Supplementary material

PCA Case vignettes

Case 1 (patient 4 in Supplementary Table .1.)

A 64 year old, right-handed gentleman presented to the opticians 3 years prior to the formal diagnosis of PCA. He described a gradually progressive, initially non-specific difficulty focusing, and later intermittent difficulty finding everyday objects at home, and identifying specific features in objects. This progressed such that he had problems registering the movement of cars and buses, on one occasion nearly being run over by a car that he did not see approaching as he crossed the road. He is now unable to read, cannot watch movies (as he is unable to follow the plot) or sports such as football (as he cannot track the players or ball), and continues to have difficulty finding objects around the house. Assessment at the opticians, and thorough ophthalmic investigations were repeatedly normal. MMSE at the latest assessment 4 years after diagnosis was 24, 23 one year previously, and 25 a year prior to that. Investigation of CSF Aβ and total tau was supportive of Alzheimer's disease.

Clinical eye movement examination revealed multiple square wave jerks on attempted steady fixation for 10 seconds. There was an incidental congenital left-sided exo- and hypertropia on the cover test. The range of ocular movements was otherwise full, with full convergence in the right eye. Saccades to visual targets were consistently hypometric horizontally, but had normal latency and velocity. Memory-guided saccades were impaired, generating roaming eye movements. Pursuit movements were markedly broken in both horizontal and vertical planes. The vestibulo-ocular reflex was intact.

Case 2 (patient 15 in Supplementary Table A.)

A 63 year-old right-handed gentleman who ran his own business noticed difficulties understanding complex spreadsheets approximately 18 months prior to his diagnosis. He had particular difficulty in understanding mathematical equations with which he had previously been very familiar. He noticed a gradual decline in his handwriting, and that he lost control of his right hand. He developed progressive visual impairment, being unable to see objects clearly, and describes them "coming in and out of view". This was associated with a progressive expressive dysphasia and subtle short term memory loss. He reported unsteadiness and lack of confidence walking, but no vertigo or dizziness. MMSE at the latest assessment was 16, 16 one year previously, and 17 a year prior to that. Amyloid imaging was supportive of Alzheimer's disease.

Examination of the eye movements 3 years after diagnosis revealed frequent square wave jerks during fixation straight ahead in the light. There was a full range of eye movements, with preserved convergence. Reflex saccades to visual targets were consistently hypometric, often not reaching the target. Saccadic latency and velocity were normal. Pursuit movements were broken horizontally, but less so vertically, where there were occasional saccadic intrusions. The vestibulo-ocular reflex was intact bilaterally, and nystagmic responses to optokinetic stimuli were normal and symmetrical.

Supplementary Table 1. Neuropsychological test scores for each PCA patient.

Patient number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	PCA Mean (SD)	*N* below 5th %ile	Normative Mean (SD)
Age (years)	72.7	56.9	78.9	63.2	58.6	51.8	69.9	59.0	59.4	56.3	70.4	65.4	53.8	50.2	62.4	66.5	56.4	57.9	72.6	82.5	63.2 (8.9)	-	-
Gender	M	M	F	M	F	F	M	F	M	F	F	M	F	F	M	F	F	M	F	F	8m, 12f	-	-
Disease duration (years)	2.7	3.9	6.9	7.2	2.6	4.8	6.9	4.0	6.4	4.3	2.4	8.8	1.8	6.2	3.4	3.5	3.4	1.9	5.6	4.5	4.6 (2.0)	-	-
General Function																							
MMSE (/30)[a]	28	16	16	23	24	22	13	13	19	19	26	17	18	15	16	15	24	21	18	13	18.8 (4.5)	-	-
sRMT words (/25)[b]	22	NT	19	20	24	24	22	16	19	23	25	16	21	22	22	20	21	20	16	25	20.9 (2.8)	8	23.7 (1.8)
sRMT faces (/25)[b]	20	NT	13	23	18	19	12	22	14	UT	22	NT	25	17	24	24	22	22	19	17	19.6 (4.0)	8	22.8 (1.9)
Concrete Synonyms (/25)[c]	20	22	21	18	24	21	22	16	20	15	24	21	23	19	23	23	NT	23	18	21	20.7 (2.6)	1	20.8 (3.0)
Naming from description (/20)[d]	19	6	4	9	14	15	13	14	18	10	19	5	4	15	15	8	NT	17	6	12	11.7 (5.1)	15	18.9 (1.5)
Non-visual parietal																							
Calculation (/26)[e]	21	7	10	14	9	9	11	4	12	5	17	4	9	12	4	9	16	9	11	11	10.2 (4.5)	17	20.7 (3.1)
Spelling (/20)[f]	16	14	9	7	11	7	5	3	9	0	18	4	5	7	2	6	8	5	2	6	7.2 (4.7)	14	19.5 (6.5)
Perceptual																							
Acuity[g]	6/9	6/12	6/18	6/9	6/9	6/9	UT	6/12	6/9	UT	6/9	UT	6/9	6/9	6/9	6/12	NT	6/9	6/12	6/12	-	-	-
Figure ground (/20)[h]	17	17	11	18	12	17	UT	20	16	15	19	13	18	16	19	20	NT	15	13	13	16.1 (2.8)	16	19.9 (0.3)
Fragmented letters (/10)[h]	2	3	0	19	2	0	UT	6	4	UT	2	NT	15	2	4	18	NT	0	0	0	4.8 (6.5)	14	18.8 (1.4)
Object decision (/20)[h]	11	10	8	15	6	12	NT	12	4	6	16	NT	16	4	15	15	14	7	2	8	10.1 (4.6)	13	17.7 (1.9)
Number location (/10)[h]	6	NT	UT	7	NT	0	UT	UT	0	1	2	NT	6	0	2	7	3	0	1	4	2.8 (2.7)	14	9.4 (1.1)
Dot counting (/10)[h]	6	0	3	10	NT	3	UT	0	0	3	4	NT	9	2	2	9	NT	5	7	4	4.2 (3.3)	15	9.9 (0.2)

Note: Raw scores for each PCA patient are presented, with mean and standard deviation scores for the PCA patient group and relevant normative data.

UT = untestable, NT = not tested.

Normative data samples: [a] Mini-mental state examination; Folstein et al. 1975; [b] Warrington 1996; [c] Warrington et al., 1998; [d] Randlesome (unpublished data N = 100); [e] Crutch (unpublished data); [f] Baxter and Warrington 1994; [g] cortical visual screening test (CORVIST) James et al. 2001; [h] Warrington and James 1991.

Description of neuropsychological tests

sRMT – a recognition memory test with a learning phase of 25 items briefly presented, followed by a two alternative forced choice phase in which the participant identifies the learned items from distractor items.

Concrete synonyms - participants are asked to say which of two related words is most closely associated with a given word.

Naming from description – participants are asked to name objects from a verbal description.

Calculation – A test of addition, of graded difficulty, starting with easy items and becoming more difficult.

Spelling – A spelling test of graded difficulty

Acuity – discrimination of squares, circles and triangles of decreasing size, giving a Snellen acuity equivalent score.

Figure ground – Two alternative forced choice task in which the participant identifies whether a speckled black and white pattern has a degraded 'X' present (50% of trials) or no 'X' present (50% of trials).

Fragmented letters – Participants are asked to identify black capital letters that have been degraded by the introduction of a white speckled overlay.

Object decision – The participant is shown a page of 4 silhouettes, and is asked to identify the silhouette of a real object from three distractors.

Number location – The participant is shown two squares on a page, one above the other. The top square has many numbers in it, the lower square has one black dot. The participant is asked to identify which number in the top square is in the same position as the dot in the lower square.

Dot counting – Participants are shown a page with 5-9 black dots on a white background and asked to count the dots.

Supplementary Table 2. Division of 34 Desikan regions into 5 groups

* The region labelled posterior cingulate in the Desikan atlas (Desikan et al., 2006) is directly inferior to the paracentral lobule, rather than the posterior-most end of the cingulate, and was therefore placed in the central region of interest.

Region of interest	**Desikan region**
central	paracentral
central	postcentral
central	precentral
central	posteriorcingulate *
frontal	caudalanteriorcingulate
frontal	caudalmiddlefrontal
frontal	frontalpole
frontal	lateralorbitofrontal
frontal	medialorbitofrontal
frontal	parsopercularis
frontal	parsorbitalis
frontal	parstriangularis
frontal	rostralanteriorcingulate
frontal	rostralmiddlefrontal
frontal	superiorfrontal
occipital	lateraloccipital
occipital	lingual
occipital	pericalcarine
occipital	cuneus
parietal	inferiorparietal
parietal	isthmuscingulate
parietal	precuneus
parietal	superiorparietal
parietal	supramarginal
temporal	bankssts
temporal	entorhinal
temporal	fusiform
temporal	inferiortemporal
temporal	insula
temporal	middletemporal
temporal	parahippocampal
temporal	superiortemporal
temporal	temporalpole
temporal	transversetemporal

Supplementary Table 3
The Cohen's d measure of effect size is presented for each of the group comparisons and metrics. The two groups differ by d of a standard deviation, e.g. a d of 0.5 means they differ by half a SD, and is considered a medium effect size. An effect size of 0.2 is considered small, whilst an effect size of 0.8 or greater is considered large.

Cohen's d		PCA vs tAD	PCA vs Control	tAD vs Control
Fixation stability				
Square wave jerk (SWJ) frequency		0.64	0.58	1.11
Large intrusive saccade frequency		0.26	1.05	0.59
Longest period of fixation (ms)		0.08	1.03	1.11
Saccade task				
Time to fixation on target (ms)	5°	0.98	1.03	0.08
	10°	1.14	1.61	0.48
	15°	0.56	1.15	0.57
Latency (ms)	5°	1.10	1.22	0.31
	10°	1.17	1.83	0.67
	15°	0.46	1.20	0.96
Amplitude error (°)	5°	1.65	1.39	0.39
	10°	1.25	1.61	0.13
	15°	1.40	2.03	0.40
Velocity (°/s)		1.19	0.50	0.69
Number of saccades made		0.79	1.55	0.72
Sinusoidal pursuit				
Pursuit gain		0.50	1.39	0.97
Number of saccades per trial		0.06	1.27	1.33

Supplementary Table 4. Results of a ROC (Receiver Operator Characteristic) analysis for the classification of PCA and tAD patients.

The cut off chosen is that which maximises the percentage of patients correctly classified (accuracy). Sensitivity indicates the percentage of PCA patients correctly identified as having PCA. Specificity indicates the proportion of tAD patients correctly identified as having tAD. AUC=area under the receiver operator characteristic curve.

	Metric	AUC *	Cut-off	Accuracy (%)	Sensitivity (%)	Specificity (%)
Fixation	*Square wave jerks (number per trial)*	0.66	5	73.0	90.0	52.9
	Large intrusive saccades (number per trial)	0.59	4	67.6	55.0	82.4
	Longest period of fixation (ms)	0.51	2420	59.5	70.0	47.1
Saccade	*Saccade amplitude error (degrees of visual angle)*	0.87	2.1	89.3	93.8	83.3
	Saccade latency (ms)	0.80	240.4	75.0	87.5	58.3
	Number of saccades (number per trial)	0.82	1.43	82.1	93.8	66.7
	Time to fixation upon target (ms)	0.83	397.0	78.6	87.5	66.7
Pursuit	*Pursuit gain*	0.64	0.3	66.7	41.2	93.8
	Number of saccades per trial	0.46	11.2	54.6	76.5	31.3

Supplementary Table 5. Results of a ROC (Receiver Operator Characteristic) analysis for the classification of patients (PCA and tAD combined) versus controls.

The cut off chosen is that which maximises the percentage of patients correctly classified (accuracy). Sensitivity indicates the percentage of patients correctly identified as being in the patient category. Specificity indicates the proportion of healthy controls correctly identified as controls. AUC=area under the receiver operator characteristic curve.

	Metric	AUC *	Cut-off	Accuracy (%)	Sensitivity (%)	Specificity (%)
Fixation	*Square wave jerks (number per trial)*	0.73	2	71.2	73.0	68.2
	Large intrusive saccades (number per trial)	0.73	1	71.2	67.6	77.3
	Longest period of fixation (ms)	0.80	5804	76.3	72.7	78.4
Saccade	*Saccade amplitude error (degrees of visual angle)*	0.74	2.0	72.0	86.4	60.7
	Saccade latency (ms)	0.79	254.7	72.0	60.7	86.4
	Number of saccades (number per trial)	0.87	1.3	80.0	82.1	77.3
	Time to fixation upon target (ms)	0.78	371	72.0	71.4	72.7
Pursuit	*Pursuit gain*	0.79	0.66	76.4	50.0	93.9
	Number of saccades per trial	0.81	11.16	80.0	72.7	90.9