Posterior Cortical Atrophy

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Case studies:	2
References:	48

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Abstract

Purpose of the review

To present an overview of the clinical syndrome of posterior cortical atrophy, its pathological underpinnings, clinical presentation, investigation findings, diagnostic criteria, and management.

Recent findings

Posterior cortical atrophy is usually an atypical form of Alzheimer’ s disease with relatively young age at onset. New diagnostic criteria allow for patients to be diagnosed on a syndromic basis; as having primary visual (pure) or more complex (plus) forms; and, where possible on the basis of biomarkers or histopathology, by underlying pathology. Imaging techniques are demonstrating where pathological processes are broadly concordant (posterior cortical atrophy, hypometabolism, tau deposition) and discordant (widespread amyloid deposition); and international efforts are underway to establish the genetic underpinnings of this typically sporadic form of AD. In the absence of specific disease modifying therapies there are a number of practical suggestions that can be offered to patients and their families to facilitate reading, activities of daily life and to promote independence and improve quality of life

Summary

Whilst rare, posterior cortical atrophy is an important diagnostic entity for neurologists, ophthalmologists and opticians to recognise to allow for early accurate

diagnosis and appropriate patient management. Posterior cortical atrophy provides an important opportunity to investigate the causes of selective vulnerability in Alzheimer’ s disease.

Learning objective

To describe the clinical features of posterior cortical atrophy, understand its molecular underpinnings, relevant investigations, diagnostic criteria and management.

Introduction

Posterior cortical atrophy (PCA) is a neurodegenerative syndrome where the brunt of pathology falls on the parietal and occipital lobes [Crutch 2012]. Whilst patients with progressive visual impairment with normal acuity had previously been described, the term PCA was introduced by Benson and colleagues who described a series of patients with deficits in higher order visual processing, and features consistent with aspects of Gerstmann's and Balint's syndromes, but with relatively preserved episodic memory until later in the disease [Benson 1988] (**Case Study 1**). Subsequent case series determined that the most common underlying pathology was Alzheimer's disease (AD) [Hof 1990, Galton 2000, Tang-Wai 2004] leading to alternative nomenclature including the visual variant of AD and bi-parietal AD [Ross 1996, Galton 2000]. However, as PCA can be due to alternate pathologies, including corticobasal degeneration [Tang-Wai 2003], Lewy body disease, and (very rarely) prion disease, the overarching term Posterior Cortical Atrophy is now preferred to describe the syndrome, with contemporary criteria allowing for subdivisions into PCA-pure, PCA-plus and pathological subtypes depending on the clinical presentation and availability of biomarker evidence of underlying pathology [Crutch 2017].

* Case Study 1 about here

Epidemiology

Changing definitions of PCA over recent years, and its relative rarity make estimation of incidence and prevalence difficult. However, a striking feature of this syndrome is that the majority of affected individuals have an unusually early age at disease onset, typically presenting between the ages of fifty and sixty-five years old, although patients with onset in the ninth decade are described [Tang-Wai 2004, Schott 2016]. In the largest series of PCA described to date, of 302 patients the mean (SD) age of onset was 58.9 (6.9) yrs, with 82.5% fulfilling criteria for young onset dementia (onset age before 65) [Schott 2016] (**Figure 1**). The proportion of patients with AD presenting with PCA vary and are likely to depend on clinical context, but have been estimated to be ~5% in a specialist cognitive clinic [Snowden 2007], and up to 13% of cases with young onset AD [Koedam 2010]. As well as patients with clear a PCA presentation, a population based study showed that 14% of patients diagnosed with AD had cognitive profiles consistent with prominent visuospatial problems [Crane 2017], suggesting both that visual problems are under-recognised in "typical" AD, and raising questions as to whether PCA is a distinct entity [Tang-Wai and Mapstone 2006] or on a phenotypic continuum [Stopford 2008]. Whilst some PCA studies have reported a slight over-representation of women [Schott 2016] which may simply reflect that AD is more prevalent in women, others have reported no sex differences [Mendez 2002, McMonagle 2006, Renner 2004]. There are few prospective studies of disease duration in PCA: whilst patients with young onset AD may have faster disease progression than those with later onset disease, many patients with PCA have a more protracted course extending well over a decade.

* Figure 1 about here

Pathological underpinnings

Most patients with PCA have underlying AD [Hof 1990, Renner 2004, Tang-Wai 2004, Galton 2000], although cases of PCA can be associated with Lewy body pathology [Renner 2004, Tang-Wai 2004] – either in isolation, or commonly in combination with AD – and very rarely subcortical gliosis and prion disease [Renner 2004, Townley 2018] Most cases coming to post mortem will naturally have end stage disease, but even at the late stages differences in the distribution of neurofibrillary tangles compared to patients with typical AD have been noted, with particular involvement of primary visual cortices and visual association areas [Hof 1990, Hof 1997]. Conversely, most studies have not found major differences in amyloid burden across the cortex compared to other forms of AD [Renner 2004, Tang-Wai 2004].

Clinical presentation

The core features of PCA include visuospatial and perceptual deficits, and features of Gerstmann syndrome (acalculia, left right disorientation, agnosia and agraphia) and Balint' s syndrome (ocular motor apraxia, optic ataxia, and simultanagnosia, alongside alexia and apraxia) [McMonagle 2006, Crutch 2012]. In contrast to typical AD, episodic memory is relatively preserved at onset; and compared to frontotemporal dementia, aside from anxiety which is a common feature [Suarez-Gonzalez 2016], personality and behaviour are not usually affected and insight is preserved.

History

Due to its relative rarity, posterior cortical atrophy is often diagnosed late, and by the time patients present to neurologists, symptoms will often have been present for many months or years. (**Case Study 2**). Very early symptoms can be rather nebulous: patients often describe non-specific anxiety and a sense that something is wrong, before more concrete problems – usually centred around vision – become apparent. A history of repeated visits to opticians and ophthalmologists and multiple unsuccessful changes in spectacles in an attempt to correct acuity is often present; patients can often express themselves very clearly and so are not considered as having a "dementia" (**Video Clip 1**); or are diagnosed as having had a stroke before progressive problems emerge (**Video Clip 2**). Patients often describe minor damage to the car due to problems judging distances whilst parking. Problems reading analogue clocks, and digitised pixelated signs are common early features.

* Case Study 2 about here

* Video Clip 1 about here

* Video Clip 2 around here

With with time difficulties with reading emerge in the vast majority of patients [Mendez 2002, McMonagle 2006]. Patients typically get lost whilst reading text, particularly when moving from line to line or when there is too much competing textual information – so-called "crowding" [Yong 2014]; or can describe a sense

that words are moving or slipping off the page [Crutch 2011]. Most patients with PCA will be unable to read within a few years of symptom onset. Occasionally patients can describe abnormalities with colour vision describing washes of colour or prolonged after-images [Chan 2001]. Patients and carers can describe difficulties in finding items in front of them particularly in more cluttered environments (simultanagnosia, see below) or a sensation that items are moving (**Video Clip 3**). Patients often become anxious about travelling on escalators, particularly when travelling downwards; can be cautious crossing the road due to difficulties judging the speed of traffic; and can have difficulty with revolving doors (Video Clip 1), identifying steps or slopes when walking on patterned carpets. Featureless environments such as white tiled bathrooms and shiny surfaces can be particularly disorientating. Patents will often develop impaired facial recognition (prosopagnosia) [Mendez 2002, Tang-Wai 2004; McMonagle 2006], often whilst still being able to identify people by voice. Some individuals describe unusual symptoms which can be misconstrued as non-organic: these include finding it easier to read small rather than large text; and difficulties identifying static objects whilst being able to track items in motion. An extreme example of this phenomenon are rare patients who can play ball sports (e.g. tennis or badminton), but are unable to locate the ball or shuttlecock when it is on the floor.

* Video Clip 3 about here

Outside of the visual domain, common symptoms are those attributable to impairments of dominant parietal lobe function [Tang-Wai 2004, McMonagle 2006],

including difficult with calculation and handling money, or spelling. Dyspraxia – acquired deficits in performing complex motor programmes – is very common [McMonagle 2006, Kas 2011]. Combinations of visual problems and dyspraxia have significant functional consequences including difficulty dressing (e.g. problems doing up buttons or zips, tying laces of neckties, putting on clothes back to front, or finding the sleeves of coats), cooking, and using cell phones, remote controls and computers.

Episodic memory and executive impairments are typically not observed in the early stages – although patients may fail certain memory and executive tasks owing to visual, imagery and other deficits – but emerge as the disease progresses. Language impairment is typically considered as a late feature of this disorder, although there is evidence that earlier anomia is relatively common when specifically looked for [Tang-Wai 2004, Migliaccio 2009, Magnin 2013, Crutch 2013] This is likely to reflect that whilst in their purest forms the different canonical symptoms of AD can easily be distinguished, in practice, and as would be expected for a neurodegenerative process which spreads over time, there is a degree of overlap between different syndromic variants which becomes increasingly apparent as the disease advances.

Aside from dyspraxia, a number of other motor features can be seen in PCA, including limb rigidity, myoclonus and tremor [Ryan 2014]. Whilst these can reflect underlying pathologies other than Alzheimer's disease (e.g. corticobasal degeneration [McMonagle 2006] or where parkinsonism is present, dementia with Lewy bodies) these can also be seen in PCA underpinned by Alzheimer's pathology [Ryan 2014].

As PCA progresses, symptoms inevitably decline and the majority of patients will become functionally blind which has major implications for the level of care that is required and can be the cause of considerable distress to the individual who will often have good insight into his/her problems. Being unable to read, use other communication devices, and becoming increasingly dependent on others often leads individuals to feel disempowered and depressed (Suárez-González 2015) Patients who already have severe visual problems will become at high risk of falls as other cognitive and motor problems emerge. In its latter stages, PCA is often indistinguishable from advanced, typical, AD.

Atypical presentations:

There has been considerable debate as to whether the presence of early visual symptoms is the *sine qua non* for a diagnosis of posterior cortical atrophy Suárez-González 2016), or whether presentations with other parietal features (early prominent dyspraxia for instance) with subsequent emergence of more typical visual features should still be classified under the PCA umbrella. This has implications for diagnostic criteria, as patients with early motor features can overlap with other conditions such as corticobasal syndrome, an issue which is now addressed in the most recent consensus criteria (Crutch 2017, see below). In terms of underlying pathology, cases with corticobasal degeneration and dementia with Lewy bodies may be indistinguishable from patients presenting with AD. However, the presence of features typical for these conditions, e.g. alien limb phenomena for corticobasal

degeneration or early hallucinations and Parkinsonism for dementia with Lewy bodies, may provide evidence for these alternate pathologies. Whilst the Heidenhein variant of prion disease which presents with early visual impairment can in theory be mistaken for PCA, other clinical features including the (usual) rapidity of the presentation, the nature of the visual disturbance – which in prion disease is often associated with frightening visual distortions – usually mean this is not a major diagnostic challenge. In rare overlap cases, the MR imaging features and evidence of diffusion changes in particular are particularly valuable (see below) [Townley 2018]

Bedside cognitive assessment

The bedside cognitive exam can be particularly revealing in PCA. Screening cognitive tests such as the Mini-mental state examination [Folstein 1975], or Adenbrooke's Cognitive Examination (ACE-III) [Hsieh, 2013] will often clearly demonstrate preservation of orientation, repetition and recall, with severe difficulties in dominant parietal tasks, e.g. calculation and spelling, and right parietal function (copying complex figures or clock drawing).

On additional testing, there is often a marked discrepancy between an individual's ability to read single letters and short words compared to blocks of texts when they will often get lost moving from word to word or line to line (**Figure 2a**); this may be improved if they are allowed to use their finger to track. *Simultanagnosia* – the inability to interpret the entirety of a visual scene – can often be demonstrated by asking an individual to describe a complex picture: rather than describing it in its

entirety, individuals with PCA will often hone in on specific features failing to see the picture as a whole. This can be demonstrated on a research basis using eye tracking (**Figure 2b**). A particularly striking and very common feature of PCA is the presence of an *apperceptive agnosia*. This can be easily demonstrated by showing patients degraded letters (**Figure 3**), numbers or objects which they typically cannot make sense of, and then showing them the same letters in completed form which they can. Right parietal dysfunction can also be demonstrated through difficulties in dot counting, line bisection, or clock drawing.

* Figure 2 about here

* Figure 3 about here

Dominant parietal dysfunction – e.g. features of *Balint's syndrome* – can be demonstrated through bedside tests of calculation and spelling, although these should be administered verbally. Similarly, demonstration of apraxia should be done in a manner such as to exclude problems solely being related to visual difficulties, e.g. asking individuals to put their thumb on their ring finger or to salute, rather than asking them to copy the examiner's hand movements.

Visual disorientation – likely reflecting combinations of *simultanagnosia* and *optic ataxia* – where present is a striking sign: the individual is seated in front of the examiner and asked to concentrate on their nose as would be done with field testing. The instruction however is to reach and take the examiner's moving hand in their peripheral vision. Typically, a patient with PCA will be able to see the hand and will

often copy the hand movements, but will have difficulties locating it in space (**Video Clip 4**). This phenomenon be much more apparent in one hemifield than the other, may be present in both, and is often present in central vision, distinguishing PCA misreaching from classic optic ataxia. In more advanced cases, the patient individual will instead of reaching for the target, reach instead towards the examiners tie (the "tie sign") or face.

* Video Clip 4 about here

Physical examination

In patients with typical PCA due to AD, aside from demonstrating the higher order visual signs and dyspraxia described above, the neurological examination is typically unremarkable although, as mentioned above, a proportion of individuals will have mild motor signs or myoclonus [Ryan 2014]. Specific features that should be assessed include: the presence of significant Parkinsonism which may reflect underlying Lewy body pathology; or very asymmetric motor features (dystonia, dyspraxia, myoclonus and alien limbs) which might reflect a corticobasal syndrome. Patients will not typically have upper motor neuron signs, or features of amyotrophy. Watching an individual walk may be very informative both as mild balance problems are not infrequently encountered by patients with PCA, and the functional consequences of higher order visual problems may be demonstrated if patients bump into walls or door frames whilst walking.

Investigations

Visual fields

Whilst formal ocular assessment performed carefully can demonstrate normal acuity and fundi, visual field testing in PCA often reveals hemifield impairments or constriction [Pelak 2011] including unusual and variable field deficits not confirming to classical cortical lesions [Millington 2017] which can be mistaken as being non-organic (Figure 4).

* Figure 4 about here

Neuropsychology

Detailed neuropsychology provides objective evidence for the cognitive domains that are both affected and preserved in PCA, with implications both for diagnosis, but also potentially for management. A standard neuropsychometric battery can be employed in patients with PCA, but a few caveats are required. It is important that the testing psychologist is aware of the individual's difficulties with vision, ensuring that test material is wherever possible presented in verbal rather than visual form: for instance, nominal skills may be better determined by naming to description than to a picture. Similarly, assessment of premorbid IQ based on reading words from the National Adult Reading Test, may or may not be reliable depending on the extent of visual impairment.

Patients with PCA will typically show a marked discrepancy between performance IQ (low), and verbal IQ; and deficits in parietal tasks with preservation of memory and executive tests, provided imagery and other deficits are taken into account (e.g. recognition memory performance may remain preserved when recall appears impaired) (Figure 5). On this basis, neuropsychological criteria for PCA have been described on a research basis, for instance requiring in addition to fulfilment of clinical criteria, evidence for impairments (performance at <5% percentile) on at least two out of four parietal tests (objection perception, space perception, calculation, spelling) with evidence of preservation (> 5th percentile) on a recognition memory tests [Lehmann 2011].

* Figure 5 about here

Structural imaging

As its name implies, most individuals with PCA will have prominent volume loss reflecting neuronal tissue loss in posterior brain regions (**Figure 6**). On a group level, numerous studies have confirmed reductions in occipital, posterior parietal, and posterior temporal volume and cortical thinning in patients with PCA compared to both controls and patients with typical Alzheimer' s disease [Whitwell 2007, Lehmann 2011]. In practice, on an individual level posterior volume loss is very clear in some cases, but others with very clear symptoms can have little volume loss, made more difficult by natural variability of the parietal lobe anatomy. Volumetric T1 acquisitions in the coronal plane, supplemented by sagittal views are often best for

appreciating the distribution and extent of atrophy, and visual rating scales such as those introduced by Koedam *at al* [Koedam 2011] may be helpful in providing an objective measure of parietal volume loss (**Figure 7**). However, in the presence of a typical history for PCA, the absence of marked parietal volume loss should not exclude the diagnosis. Hippocampal volumes are typically relatively preserved in PCA compared to typical AD, in keeping with the relative preservation of episodic memory. In the correct clinical context, it is also important to exclude vascular disease, inflammation and mass lesions within the posterior cortices which can mimic neurodegeneration; and where prion disease is possible, diffusion weighted imaging may be very helpful, typically showing cortical ribboning in occipital lobes in the Heidenhein variant [Townley 2018] (**Figure 8**)

* Figure 6 about here

* Figure 7 about here

* Figure 8 about here

Functional imaging

In cases where the clinical phenotype of PCA is clear and there is posterior atrophy on MR imaging further imaging is not typically required. However, in equivocal cases, FDG PET may be extremely valuable in demonstrating hypometabolism within the parietal-occipital cortices [Nestor 2003, Rosenbloom 2010], which is typically more extensive than the pattern of atrophy, and may be seen earlier (Figure 9). Whilst not in a routine clinical use, there is evidence that arterial spin labelling MRI

which provides a measure of cortical blood flow, may provide similar information, albeit reflecting blood flow rather than metabolism [Lehmann 2016].

* Figure 9 about here

Molecular imaging

As patients with PCA by definition have atypical disease and almost all present with young onset dementia, most will fall within good use criteria of the use of amyloid PET imaging [Johnson 2013]. Where this is available, amyloid PET can provide invaluable evidence for underlying AD. However, in contrast to the striking focality both of the symptom and structural imaging changes, the pattern of amyloid deposition is usually seen across the cortex, with amyloid PET scans from patients with PCA often being indistinguishable from patients with more typical forms of the disease [Lehmann 2013, Rosenbloom 2011, Ossenkoppele 2015]. Thus, whilst amyloid PET has a role in defining pathology, it is not useful in defining AD syndromes. By contrast, tau PET scanning, which is currently only available on a research setting, often shows very striking posterior cortical deposition of tau pathology Ossenkoppele 2015]. (**Figure 10**).

* Figure 10 about here

Cerebrospinal fluid

In keeping with PCA usually being underpinned by AD, CSF Aβ1-42 is depressed and concentrations of total- and phosphorylated tau are increased. However, whilst levels of Aβ1-42 depression are similar to other forms of AD, there is some evidence that levels of tau and phosphorylated tau are not as elevated as in typical AD, perhaps relating to either different intensities or extent neurodegeneration [Paterson 2016]. In practice therefore, clinicians should be aware that tau/Aβ1-42 ratios may be less elevated in PCA compared to typical AD. As with other forms of Alzheimer' s disease, the total cell count and protein are not elevated: where these are seen, other diagnoses should be considered.

Genetic testing

PCA due to AD is a sporadic condition and routine testing for the autosomal dominant forms of the disease is not usually indicated. Testing for ApoE genotyping is not recommended as part of the diagnostic work up for any form of AD, and this is particularly the case for PCA where there is evidence that possession of an APOE E4 allele may be less frequent than in typical cases [Schott 2016].

Diagnostic criteria

Original diagnostic criteria from Mendez [Mendez 2002] and Tang-Wai [2004], have been superseded by that from the international consortium in 2017 [Crutch 2017]. These updated criteria using a three-level classification. Level one describes the core clinical, cognitive, and neuroimaging features and exclusions, i.e. the clinico-

radiological syndrome (see Table 1 for comparison with previous criteria). Level two distinguishes between a "pure" PCA syndrome and, allowing for individuals who also fulfil criteria for another neurodegenerative syndrome, a "PCA-plus" categorisation. Level 3 classifies patients with PCA attributable to different underlying disease, e.g. PCA due to Alzheimer's disease, PCA due to Lewy bodies, PCA due to CBD, and PCA due to prion disease based on the availability of biomarkers (or pathology) that can define the underlying pathology. This classification aims also to be complementary to the diagnostic classifications for Alzheimer's disease – which increasingly recognise PCA as an atypical form of AD [Dubois 2010, McKhann 2011]– providing a framework that can be adapted for different purposes. Thus, for the purpose of providing appropriate support to individuals, the underlying pathology may be less relevant than the clinical picture; whilst for research studies aiming to determine the causes of phenotypic heterogeneity it may be important to classifying patients both on the basis of syndrome and pathology.

* Table 1 here

Management

Medical treatment

Drug treatments for PCA should be directed to the underlying pathological substrate. For most patients with PCA, due to AD, treatment with cholinesterase inhibitors or memantine as would be done in standard practice is therefore appropriate. Whilst

pivotal clinical trials for the licensing of these drugs focussed on typical amnestic AD, small open label studies of PCA have also revealed benefits in this subgroup specifically [Kim 2005]

Progressive visual impairment and increasing dependence emerging in the face of intact insight often results in significant anxiety, depression and feelings of guilt [Suarez-Gonzalez, 2015]. Whilst there are no controlled trials, anecdotal evidence suggests that patients may benefit from counselling and other psychological approaches, and also to standard pharmacological treatments for mood and anxiety e.g. with selective serotonin uptake inhibitors. Where myoclonus emerges and becomes problematic, anecdotal evidence suggests small doses of Levetiracetam may be helpful.

Non-pharmacological treatments:

In the absence of disease modifying therapies, the mainstay of management of these conditions is the provision of practical and psychological support to the affected patient and their caregivers. Even in the absence of specific therapies, an accurate diagnosis is a vital staging point in an individual patient' s journey, not least as diagnosis is often delayed and symptoms overlooked, misinterpreted or ignored for many years [**Case Study 2**]. Most patients will have stopped, or been stopped from, driving by the time a diagnosis is made, but ensuring patients fitness to drive is clearly of paramount importance.

The major functional problems in PCA involve everyday skills and self-care [Shakespeare 2015]. Loss of ability to read may be helped with the provision of audio books. Technological advances such as voice recognition on smartphones, computers and mobile devices can be invaluable in maintaining an individual's independence. Specific apps have been developed to help the reading problems in PCA, moving text into the individual's central vision at an appropriate speed and thus avoiding the need to make saccadic movements from word to word (Yong 2015; http://www.readclear.co.uk). When out of the home, the provision of a white stick (symbol cane) is a simple measure that ensures that other pedestrians are aware of the patient's potential impairments. Within the house, measures to help with identification of objects and navigation e.g. by putting coloured tapes on doorframes, or labelling specific items may be helpful. As the disease progresses, home adaptions to minimise stair use, help with bathing and washing may be required. Involving a multidisciplinary team with occupational therapy is often invaluable. Practical tips for patients with PCA and their families have been developed and are summarised in **Table 2**. The relative rarity of PCA can lead to isolation. The development of specific support groups (see suggested websites) for these individuals both locally, and increasingly nationally and internationally can provide a valuable source of support to individuals and their families.

* Table 2 about here

Future directions

PCA has the potential to provide invaluable insights into the factors underpinning the development of AD generally and factors influencing phenotypic diversity [Mattson, 2016]. It is unknown for instance why patients develop these symptoms on a sporadic basis, and do so considerably younger than patients with typical AD. The single biggest genetic study in AD confirmed that possession of an ApoE E4 allele was a risk factor for PCA, but conferred less risk than for typical AD. This study highlighted a number of potential risk genes which may influence risk, some of which are implicated in neurodevelopment [Schott 2016]. A recent study has also provided evidence that patients with PCA posterior cortical atrophy are more likely to report non-language mathematical and visuospatial learning disabilities compared to patients with typical AD and controls [Miller 2018]. From a pathological perspective, there is emerging evidence for different strains of Aβ in PCA compared to typical AD, raising the suggestion that different forms of Aβ may propagate through different brain networks and associate with different forms of the disease [Rasmussen 2017]. These findings, whilst in their infancy, may in due course provide a more detailed understanding of the mechanisms underlying the development of both PCA and typical AD, and lead to the development of new, and more specific treatment of these conditions.

Conclusion

Posterior cortical atrophy is a rare but important neurodegeneration syndrome typically underpinned by AD. Patients with this condition are often diagnosed late, or are misdiagnosed as having a primary visual or psychologically mediated illness. Recognition of PCA as a distinct syndrome and determining of its underlying cause allows for both appropriate non pharmacological and pharmacological treatments to be instigated and appropriate support provided for patients and families. PCA provides a valuable paradigm for exploring the causes of phenotypic heterogeneity in AD.

Recommended websites:

A UK website providing a rich support of information for patients and carers with PCA:
http://www.raredementiasupport.org/pca/

A US website run by carers and supporters for patients with PCA:
https://www.pinterest.co.uk/pcasupportusa/

An app to help reading in patients with PCA and related disorders:
http://www.readclear.co.uk

Figure 1 Age of disease onset in PCA.
Data from an international study of 302 patients.

New figure, based on data from Schott et al 2016

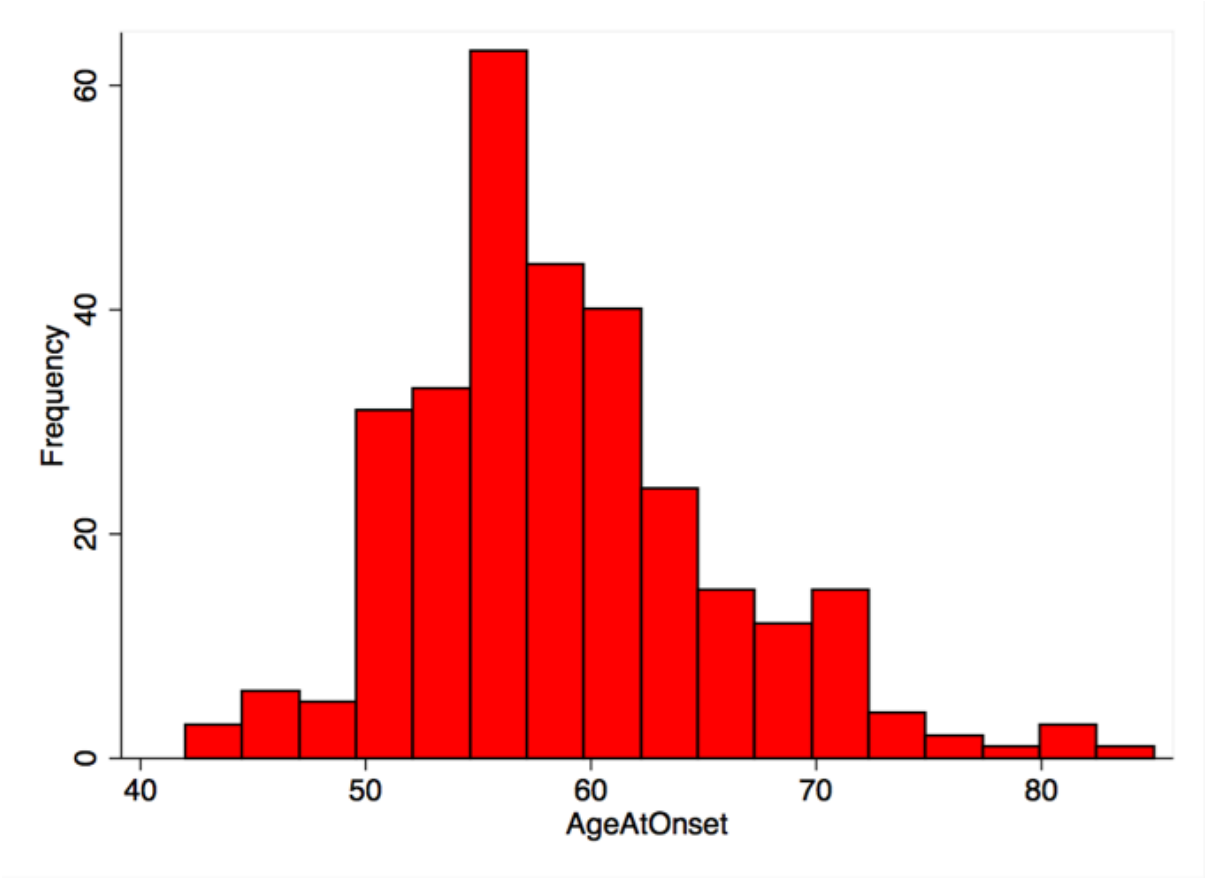
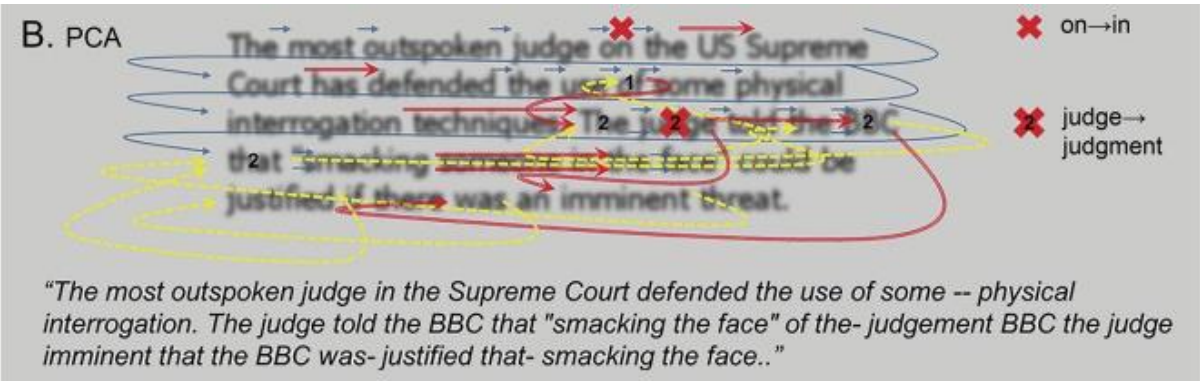


Figure 2. Visual dysfunction in PCA.

(a) Eye tracking demonstrates Impaired reading in PCA

Arrows outline reading order; red arrows indicate omission of subsequent words through reading later sections of text, and yellow arrows indicate reading of earlier sections of text. Transcripts of the participants' corresponding spoken output are beneath each example (italicized text). Each hyphen in the transcript beneath each example indicates a pause of 3 seconds. Numbers refer to where words were repeated.

Reproduced from Yong et al Neurology. 2015



(b) Eye tracking studies in healthy individuals (A) and PCA (B) demonstrate simultanagnosia. Circles represent fixation locations and circle size fixation durations. Individuals with PCA fixate on prominent features initially (eg, dome on pier), but subsequently fixate on relatively uninformative aspects of the scene (eg, sea or sky) and miss important d contextual details (eg, beachfront or near the end of the pier).

Reproduced from Crutch et al, Lancet Neurology 2012

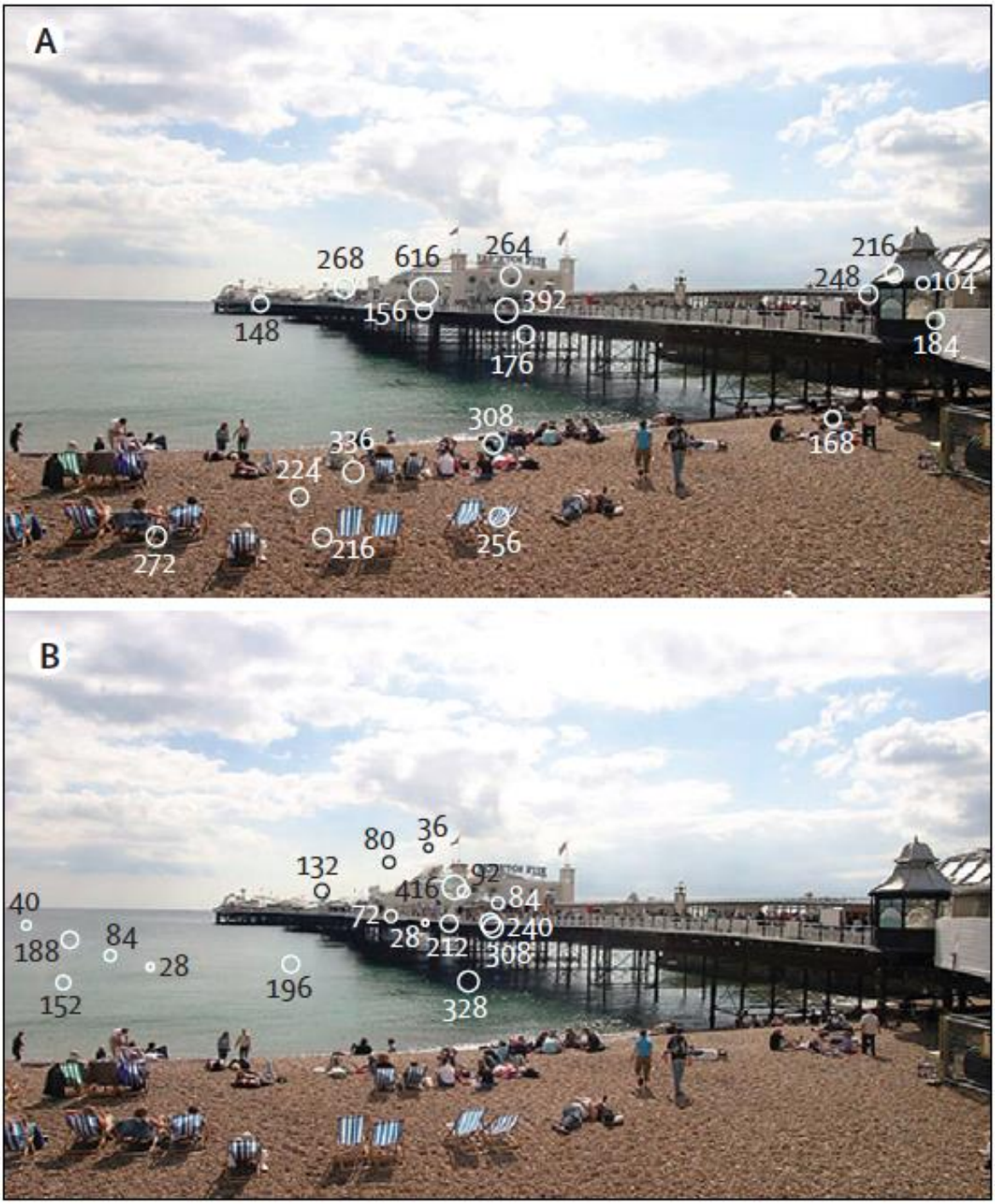

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Figure 3 Fragmented letters.
Individuals with PCA will often be able to read individuals letters, but not when they are presented in degraded form (apperceptive agnosia)

Reproduced from the Queen Square Screening Test For Cognitive Deficits, with permission from Prof EK Warrington

Figure 4 Visual fields in PCA.

In patients 2 and 10 visual field deficits are limited to a hemifield; in patients 3 and 4 both hemifields are affected to some extent. Adapted from *Millington et al Neuroimage Clinical 2017*

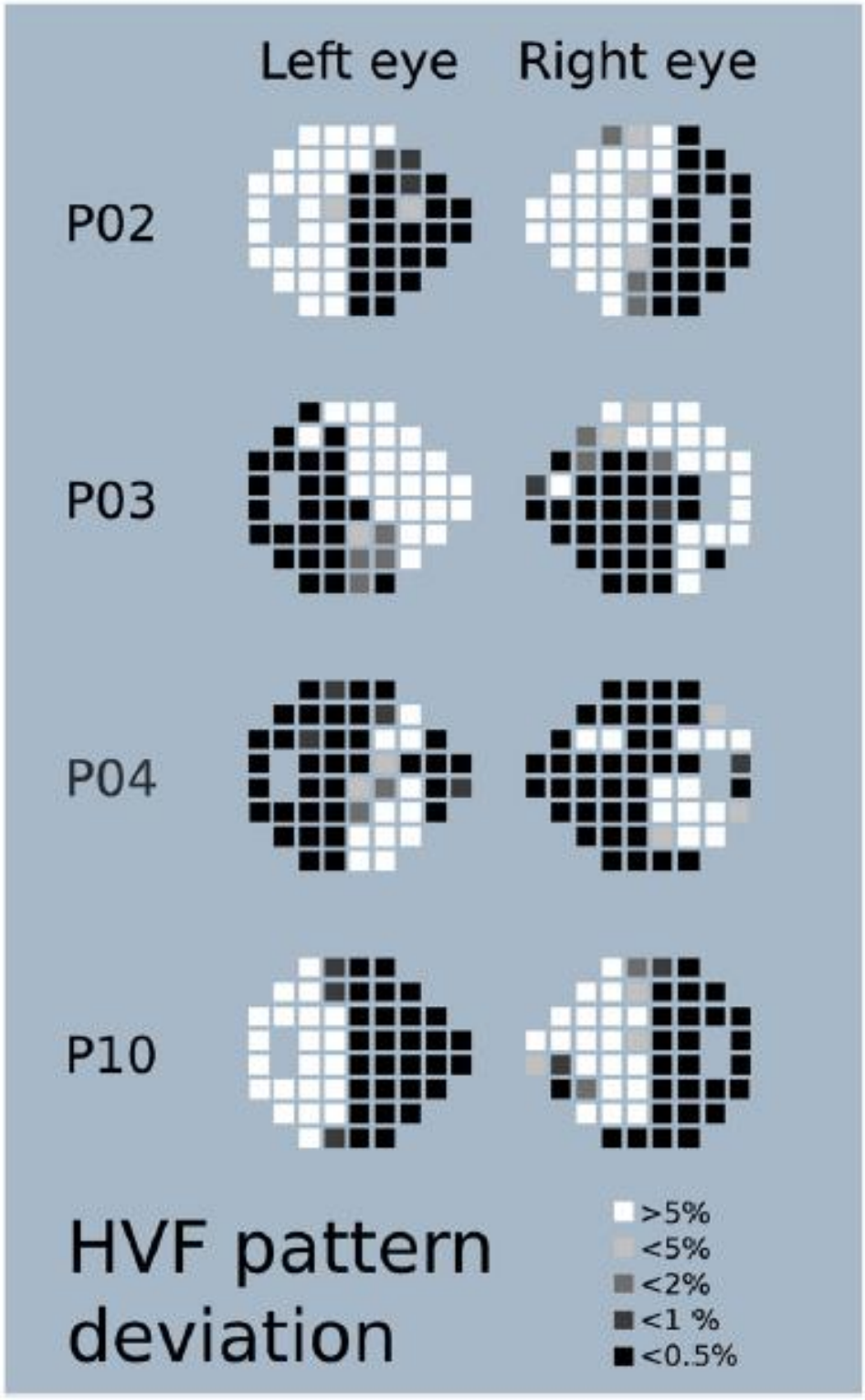

Figure 5 Pattern of cognitive impairment in PCA.
Involvement of different cognitive domains is represented by the retreat of colour in each segment toward the centre of the circle.

Reproduce from Oxford textbook of Cognitive Neurology and Dementia (Eds Husain and Schott] OUP. Chapter 11 Neuropsychological assessment (Caine and Crutch) Fig 11.3 DOI:10.1093/med/9780199655946.003.0011

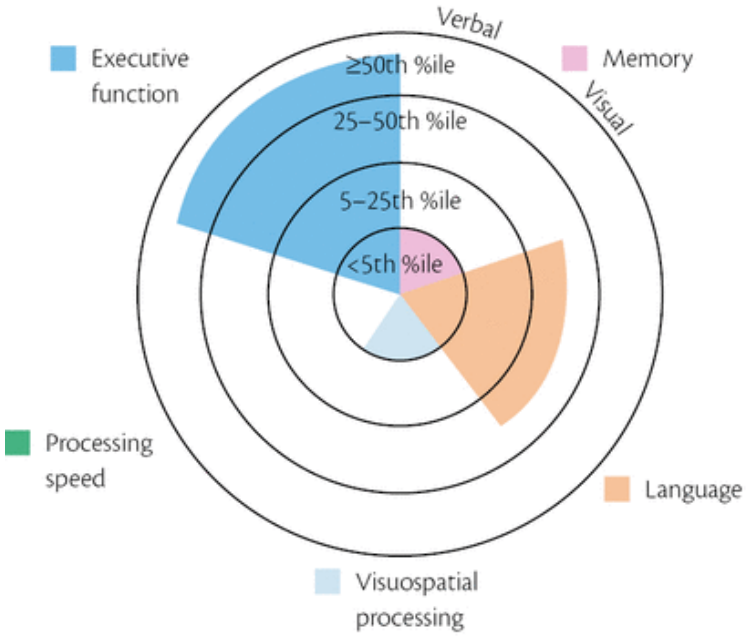

Figure 6 Typical MRI imaging in PCA

Sagittal (left) and coronal (right) panels show marked parietal lobe volume loss

* *New Image*

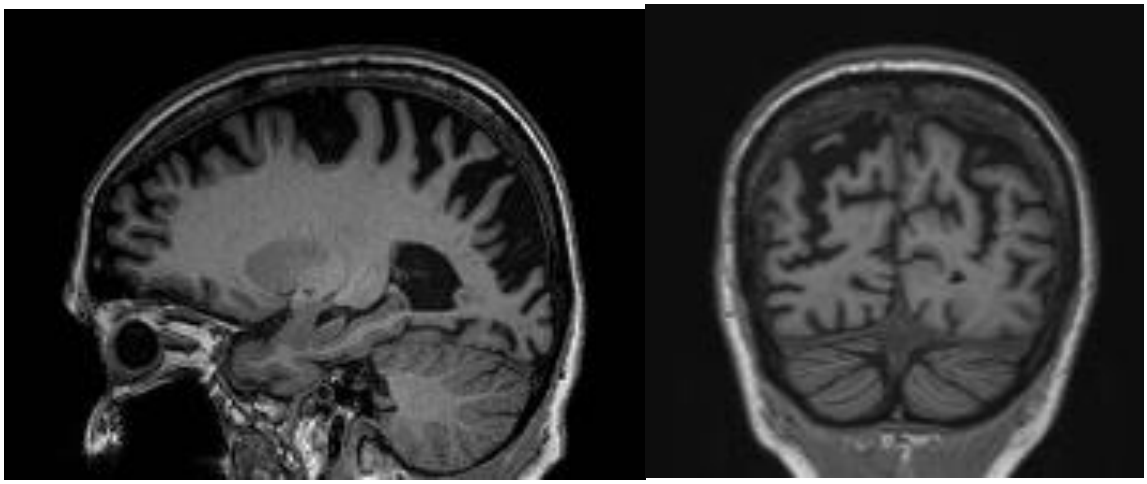

Figure 7 Visual rating scale for the posterior brain regions.

In sagittal, axial and coronal orientation, this rating scale rates 0 = no atrophy, 1 = minimal atrophy, 2 = moderate atrophy and 3 = severe atrophy (*PSC* posterior cingulate sulcus, *POS* parieto-occipital sulcus, *PRE* precuneus and *PAR* parietal lobe)

Reproduced from Koedam et al 2011

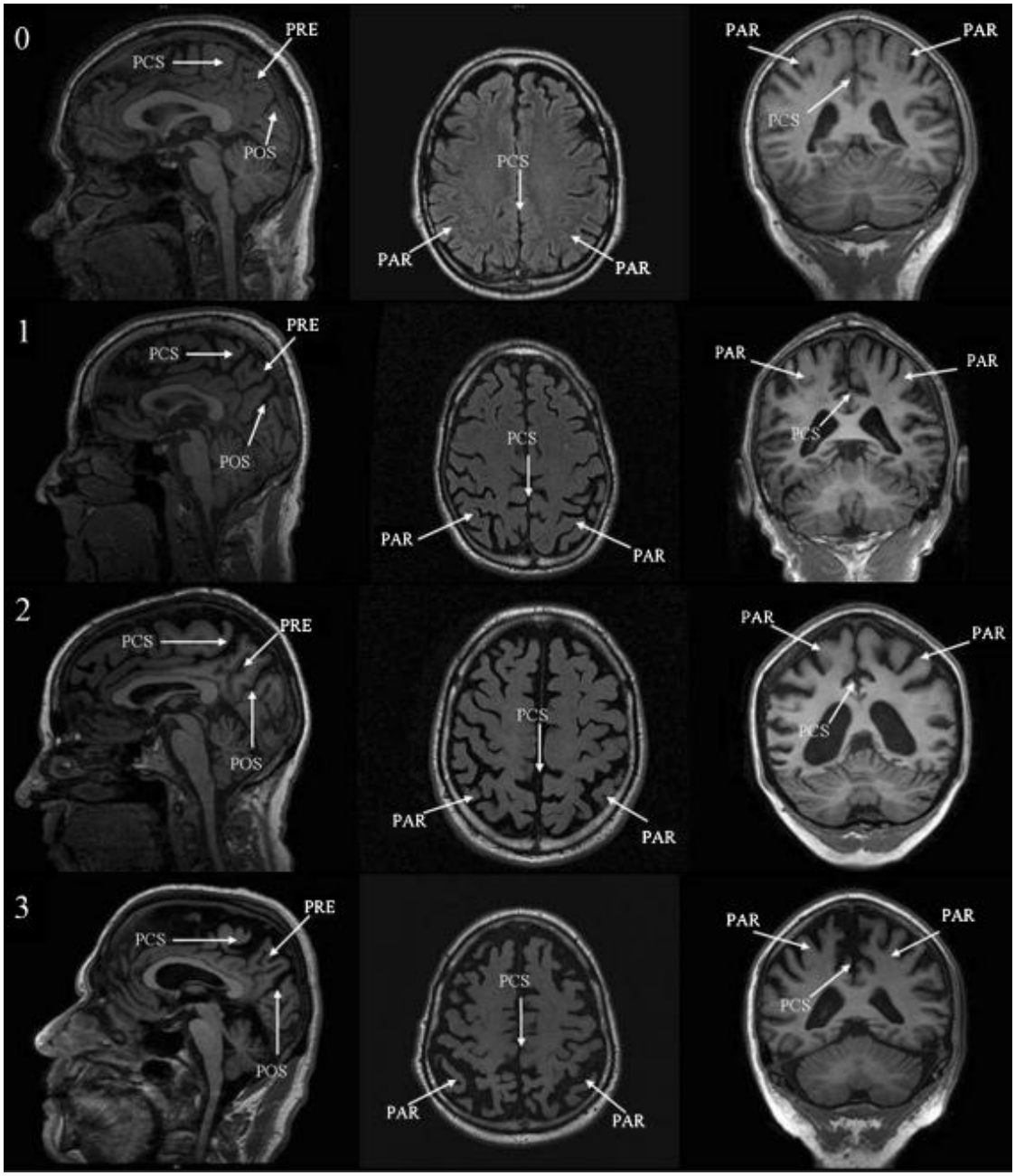
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Figure 8 Cortical ribboning – Heidenhein variant
Diffusion weighted imaging (1.5T MRI) shows right occipital lobe cortical ribboning in a patient presenting with a PCA phenotype

Reproduced from Townley 2018 (Fig 1a, left panel)

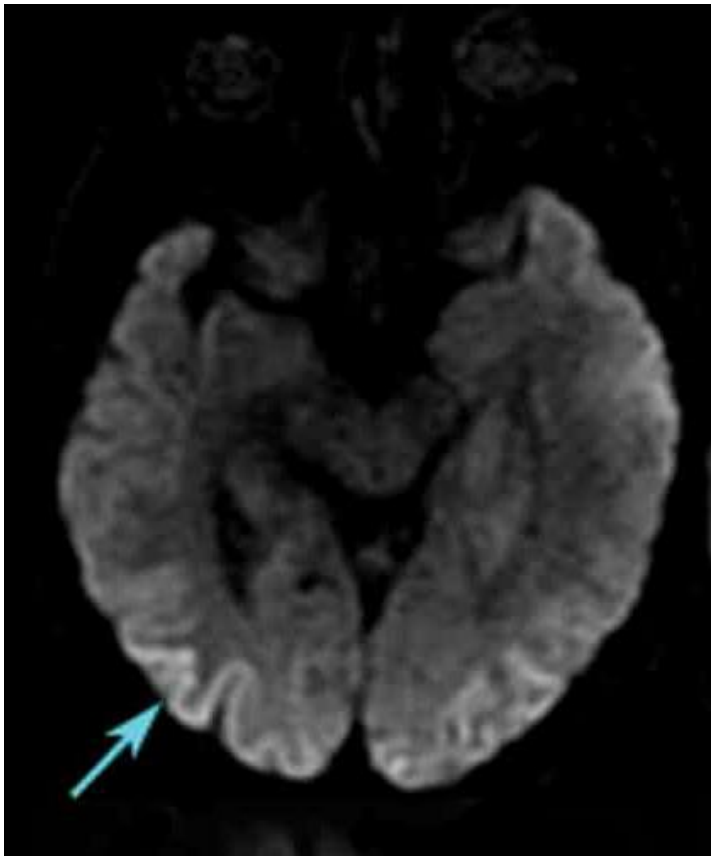


Figure 9 Multi-modal imaging in PCA

Single-participant axial images for one control participant and five patients with PCA showing cerebral blood flow (ASL), glucose metabolism (FDG-PET), atrophy (structural MRI), and amyloid deposition (florbetapir-PET). Amyloid deposition varies between individuals but is distributed throughout the cortex in all. Cerebral blood flow, hypometabolism and atrophy are by contrast all restricted to posterior cortical areas.

Reproduced from Lehmann et al, 2016

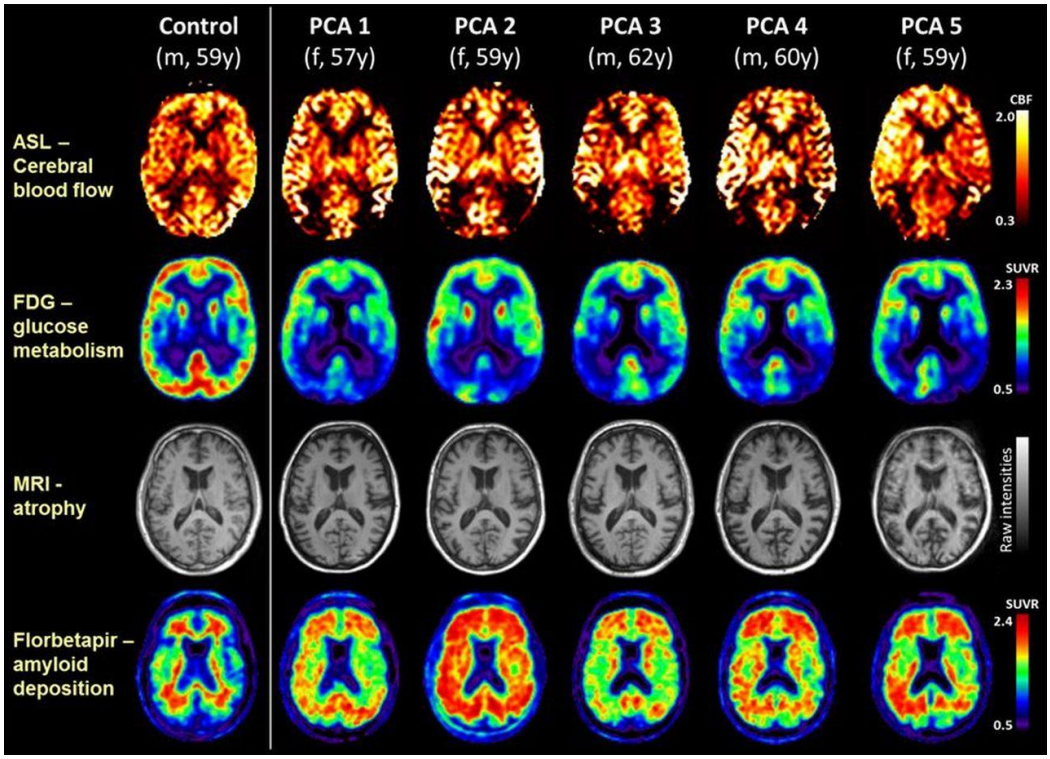
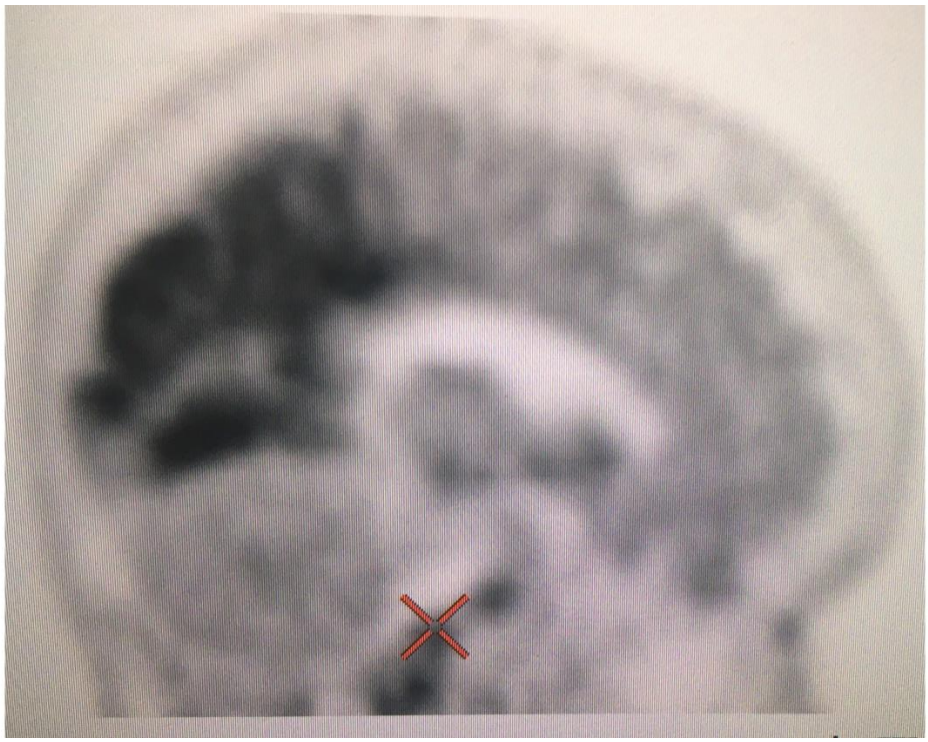


Figure 10 Tau imaging in PCA.
Flortaucipir (AV1451) PET imaging reveals focal parietal tau pathology.

New image



Case study 1 Report from Frank Benson' s original report of PCA

A 64-year-old former bank executive presented with episodes of anxiety that complicated a slowly progressive disturbance of vision and language. About eight years earlier, he had noted difficulty reading; he remained at his job, but his secretary had to read to him. Although still able to write, he could not read what he produced. Eventually, he also lost the ability to write and had difficulty finding his way in familiar areas (environmental agnosia) and in performing visually mediated tasks. The problems slowly progressed; he stated that what he saw disappeared before he could sense what it was. …On examination, he was alert, oriented, attentive, and in reasonably good physical health. His manner was gracious and his insight was painfully apparent.'

Case study 2 Delayed diagnosis of PCA

* New case report

Mrs A first visited an optician at the age of 50 years old, having noted difficulties driving and problems filling syringes and taking stitches out in her work as a hospital nurse. The optician noted a 'difficulty with peripheral vision' and referred her to an ophthalmologist who determined no ophthalmological basis for her difficulties. She subsequently returned to the optician who prescribed multi-focal lenses followed by two further pairs of spectacles at a total cost of $3000. Meanwhile Mrs A moved to a general practice nursing role, but noticed further difficulties with visually demanding tasks such as writing patient notes, reading prescriptions and transcribing information onto a computer. Her husband was also increasingly aware that Mrs A was not always seeing everything around her, particularly on the left; she became lost during barn dances and on one occasion they became separated when he turned left into the subway station they were walking to whilst she carried straight on. Over the course of six years, Mrs A attended for five hospital visits including one memory clinic appointment, the clinic letter from which asserted 'there does not appear to be any evidence of a dementia'. It was only when her husband and son themselves went through the radiological report from a brain scan and picked out the terms 'posterior', 'cortex', 'atrophy', and 'parietal' that diagnostic progress was made. He husband reported "I just Googled those words and what came up was Posterior Cortical Atrophy." Subsequent neuropsychological assessment revealed significant early visual, visuoperceptual and visuospatial dysfunction: despite good visual acuity (Snellen equivalent: 6/9), she failed tests of shape discrimination, dot counting and fragmented letter perception. There were additional deficits in numeracy, praxis and auditory-verbal short-term memory. These deficits were observed in the context of relatively well-preserved episodic memory on verbal recognition tasks, and only occasional errors in the phonological components of word retrieval. Regarding the PCA consensus criteria this cognitive profile is consistent with the PCA syndrome [Classification Level 1]. Neurological examination and review of neuropsychiatric symptoms revealed no evidence of symptoms consistent with any additional neurodegenerative syndromes [therefore 'PCA Pure' at Classification Level 2]. Standard visual rating of ^{18}F amyloid imaging yielded results consistent with Alzheimer's disease pathology [supportive of PCA-AD at Classification Level 3].

Video Clip 1 The late author Sir Terry Pratchett describes having PCA
https://www.youtube.com/watch?v=H0HIqfMV2cU

Video Clip 2 Living with PCA – and early misdiagnosis of stroke
https://www.youtube.com/watch?v=rAVUApnsk4M

Video Clip 3 A video animation depicting visual problems experienced in PCA
https://www.youtube.com/watch?v=a4eTGmejkRM

Video Clip 4 Visual disorientation in PCA.
Not previously published

Download here:
https://www.dropbox.com/s/7rwupl9h90wfeyi/Visual%20disorientation.pptx?dl=0

Consent form here:
https://www.dropbox.com/s/6mevfsn01z5douu/Continuum%20consent%20form.jpg?dl=0

The patient is asked to fixate on the examiner's face and to reach out and take the examiner's moving hand. He is able to see the moving hand (which he imitates), but has major difficulties in locating it in space.

Table 1 Evolving diagnostic criteria for PCA. Clinical Diagnostic Criteria for PCA from Tang-Wai (2004) and Mendez (2002); core features of the PCA clinico-radiological syndrome from Crutch (2017).

Tang-Wai et al., 2004	Mendez et al., 2002	Crutch et al., 2017
Core features Insidious onset and gradual progression Presentation of visual complaints in the absence of significant primary ocular disease Relative preservation of anterograde memory and insight early in the disorder Disabling visual impairment throughout the disorder Absence of stroke or tumor Absence of early parkinsonism and hallucinations *Any of the following findings:* Simultanagnosia with or without optic ataxia or ocular apraxia Constructional dyspraxia Visual field defect Environmental disorientation Any of the elements of Gerstmann syndrome **Supportive features** Alexia Presenile onset Ideomotor or dressing apraxia Prosopagnosia **Investigations** Neuropsychology: deficits referable to parietal and/or occipital regions	**Core diagnostic features (all must be present)** Insidious onset and gradual progression Presentation with visual complaints with intact primary visual functions Evidence of predominant complex visual disorder on examination Elements of Balint's syndrome Visual agnosia Dressing apraxia Environmental disorientation Proportionally less impaired deficits in memory and verbal fluency Relatively preserved insight with or without depression **Supportive diagnostic features** Presenile onset Alexia Elements of Gerstmann's syndrome Ideomotor apraxia Physical examination within normal limits **Investigations** Neuropsychology: predominantly impaired perceptual deficits Neuroimaging: predominantly occipitoparietal abnormality (especially on functional	**Clinical features** Insidious onset Gradual progression Prominent early disturbance of visual ± other posterior cognitive functions Absence of tumor, significant vascular disease include stroke, afferent visual cause or identifiable cause (e.g. kidney failure) sufficient to explain symptoms. **Cognitive features** Space perception deficit Simultanagnosia Object perception deficit Constructional dyspraxia Environmental agnosia Oculomotor apraxia Dressing apraxia Optic ataxia Alexia Left/right disorientation Acalculia Limb apraxia (not limb-kinetic) Apperceptive prosopagnosia Agraphia Homonymous visual field defect Finger agnosia Relatively spared anterograde memory, speech, nonvisual language, executive function and behaviour. **Investigations** Neuropsychology: deficits

Neuroimaging: Focal or asymmetric atrophy in parietal and/or occipital regions on structural imaging Focal or asymmetric hypoperfusion/hypometabolism in parietal and/or occipital regions on functional imaging.	neuroimaging) with relative sparing of frontal and mesiotemporal regions.	predominantly within space and object perception domains Neuroimaging: predominant occipito-parietal or occipito-temporal atrophy/ hypometabolism/ hypoperfusion on MRI/FDG-PET/SPECT

Table 2 Home Safety Tips & Recommendations for patients with PCA and other dementias with visual dysfunction

Adapted with permission from Alison Lake OT, Maria Martinez MSW and David F. Tang-Wai MDCM FRCPC, UHN Multidisciplinary Memory Clinic, University of Toronto

GENERAL ENVIRONMENT:

Simplify the environment

- Remove clutter and objects no longer in use; keep pathways clear.
- Remove unsafe furniture and accents: i.e. low height stools, chairs or tables.
- Options to decrease the potential falls risk from scatter rugs and door mats:
    - Remove unsafe scatter rugs/mats
    - Install non-slip under-padding
    - Replace with rugs/mats with a rubber backing
    - Secure all edges with double sided carpet tape (not for outdoor use)
- Relocate and secure trailing cords that are in high traffic areas.
- Ensure adequate lighting: use night lights, install extra lights fixtures.
- Leave lights on prior to nightfall.
- Diffuse bright light areas. Reduce glare by covering windows with binds, shades or sheer curtains to block direct bright sunlight. Avoid using bare light bulbs without shades.
- Obtain a door alarm and /or safety lock.
- Place stickers on large glass windows or large glass doors to prevent people from bumping or walking into to them.

Increase contrast

- Label room doors; use yellow paper with black writing.
- Paint doorframes and light switch plates in a contrasting colour to the wall.
- Contrasting colour dot to mark the number/button to release automatic door.
- Contrasting colour strips (paint or tape) or tactile cue at top and bottom of stairs, as well as on the edge of each individual step (both inside and outside).
- Use contrasting coloured adhesive strips to mark pathways to important areas: bathroom, kitchen, living room, laundry.

Kitchen

- Mark burners and stove dials with contrasting colour to make it easier to identify and to know when elements are hot.
- Dials at the front of the stove are more desirable then dials at the back of the stove in order to avoid reaching over the elements.
- Mark frequently used settings on the oven or other dials (e.g. 350 degrees or normal cycle for the dishwasher) with a bumper dot or contrasting tactile marker.
- Supervise the person while using the stove, and if necessary, disconnect the stove and other appliances when they are home alone.
- Mark the 1-minute button on the microwave with a contrasting colour bumper dot, tactile marker, bright tape or nail polish.
- Place cleaning supplies away from food supplies **** very important****
- Dispose of hazardous substances that are no longer needed and store other potentially hazardous substances in secured storage (locked cupboard, childproof door locks).
- Keep cupboard doors and drawers closed at all times and ensure everything is putaway in its proper place.
- Problem-solve an appropriate organizational structure to the kitchen; consider having one designated area of counter space for preferred and usual foods. Trial placing frequently used items on a contrasting mat or tray, located in the same place every day. This is in an attempt to increase independence in finding items and participating in meal preparation.
- Store/relocate frequently used items at accessible and visible level.
- Keep counters clear and minimize clutter.
- Consider using appliances with automatic shut-off; i.e., kettle.
- Other items to optimize safety, independence and participation in the kitchen:
    - Elbow-length oven mitts to ensure maximum protection.
    - Knife guard aid to enable safe use and pressure when cutting.
    - Cutting board with a black side and a white side to enhance contrast while cutting
    - Gooseneck lamp above the cutting area may also assist with vision
    - Large print timer
    - Liquid measure tool to assist in pouring liquids and avoid spills
    - Re-label jars and canned goods using a thick black marker, white recipe card, single words, and elastic bands.
    - Penfriend Audio Labeler or similar

Eating

- Use bright coloured contrasting dishes and ensure they are all one solid colour (no patterns and no ridged edges)
- Use a dark solid-coloured placemat if using light-coloured plates and use a light solid-coloured placemat if using dark plates.
- Light-coloured food will be easier to see on a solid dark-coloured dish and dark food on a light dish.
- Avoid patterned table clothes.
- Maintain a strict pattern for mealtime set-up. For example, always place the same utensils, drinking glass and condiments in the same place for every meal
- Avoid cluttering the eating area and only have necessary items within reach
- Use verbal directions as reminders of where items are located; i.e., "your glass is on your right," and "salt and pepper is on your left."
- Use plate guards during meal times

Bedroom

- Use bright, contrasting colour fitted sheet, top sheet, pillow cases. Each should be a different colour to optimize identification and orientation to and within the bed.
- Place a bright coloured mat on nightstand to contrast against items placed on it.

Dressing

- Label drawers and shelves with high contrast wording or pictures
- Remove clothes that are no longer being used; including permanent removal of clothes no longer worn and temporary storage of out-of-season clothing
- Simplify and organize arrangement of clothing; for example, group similar items together, one drawer for shirts and another drawer for pants
- Lay out clothing for the day
- Minimize clothing requiring buttons and zippers and replace with elastic waists, pull-over/on, and loose clothing
- Pin socks together when placing them in the laundry so they will stay matched.

Bathroom

- Reduce clutter on bathroom floor, countertop, in drawers and cabinets.

- Use high-contrast non-slip bath mat and install high-contrast grab bars in the shower or bathtub; use contrasting tactile strip on existing grab bars to differentiate from tub or towel bar.
- Pick up bathmat after each use and store appropriately to prevent falls.
- If there is noted difficulty accurately locating the toilet you may consider obtaining a toilet seat in a contrasting bright colour. Also consider obtaining a raised toilet seat with arms and the tape arms with a bright colour in contrast against the toilet seat
- Tape toilet-flushing handle in a contrasting bright colour.
- Label important areas in the bathroom: toilet, sink, bathroom door (yellow paper with black writing).
- Tape sink faucet handles with bright colour tape (use primary colour such as red, green, blue) to distinguish handle from the rest of the sink
- Keep soap in a bright container (i.e., red) with contrasting colour soap (i.e, white)
- Use sign as reminder to wash hands, flush toilet, brush teeth etc.
- Keep frequently used items (toothbrush, paste) in small shallow basket or on a mat to contrast items against the counter.
- Use toothpaste that contrasts in colour to the toothbrush and bristles: i.e. red toothpaste on white brush and bristles.
- Cover mirrors if necessary: often people with vision problems may not be able to recognize the item as a mirror.

Personal care

- Nails: Ensure nail care is done by a professional. Can be provided in-home.
- Footwear: Ensure appropriate footwear is used: flat, non-slip sole, enclosed toe and heel, Velcro fasteners.

Medication routine

- Supervision of medication routine is usually recommended
- Store medications in a secure place
- Remove and properly dispose of medications that are no longer needed or have expired
- Inquire whether the medication routine can be simplified (i.e., to once-a-day instead of three times a day)
- Other ways to simplify a meds routine: Pre-filled blister packs; dossette; list of current medications; medication schedule; medication alarms/reminders.

Stairs

- Ensure adequate lighting on the stairs; with switches at both the top and bottom
- Install secure railings on at least one if not both sides
- Install railing extensions beyond the top and bottom of the stairs.
- Remove or replace unsafe flooring with a non-slip surface.
- Contrasting coloured tape or paint on the edge of each step.
- Contrasting coloured tape or paint and/or tactile strip at the top and bottom of the

With progression:

- Safety gate to prevent use of stairs
- Arrange living area on one level

Communication and scheduling

- Use a phone with large print and high contrast numbers, as well as one-touch programmable numbers
- Program emergency and frequently used numbers to the one-touch programmable numbers and add tactile markers to increase ease of identification
- Set up a "memory centre" with the phone, keys, note pad, whiteboard with large writing area and black marker
- Include a paper, pen/pencil and task lamp beside the phone for messages.
- Place telephone on bright contrasting colour mat.
- Use contrasting coloured tape to outline phone cradle.
- If possible, utilize a service that requires voice activation for phone dialling
- Use talking watches or clocks to indicate the time and appointments.

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