**	**10**
Brixton Spatial Anticipation	18 errors, SS 5	Moderate Average
Processing speed		
Symbol-Digit Modality	29	24
Other skills		
AMIPB Figure Copy	76/80	25-50
VOSP Object Decision	20/20	>5
Graded Difficulty Arithmetic Test	**4**	**7**

Normative scores are given as percentiles where relevant / available; abnormal results (score at or < 10th percentile where norms available) are coded in bold. **a**, lost points for registration, sentence repetition, following 3-stage command, copying pentagons; **b**, based on Wechsler Adult Intelligence Scale; **c**, 3-syllable, low frequency words; **d**, length-dependent emergence of phonological and omission errors (for sentences > 5 syllables long). AMIPB, Adult Memory and Information Processing Battery; MMSE, Mini-Mental State Examination score' N/A, not applicable; NART, National Adult Reading Test; RMT, Recognition Memory Test; VOSP, Visual Object and Space Perception Battery – Object Decision test; WMS-R, Wechsler Memory Scale (Revised).