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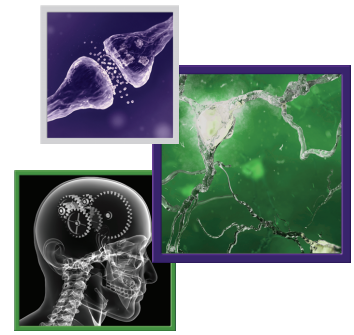
Neurodegenerative Disease Management



Diagnostic evaluation and monitoring of patients with posterior cortical atrophy

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Practice points

- Posterior cortical atrophy (PCA) is a complex syndrome that typically presents with initial reports of visual impairments that interfere with daily life but that are not adequately addressed through conventional ophthalmologic/optometry interventions.
- Thorough investigation of signs and symptoms and their impact on daily functioning are critical first steps in the clinical formulation of PCA.
- Taking a multidisciplinary approach that includes neuroopthalmology, neurology, neuropsychology and occupational therapy is important in both diagnosis and monitoring, given the complex interplay of visual and behavioral symptoms patients with PCA struggle with.
- Neuroimaging tools and fluid biomarkers can be helpful in diagnostic formulation: this includes looking for patterns of regional atrophy of posterior cortical regions on structural MRI, amyloid PET (if available) to identify likely underlying pathology and cerebrospinal fluid biomarkers indicative of Alzheimer's disease pathology.
- It is important to keep in mind how patients' visuoperceptual impairments may impact assessment of other cognitive domains, and that methods that do not rely on visuoperceptual abilities be used in cognitive evaluation.
- Given the relative preservation of insight and memory in PCA, symptoms of depression and anxiety may be prominent particularly early in the course of the disease. Early detection and treatment of psychiatric symptoms in PCA is important in optimizing functioning and independence in daily life.
- While there is currently no treatment that stops or slows progress of PCA, there are resources and services available to support patients and caregivers to maintain independence in functioning.

Posterior cortical atrophy (PCA) is a progressive neurocognitive syndrome, most commonly associated with the loss of complex visuospatial functions. Diagnosis is challenging, and international consensus classification and nomenclature for PCA subtypes have only recently been reached. Presently, no established treatments exist. Efforts to develop treatments are hampered by the lack of standardized methods to monitor illness progression. Although measures developed from work with Alzheimer's disease and other dementias provide a foundation for diagnosing and monitoring progression, PCA presents unique challenges for clinicians counseling patients and families on clinical status and prognosis, and experts designing clinical trials of interventions. Here, we review issues facing PCA clinical research and care, summarize our approach to diagnosis and monitoring of disease progression, and outline ideas for developing tools for these purposes.

First draft submitted: 23 December 2018; Accepted for publication: 3 May 2019; Published online: 8 August 2019

Future Medicine

Keywords: Alzheimer's disease • biomarkers • cerebral cortex • clinical trials • MRI • neuropsychology • positron emission tomography • posterior cortical atrophy

Posterior cortical atrophy (PCA) is a gradually progressive neurodegenerative syndrome often considered a 'visual variant' of Alzheimer's disease (AD). This cognitive–behavioral syndrome involves the selective loss of visual and/or other cognitive functions associated with neurodegeneration of posterior areas of the cerebral cortex, particularly parietal, occipital and sometimes posterior temporal regions. Visual fields or other elementary cortical visual functions may be prematurely affected as well. Memory, executive function, language, insight and comportment are typically relatively preserved, while anxiety or depression are common. Although in 60–80% of patients the pathology ultimately is determined to be AD, other neurodegenerative diseases may be responsible for PCA.

Here, we discuss our perspective on the diagnostic evaluation of patients suspected of having PCA based on direct clinical and research experience through our PCA program, and review our approach to the longitudinal monitoring and management of patients with the condition.

The original description of the PCA syndrome is attributed to Benson *et al.* [1], but multiple previous case reports describe patients with AD pathology who had prominent visual disturbances early in the course of the disorder [2]. In 1993, a detailed clinicopathologic report describing 'the visual variant of AD' called attention to the severe early visual and spatial impairment with occipito-temporoparietal plaque and tangle neuropathology [3]. Contemporary clinical diagnostic criteria emphasize the presence of progressive visual impairment with relative sparing of memory, language, behavior and insight [4,5]. The diagnostic criteria and terminology used to classify PCA vary, with some diagnostic criteria focusing on visual impairment [4,5], but others including a broader definition that includes disorders of language, movement, and somatosensory function associated with involvement of posterior cortical dysfunction [6]. As diagnostic criteria have evolved, some of these criteria have attempted to encompass both clinical and pathological features. For example, recently developed criteria for atypical AD include PCA [7], but the specific clinical phenotype is not described in detail and does not include PCA syndrome negative for AD biomarkers. Consistent with McKhann *et al.* [7], we employ a diagnostic formulation that specifies: the overall level of cognitive impairment (mild cognitive impairment [MCI] or dementia), the clinical syndrome of PCA (both of which are critically important for care and support planning), and the likely etiology (typically but not always AD). To address inconsistencies in defining PCA, an international working group convened in 2012 to develop consensus recommendations for diagnosis and classification of the syndrome. These criteria specify core features of PCA as well as putative subtypes recognized by the group, resulting in a classification framework based on multidisciplinary knowledge [8,9]. The consensus research diagnostic criteria are reproduced in Box 1.

Although current literature largely equates PCA with the visual variant of AD, studies suggest that AD neuropathology may account for anywhere between 65–77/–100% of all PCA cases [5,6,10]. Some studies have found other pathologies (Lewy body, corticobasal degeneration, prion diseases, frontotemporal lobar degeneration or rarely other neurodegenerative diseases) underlie a minority of PCA cases [5,11,12].

An additional challenge relates to epidemiology. The prevalence of PCA has been difficult to determine given the heterogeneity and inconsistency in diagnostic criteria across research and clinical settings. In some clinical cohorts at specialty dementia diagnostic centers, 5% of patients suspected of having some form of AD have the PCA syndrome [13]. Although there is some suggestion that there is a greater prevalence of PCA in women than men [5,13,14], a review of the literature points toward a roughly even distribution among men and women. Most investigators view PCA as a syndrome of relatively early age of onset (<70 years of age; [15]), although patients in our cohort have presented as late as age 78, and even later ages of onset have been reported.

General framework of neurodegenerative cognitive disorders along the mild cognitive impairment–dementia spectrum

Diagnostic terminology in the field of neurodegenerative cognitive disorders can be confusing in part because it variably refers to the clinical syndrome, neuropathology or a clinicopathologic entity. This terminology is evolving actively as an increasing number of *in vivo* biomarkers of neuropathology become available. Prior diagnostic criteria for dementia required memory loss (DSM–IV) [16], but it is now recognized that dementia is an acquired cognitive impairment that might initially affect domains other than memory (DSM–V) [7]. Prior clinical diagnostic criteria for AD required patients have dementia in order for a diagnosis to be made) [16], but contemporary criteria acknowledge that there are a variety of clinical phenotypes with which patients with likely AD pathology may

Box 1. International consensus research diagnostic criteria for posterior cortical atrophy.

Clinical features
- Insidious onset
- Gradual progression
- Prominent early disturbance of visual function and/or other posterior cognitive functions

Cognitive features

At least three of the following must be present as early or presenting features and were the predominant features initially impacting activities of daily living:
- Space perception deficit
- Simultanagnosia
- Object perception
- Constructional dyspraxia
- Environmental agnosia
- Oculomotor apraxia
- Dressing apraxia
- Optic ataxia
- Alexia
- Left/right disorientation
- Acalculia
- Limb apraxia
- Prosopagnosia
- Agraphia
- Homonymous visual field deficit
- Finger agnosia

All of the following must be evident:
- Relatively spared anterograde memory function
- Relatively spared speech and nonvisual language functions
- Relatively spared executive functions
- Relatively spared behavior and personality

Neuroimaging
- Predominant occipito-parietal or occipito-temporal atrophy (MRI) or hypometabolism (FDG-PET) or hypoperfusion (SPECT)

Exclusion criteria
- Evidence of a brain tumor or other mass lesion, cerebrovascular disease, afferent visual cause or other identifiable causes for cognitive impairment (e.g., renal failure)

Reproduced with permission from [9].

present. Furthermore, with contemporary biomarkers, it is possible to diagnose patients with cognitive impairment likely due to AD at the stage of MCI, prior to dementia [17].

In an attempt to systematize the clinical approach to this spectrum of disorders, we advocate for a three-step diagnostic formulation in cases of suspected neurodegenerative cognitive impairment, summarized in Figure 1 and more explicitly delineated elsewhere [18]. The first step denotes a patient's overall clinical status as one of normal cognition, subjective cognitive decline, MCI or dementia. This designation is based on a clinical judgment regarding the impact of cognitive impairment on a patient's ability to carry out usual activities in daily life independently. The second step aims to determine whether the patient's symptoms and signs match a recognized clinical syndrome or phenotype, such as amnesic MCI, behavioral variant frontotemporal dementia, primary progressive aphasia or the PCA syndrome. The third step aims to establish the likely etiology of the clinical syndrome using prior probabilistic clinicopathologic knowledge and laboratory tests and biomarkers, including structural MRI and FDG-PET and biomarkers of specific molecular pathological features, where available.

Based on this framework, many patients with PCA would present with nonamnesic MCI or mild dementia with a syndrome of predominant visual or visuospatial impairment (PCA syndrome). The likely etiology would be captured by describing the diagnosis as, for example, PCA likely due to AD pathology, PCA likely due to Lewy body disease or PCA likely due to corticobasal degeneration. Some patients present at a stage when they are still clearly independent in daily function – consistent with a nonamnesic MCI stage – while other patients have lost enough independent functioning to be considered at the very mild or mild stage of dementia.

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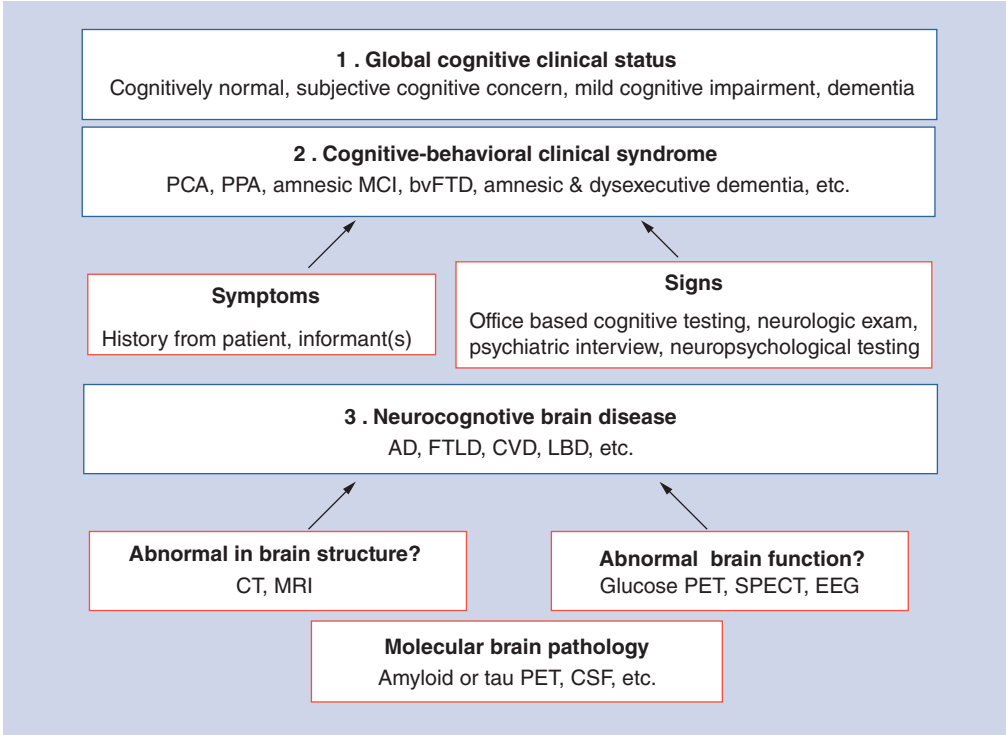

Figure 1. Diagnostic formulation of neurocognitive disorders. We advocate for a three-tiered approach to diagnostic formulation in cases of suspected neurodegenerative cognitive impairment. The first tier denotes a patient's overall clinical status as one of normal cognition, subjective cognitive decline, MCI or dementia. The second tier aims to determine whether the patient's symptoms and signs match a recognized clinical syndrome or phenotype, such as PCA, PPA, amnesic MCI, bvFTD or amnesic and dysexecutive dementia. The third tier aims to establish the likely etiology of the clinical syndrome using prior probabilistic clinicopathologic knowledge, laboratory tests and biomarkers, including measures of brain structure (CT or MRI scans), brain function (FDG or glucose PET or SPECT scans, in some cases EEG and biomarkers of specific molecular pathological features measured with specialized PET scans or CSF, where available.
AD: Alzheimer's diesea; bvFTD: Behavioral variant frontotemporal dementia; CSF: Cerebrospinal fluid; CT: Computed tomography; CVD: Cardiovascular disease; EEG: Electroencephalogram; FDG: Flurodeoxyglucose; FTLD: Frontotemporal lobar degeneration; LBD: Lewey body disease; MCI: Mild cognitive impairment; MRI: Magnetic resonance imaging; PCA: Posterior cortical atrophy; PET: Positron emission tomography; PPA: Primary progressive aphasia; SPECT: Single-photon emission computed tomography.
Data taken from [18].

Clinical constructs of posterior cortical atrophy: signs & symptoms

Patients who are ultimately diagnosed with PCA usually come to clinical attention initially because they are experiencing symptoms (subjective experiences) that interfere with daily life. In the case of PCA, symptoms reported typically started with visual changes that led patients to seek an evaluation by an optometrist or ophthalmologist. Despite being given prescription glasses or having their prescription changed, patients report little to no improvement in their symptoms. It is common for patients to have had symptoms for more than a year before a diagnosis of PCA is made.

When a patient first presents in our clinic, we conduct a thorough structured interview with the patient and separately, with an informant who knows the patient well (e.g., spouse or adult child). From this interview, we determine the nature of the symptoms, the context in which the symptoms are experienced, and the degree to which the symptoms interfere with normal functioning. We also review pertinent negative findings (i.e., the absence of symptoms such as memory loss, behavioral/comportmental changes, etc.). The details obtained from the in-depth characterization of these symptoms then guide us through a hypothesis-driven neurologic and neuropsychological assessment that identifies the presence and severity of signs (objective indications) of the illness. The diagnosis of PCA thus is reached based on symptoms reported by the patient (e.g., difficulty navigating in unfamiliar or familiar environments), signs detected by the clinician that may not have been noticed by the patient (e.g., the inability

to identify individual fingers during the neurologic examination), and phenomena that can be both described as a problem by the patient and observed on formal testing (e.g., difficulty seeing more than one object at a time on a cluttered surface). To the best of our knowledge, there are no published instruments yet that support the assessment of PCA symptoms, and signs of the syndrome often are evaluated qualitatively rather than quantitatively. Here, we summarize the symptoms and signs that are currently used to diagnose PCA, acknowledging that the conceptualization of some of these phenomena is rooted in traditions of cognitive neurology and neuropsychology and may be in need of revision as relevant fields of cognitive neuroscience advance.

Typically, the initial clinical presentation involves report of an insidious onset and gradual progression of predominantly visuospatial or visuoperceptual symptoms; all other cognitive and behavioral domains are relatively spared in comparison, although not always entirely normal. Patients may describe visual disturbances such as blurred or partially obscured vision ('looking through a gossamer or veil') or glare sensitivity that interferes with reading, writing or negotiating the physical environment (e.g., resulting in tripping or mis-stepping off a curb, problems navigating and orienting geographically). In the face of normal ophthalmologic findings, further probing into the symptoms reveals impairments of higher-order visual processing with or without hemianopsia or other primary cortical visual loss. For example, patients may report difficulty reading digital clocks or signage. They are unable to identify or find objects in plain sight, especially when those objects are embedded in complex, cluttered environments (e.g., keys on a desktop or in a kitchen drawer); this is a condition known as simultanagnosia. Patients may also be unable to see objects on similarly colored backgrounds (e.g., a brown purse on a brown chair) or misjudge the placement of objects (e.g., a glass too close to the edge of a table). They often misjudge distance while driving, leading to minor scrapes and dents in an automobile, or bicycle or automobile accidents. Some patients report disorientation in the environment and getting lost in familiar areas (an example of topographical disorientation, where one loses sense of direction or ability to use landmarks for navigation). Visuoperceptual, spatial or higher level somatosensory or motor control disturbances that often occur in PCA can cause problems with dressing due to difficulty orienting oneself in relation to clothing (dressing apraxia), and problems reaching accurately for objects in space. In some cases, patients with PCA have difficulty recognizing familiar objects (visual agnosia) or familiar faces (prosopagnosia).

Patients with PCA can also present with elements of Balint syndrome. While the full-blown syndrome may not be present early in the course of the disorder, patients may report symptoms of what is ultimately determined on evaluation to be signs of simultanagnosia, optic ataxia and oculomotor apraxia – the core elements of Balint syndrome. These signs are typically ascertained on formal neurologic or neuropsychological examination, although experienced clinicians can recognize signs based on patients' descriptions of symptoms alone. For example, in the case of simultanagnosia, patients may report perceiving only parts of what is around them in a room or a scene, resulting in an inability to appreciate the overall meaning of what they see. They may be unable to attend to more than one object in view at a time, as evidenced by their description of only some of the objects or people in a room. They may also fail to direct visual attention and gaze in order to scan the visual field fully or respond to stimuli (also known as oculomotor apraxia). Finally, they may report 'clumsiness', or difficulty reaching for objects precisely (a symptom associated with optic ataxia).

PCA patients can also present with symptoms of Gerstmann syndrome. Although its validity as a distinct syndrome (rather than an artifact of observer bias, a reflection of aphasia or the result of extensive neurodegeneration) is debated [19], this syndrome includes acalculia, right–left disorientation (confusion with body-centered right and left side of space), agraphia, and finger agnosia. Acalculia may manifest as an impaired ability to perform simple calculations or a loss of numeracy (the appreciation of number values and magnitude, and/or the ability to reason and apply simple numerical concepts). Difficulty with calculations may occur also because of reading or writing impairment or disordered spatial organization of numbers on a page due to neglect, misalignment or number inversions. In these cases, patients report difficulties balancing their checkbooks, paying bills, transcribing numbers for addresses, counting out money for purchases or understanding measurements (e.g., for a recipe). Agraphia in these patients typically reflects visuoperceptual and visuospatial problems that result in an inability to write in a straight line or with normal spacing of letters and words, to copy the written word, or to sequence and orient writing properly. In a subset of cases, agraphia may also reflect spelling problems that result from a loss of orthographic knowledge. Finger agnosia typically is not apparent as it has less impact on daily functioning, as dexterity is relatively normal and does not manifest unless tested directly.

A dyslexic syndrome often develops in PCA, reflecting an inability to recognize the printed word or to generate eye movements/saccades from word to word such that they are able to track text on a page or move their gaze

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from the end of a printed line to the beginning of the next line. Patients may also experience more peripheral reading problems with visually complex text (e.g., handwritten or cursive text). Mendez *et al.* [20] found that PCA patients can develop an 'apperceptive alexia', resulting from the visuoperceptual and visuospatial deficits that lead to difficulty integrating text. The authors also suggested that phonological processing dysfunction may be present and contribute to reading difficulties.

A subset of PCA patients may also have word retrieval (due to anomia or naming problems) and comprehension difficulties, most noticeably in conversation. They may ask for questions or comments to be repeated, a behavior which appears to an outsider as a hearing difficulty or memory problem rather than a language difficulty *per se*. Such language impairment is consistent with findings by Crutch *et al.*, who found that PCA patients show disturbance of phonological processing and word retrieval/access [21]. Together, the symptoms of alexia, agraphia, and diminished comprehension and naming problems in the context of normal repetition and speech production constitute what Benson *et al.* [1] referred to as a transcortical sensory aphasia syndrome.

Praxis, or the ability to perform skilled, voluntary movements, often is affected in PCA as well. Patients describe problems with hand–eye coordination, but they or informants are rarely aware of this impairment unless it is severe enough to impact functioning in daily life. Apraxia is apparent with tool use or manipulation of common objects and most noticeable when a subject is asked to pantomime their use (e.g., striking a match and blowing it out, brushing one's teeth). In these situations, patients may use body parts as a stand-in for the objects rather than manipulate an imaginary object, suggesting they either do not understand that they are to pantomime or they cannot complete the task even though they understand it. Should patients still demonstrate difficulty pantomiming the action correctly despite feedback and the examiner's efforts to correct the patient (and in the absence of a language comprehension deficit), this is likely apraxia.

Are there subtypes of posterior cortical atrophy?

There is currently limited evidence from structural neuroimaging or neuropsychological studies to suggest discrete PCA subtypes. However, the following qualitative descriptions of different phenotypes have been suggested by Crutch *et al.* [9] as a starting point for research studies.

The biparietal (dorsal) variant is defined by the presence of "early, predominant, progressive visuospatial dysfunction, with features of Gerstmann or Balint syndromes, neglect and limb-kinetic apraxia." The occipitotemporal (ventral) variant is characterized by the presence of a predominant and progressive impairment of visual identification of objects, symbols, words or faces; this variant may include patients who report symptoms of a progressive prosopagnosia. In our experience, most of these patients also exhibit symptoms or signs suggestive of dorsal system involvement. The primary visual (caudal) variant of PCA involves mainly occipital cortical degeneration with predominant impairments in basic visual perceptual abilities; however, this variant is rare relative to the first two variants. Finally, a dominant parietal variant is associated with primary impairments in calculation, praxis and spelling, and arises as a result of more prominent involvement of dominant/left posterior cortices. This variant appears not to be rare in the PCA spectrum and may in fact be a 'non-visual' presentation of the disorder with elements of Gerstmann syndrome and transcortical sensory aphasia. Notably, this presentation is not to be mistaken with disorders such as logopenic-variant primary progressive aphasia (lv-PPA): in the case of PPA, detailed investigation may reveal impairments in visual cognition, but they are not the primary symptoms or signs of the disorder.

What differentiates posterior cortical atrophy from a typical Alzheimner's disease clinical syndrome?

In contrast to PCA, typical AD dementia is characterized by initial presentation and early dysfunction in episodic memory. Visuospatial deficits occur at the stage of mild dementia, but at a level less severe than those observed in the early stages of PCA. The visuospatial deficits in typical AD are relatively mild in comparison to other symptoms and signs, and manifest on visual construction tasks or in activities reliant on spatial function (i.e., navigation). More complex deficits such as simultanagnosia and visual hemineglect do not usually occur until the moderate stage of typical AD dementia.

Onset of episodic memory dysfunction in PCA is variable and a matter of some debate and active research (e.g., [22]). In our experience there is substantial variability in the types of memory problems demonstrated in PCA. Patients may report forgetfulness for conversation details or recent events, misplacement of personal effects or describe 'action lapses', where they enter another room and momentarily forget the reason. These lapses, however, can

reflect disturbances in attention, auditory working memory or visuoperceptual functioning. Additionally, memory (specifically, learning/encoding) may be undermined by reading and writing difficulties often seen in patients with PCA (as described above), 'degrading' the stimuli that the patient is attempting to learn and remember. In some cases, it may be difficult to classify a patient as fitting best with the dominant hemisphere variant of PCA or a progressive aphasia due to the presence of language-related disturbances; this topic deserves further investigation.

PCA and AD patients not only demonstrate differences in their cognitive profiles but they also may demonstrate differences in psychiatric symptoms. PCA patients often demonstrate greater insight and awareness into their deficits compared with AD patients due in part to the relatively preserved memory for the visual changes they experience; as a result, mood symptoms (anxiety, depression, irritability) can be seen as an early symptom in PCA.

Approach to the comprehensive diagnostic evaluation of a patient with suspected posterior cortical atrophy

Neurological assessment

When evaluating a patient, our first goal is to determine whether the overall characteristics and temporal course of cognitive–behavioral symptoms are consistent with a neurodegenerative dementia-spectrum illness. Additionally, we assess whether the patient's overall functional status fits best with dementia, MCI, subjective cognitive decline (cognitive symptoms without evidence of impairment on formal testing) or normal cognition. At this stage, we think broadly in our differential diagnosis to include possibilities such as cerebrovascular disease; encephalopathy (e.g., chronic encephalopathies due to immune-mediated conditions); a primary or metastatic brain tumor; or a mood, psychiatric or sleep disorder. We focus primarily on obtaining a comprehensive initial neuropsychiatric/medical history, details regarding premorbid level of functioning, quality and changes in cognitive abilities, activities of daily living, socioemotional behavior, and comportment depending on the neuropsychiatric and medical context. To obtain this information, we rely on a combination of questionnaires (e.g., everyday cognition scale [23]; functional activities questionnaire [24]; and the activities of daily living questionnaire [25]). In certain contexts, we use a semi-structured interview to rate type and severity of symptoms that the patient and/or family perceives. In most patients presenting with an early PCA syndrome, we typically conclude this first step in the diagnostic formulation by determining that the person has MCI or very mild dementia because they are either largely independent in daily function or have lost some higher-level functions such as work, driving or bill-paying.

As part of this history-taking, we identify the specific symptoms about which the patient and/or family are concerned, surveying all major cognitive domains. When the most prominent symptoms are gradually progressive visual dysfunction suggestive of visual cortical dysfunction, we assess the presence or absence of 'neighborhood' symptoms including difficulties with calculations, writing, or body position sense; left–right confusion; problems with object location in the visual field; and visual hallucinations or illusions. It is useful also to know whether the patient's basic visual functioning had been evaluated by an ophthalmologist or optometrist and the results of the assessment to ensure that ocular pathology is not contributing to the presenting visual impairments. We almost always refer patients for a neuroophthalmologic evaluation for additional detailed evaluation of visual perception and oculomotor function if one has not already been obtained. It is important for ophthalmologists to be particularly attentive to a PCA patient's tendency to miss letters on an acuity chart and show homonymous field defects [5,26]. Homonymous hemaniopia or quadrantanopia has been found in up to 50% of PCA patients, with homonymous visual field defects increasingly recognized as an early sign of PCA [5]; in some cases, visual field defects may even precede the onset of high order visual dysfunction [27,28].

We perform a neurological exam and office-based cognitive assessment, using such standard assessment tools as the Montreal Cognitive Assessment [29] to capture overall level of impairment. Results from such global cognitive assessments may assist in facilitating clinical research or trial referral, and serve as a baseline for longitudinal monitoring. We supplement these standard assessments with personalized evaluations based on the patient's symptoms or signs, including additional tests of reading, writing, visual perceptual tasks and visual constructional tasks.

For the second major step in diagnostic formulation, we integrate information about symptoms and signs of impairment to define the syndrome. Thus, a patient presenting with a primary visual and/or spatial cognitive impairments with relative sparing of memory and other cognitive domains may meet current syndromic diagnostic criteria for PCA. In other cases, visual cognitive impairment may be a prominent feature in the clinical presentation but other impairments (in memory, executive functioning) may be clearly present, in which case the formulation may be best defined as a visually predominant multidomain dementia.

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Table 1. Examples of neuropsychological test instruments by cognitive domain used in the assessment of posterior cortical atrophy.

Cognitive domain	Primary test
Baseline/premorbid functioning	WAIS-IV information, vocabulary Tests of single-word reading (e.g., TOPF) Highest level of formal education; occupation
Attention/executive functioning	Digit span (auditory) Spatial span (Corsi block) Mental alternation test Verbal fluency measures (letters, categories; D-KEFS category switching), WAIS-IV similarities D-KEFS (Proverbs, 20 questions)
Memory	List-learning measures (e.g., CVLT-II); Story memory (e.g., WMS-IV Logical Memory)
Language	Verbal fluency (letters, categories); auditory naming test Boston Diagnostic Aphasia Exam Open-ended questions for conversational speech Sentence writing
Basic visuoperception/visuospatial skills	Object/letter cancelation; line bisection; verbal description of complex scene; BORB (size/length/orientation discrimination; overlapping figures), VOSP Benton Facial Recognition Test Queen's Square color identification Famous faces
Numeracy	Graded Difficulties Arithmetic (oral presentation); WAIS-IV Arithmetic

BORB: Birmingham object recognition battery; CVLT-II: California Verbal Learning Test - 2nd; D-KEFS: Delis–Kaplan executive function system; TOPF: Test of premorbid functioning; VOSP: Visual object space perception battery; WAIS-IV: Wechsler Adult Intelligence Scale - fourth edition; WMS-IV: Wechsler Memory Scale - fourth edition.

The history and neurological examination also support the development of the third major step in the diagnostic formulation: the likely neuropathological etiology. If the history and examination are consistent with relatively focal visual–cognitive dysfunction, atypical AD pathology may be suspected. If the history and examination identify disturbances in motor (including dexterity, tremor, myoclonus, gait, balance) or autonomic functions, or in sleep (including dream enactment), pathology associated with Lewy body disease or Corticobasal degeneration (Lewy bodies/neurites, tau) might be suspected.

Neuropsychological assessment

Neuropsychological assessment in patients with suspected PCA is typically conducted with three objectives in mind: to clarify a patient's cognitive profile and help with diagnosis; to assess the extent and severity of any cognitive impairment, with an eye towards identifying appropriate behavioral interventions or environmental strategies that optimize independent functioning; and to establish a baseline to monitor progression of the disease and modify treatment plans as needed. For patients where the diagnosis of PCA has already been made provisionally and who present with reports of visuoperceptual impairments, it is important that the test results represent a true measure of the patient's full range of cognitive abilities irrespective of visuospatial/perceptual impairment. We therefore propose the following approach to test selection and administration, by cognitive domain (see Table 1).

Baseline/premorbid level of functioning

In addition to comparing a patient's test performance to an age- and education-matched normative sample, we interpret performance relative to the patient's presumed premorbid level of functioning. Tests of 'crystallized' knowledge (e.g., Information or Vocabulary subtest of the Wechsler Adult Intelligence Scale–IV [WAIS-IV] [30]), along with an individual's highest level of formal education attained, are typically used to determine the patient's baseline; these measures are particularly appropriate in PCA given that there is no demand on visual perception of stimuli. Should visuoperceptual skills be preserved at the single-word reading level, tests that involve reading of irregularly spelled words (e.g., test of premorbid functioning [TOPF] [31]) can also be used as an estimate of premorbid ability [32].

Attention/executive functioning

Attention is the foundation upon which many other cognitive abilities are built. Thus, we often start off by assessing a patient's simple auditory attention and working memory with a digit repetition task (repeating numbers forward and backward). Additional administration of a visual parallel to this test, such as the Corsi Block tapping test,

helps the examiner assess the extent to which problems in this domain are in fact problems with attention rather than modality-specific (visual) problems affecting stimulus processing. Evaluation of more complex attentional functions (sustained attention/concentration, mental flexibility/set shifting) is completed with tests such as the Mental Alternation Test [33], a verbal variation of the Halstead–Reitan trail-making test or the category-switching test from the Delis–Kaplan Executive Function System (D-KEFS; alternating production of exemplars from two categories such as fruits and furniture items [34]). While tests of verbal fluency are traditionally thought of as indicators of rapid word retrieval, they also measure speed of thinking, and to some extent, capacity to conduct an organized search and retrieval strategy of long-term knowledge. Abstract reasoning and problem-solving can be assessed with additional subtests of the D-KEFS (20 Questions or Proverbs subtest) or the similarities subtest of the WAIS.

Memory

To the extent that patients with PCA present with visuoperceptual impairments, assessing visual memory would yield little information, given the likely inability of the patient to encode 'degraded' stimuli secondary to visuoperceptual problems. Thus, memory assessment is best achieved through auditorally presented stimuli (having patients learn and recall word lists or brief narratives). List-learning tests that involve repeated presentation of test items help to distinguish memory impairment due to poor auditory working memory from deficits in memory consolidation. In our experience, many patients with PCA have some degree of auditory-verbal working memory impairment, and thus may experience difficulty encoding word lists, particularly if only allowed a single presentation. Ensuring that material is encoded is necessary for evaluating storage and retrieval memory processes.

Language

While also a test of executive functioning, verbal fluency is considered a measure of phonological processing (when the patient is asked to generate words that begin with a specified letter), and to some extent, an estimate of the integrity of semantic memory (when tested with categories). These data give us insight into a patient's language access and retrieval. We also administer an auditory naming test (rather than the traditional picture naming test) to assess further the integrity of semantic memory and retrieval [35]. Grammar and fluency in speech are best evaluated through the patient's responses to open-ended questions or prompts (e.g., "Tell me what a typical day is for you."). Comprehension/receptive language is assessed informally throughout the evaluation based on the patient's ability to follow complex task instructions but also can be tested formally with simple and multi-step commands (e.g., Boston Diagnostic Aphasia Exam [36]). Reading at the single word, sentence, and paragraph levels are used to gauge the extent to which a reading disorder is present and caused by problems at the perceptual or semantic/conceptual level. While it would be expected that visuoperceptual and visuospatial difficulties affect word identification, understanding the patient's reading capability (comprehension, speed) is important nonetheless given the impact reading impairment has on functioning in daily life. Again, subtests of the Boston Diagnostic Aphasia Exam can be used for these purposes. A writing sample is often obtained to assess for agraphia, and can be elicited by having patients write a sentence of their choosing ("Write a sentence about what you had for breakfast today.") or a narrative describing what they perceive in a complex scene (such as the Cookie Theft Picture). The latter can also be used to assess for simultanagnosia (see 'Visuospatial/perceptual' section below).

Visuospatial/perceptual

Assuming basic visuoperception is normal at the ophthalmologic level, determining the presence of neglect or inattention to side of visual space and visual scanning would be important, as such difficulties affect performance and interpretation of results in the visual domain more generally. These assessments can be accomplished either during the neurologic or neuroopthalmalogic examinations (as described above) or on neuropsychological testing, using object or letter cancellation tests, line bisection tasks, or through a verbal description of a complex scene. Patients are often also asked to copy designs of progressive complexity to assess the extent of visuoperceptual impairments and their impact on constructional praxis (Figure 2); performance on these tasks may also help identify subtypes of PCA given that construction ability tends to localize to parietal lobe function.

While the majority of PCA patients have consistently been considered to exhibit predominantly dorsal rather than ventral stream presentations [37], it is now clear that the disorder can affect both dorsal and ventral ('where' and 'what') streams of the visual network to varying degrees. Lehmann *et al.* [38] suggested based on the neuropsychological and neuroimaging findings that fundamental components of vision are not affected uniformly in PCA; higher-order

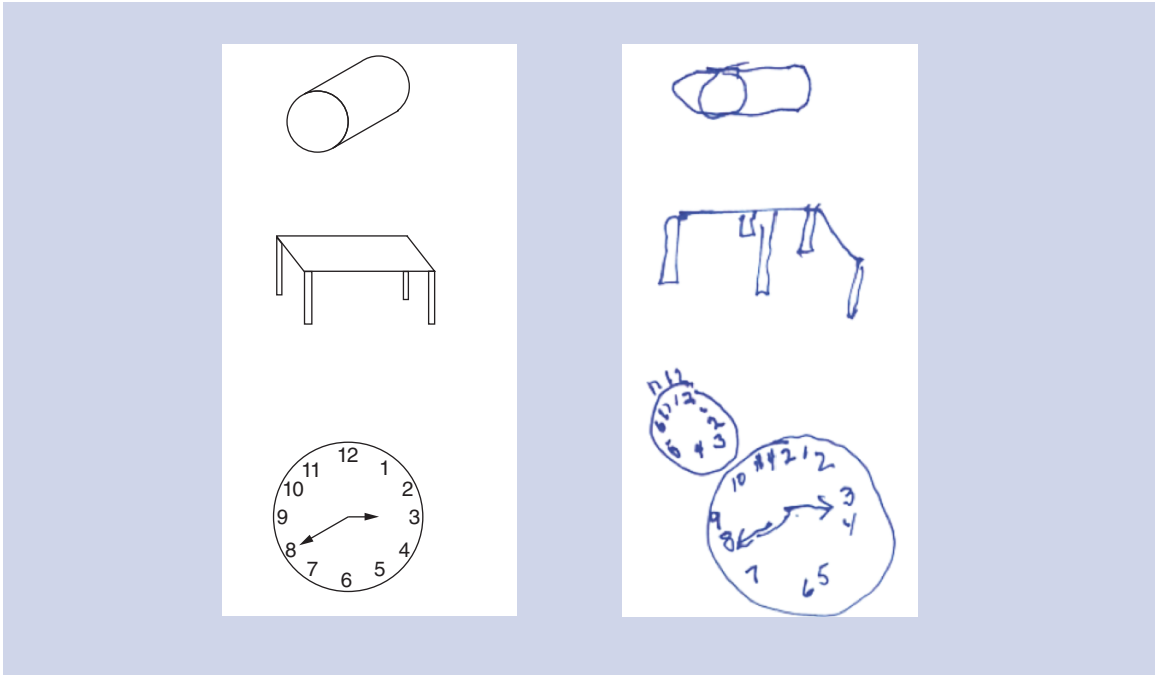

Figure 2. Example of visuoconstruction impairments in posterior cortical atrophy.

visual impairments are associated with different patterns of basic visual processing deficits. Their data do not clearly support the existence of discrete dorsal and ventral subsyndromes within PCA, suggesting that purported subtypes may be more likely to represent points along a continuum in topological distribution of cortical dysfunction. For example, in the case of a patient who exhibits what appears to be a ventral presentation (difficulties with single word, face, and object recognition), impairments may partially if not heavily reflect basic difficulties in perceiving and discriminating form. Routine assessment of lower-level visual processing is thus important to better characterize the pattern of deficits, which may have implications for the types of behavioral interventions or environmental adaptions that can be implemented.

Toward this end, we find that tests that involve size/length/orientation discrimination from the Birmingham object recognition battery (BORB) [39], figure ground detection, point localization task from the visual object space perception battery (VOSP) [40], shape detection (Efron shape discrimination test), color perception/discrimination, and visual crowding tasks (all tasks associated with the occipital lobe) may be particularly helpful in identifying impairments in basic level perceptual functions needed for object recognition. Usual/unusual view tasks could be considered a means to assess familiar objects presented under different degrees of visual complexity, with deficits on such tasks being more consistent with an apperceptive agnosia. Location and spatial relations (considered dorsal stream abilities) can be assessed through subtests of the VOSP, although many of the subtests in this battery may be too difficult for patients who are more advanced in the disease course. Should basic visual function and object identification appear to be relatively spared, assessment of simultanagnosia can be accomplished by having the patient describe a complex visual scene or identifying overlapping line drawings (a subtest of the BORB).

Assessment of facial perception and recognition is another category that warrants attention, particularly as these are important for social contact and provide an additional measure of ventral stream involvement in PCA. We assess basic face perception and discrimination with the Benton Facial Recognition Test [41]. Should face discrimination be preserved, evaluation of the patient's memory/semantic knowledge can be further assessed through a famous faces paradigm, where their ability to recognize famous individuals (politicians, figures from entertainment or sports) is tested. The inability to recognize famous or familiar faces is considered a form of face blindness or prosopagnosia, given the dissociation between perceptual processes and the loss of association with semantic information about these individuals in long-term knowledge. Prosopagnosia results in an inability not only to recognize the individual but also difficulty in providing information about them (such as their occupation, what they are famous for). It may also result in the endorsement of unfamiliar faces as incorrectly familiar.

Numeracy

As some patients present with components of a Gerstmann Syndrome such as acalculia, we also assess numeracy skills through a graded difficulties arithmetic test [42] or the arithmetic subtest of the WAIS-IV. These tests are orally presented and calibrated to fall within the patient's span of auditory attention and working memory.

Insight

While formal measures of insight and awareness of illness exist in the form of patient and informant questionnaires, we find that insight is best assessed based on clinical history, and comparison of informant and patient interview responses on formal questionnaires assessing cognitive and functional domains. Understanding the patient's level of awareness into his/her cognitive and emotional functioning is particularly important, as it has implications for the patient's judgment and decision-making, safety, level of independence, and provides direction for behavioral interventions and treatment of mood.

Clinical judgment & normatively derived scores

As alluded to above, patients with visuoperceptual problems present a unique challenge for neuropsychologists as deficits in visuoperception interfere with assessment of underlying cognitive constructs that can be evaluated using visual stimuli. To return to the example of assessing memory in PCA, it would be difficult to comment on the integrity of memory systems functioning based on performance on tests that involve copy and recall of a complex geometric design. Reliance on auditorally presented stimuli allows for a more accurate interpretation of memory functioning, although it can still be suboptimal given the presence of auditory working memory and phonological processing weaknesses that also exist in PCA. Similarly, while assessment of attention and processing speed has traditionally been tested through tasks such as Corsi block tapping, trail-making tests or digit-symbol coding measures, performance can be undermined by problems with visually guided reaching and simultanagnosia. Visuoperceptual impairments also stand to interfere with assessment of semantic memory through traditional picture naming tests. Thus, interpretation of objective test data must not only rely on interpretation of scores derived from standardized administration and normative data but must also involve clinical interpretation and judgment. Conceptualization of the overall cognitive profile should consider sparing/impairment of cognitive domains *in relation* to other cognitive areas. While a z-score transformation of all tests allows for comparison across measures and domains, an interpretable overall profile of relative strengths and weaknesses that characterize PCA would not be informative. Test results should represent the patient's full range of cognitive abilities irrespective of visuospatial/perceptual impairment. To address the limitations of a purely data-driven approach to neuropsychological test interpretation in PCA (and other syndromes), we are developing the neuropsychological assessment rating (NAR; in preparation) scale that allows for inclusion of clinical interpretation of impairment severity within major cognitive domains, taking into account both normative-based scoring and qualitative observations regarding the potential influence of impairments in one domain on performance in other domains.

Neuropsychiatric symptoms in posterior cortical atrophy

The major psychiatric symptoms in PCA include anxiety, depression and irritability, with psychosis and other symptoms being less common. Using the Neuropsychiatric Inventory in a sample of 28 patients with PCA, Suárez-González *et al.* [43] found that the most commonly reported neuropsychiatric symptoms in PCA included depression (64%), irritability (50%), anxiety (42%) and apathy (42%). Younger age of onset was associated with greater anxiety. Another study by Isella *et al.* [44] found a 95% prevalence of neuropsychiatric symptoms in 20 individuals with PCA, although with a higher prevalence of apathy (60%), followed by anxiety (55%), depression (45%) and irritability (35%) among the most common symptoms. The prevalence of neuropsychiatric symptoms was slightly higher in PCA patients (95%) than in a comparison group of subjects with typical AD dementia (85%). Neither study found an association between severity of cognitive impairment and neuropsychiatric symptoms. The presence of euphoria, disinhibition, aberrant motor behaviors and night-time behavioral disturbances were relatively rare in both studies.

Anxiety and depression may be prominent (and sometimes presenting features) early in the course of the illness [45,46], overshadowing cognitive complaints. The early presence of these symptoms may be due to relatively preserved insight. A study comparing clinical characteristics of PCA and AD patients found greater insight in PCA patients, to the extent that they were often able to serve as their own historians, as well as higher levels of depression

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and antidepressant use [4]. Thus, early presenting psychiatric features may delay syndromic diagnosis or lead to misdiagnosis with 'pseudodementia' (dementia syndrome of depression).

Psychotic symptoms tend to be infrequent early in the course of PCA, with a reported 25% prevalence of delusions and 7% prevalence of auditory hallucinations [43]. While visual hallucinations are not uncommon in PCA syndrome, they may point toward underlying Lewy Body pathology. Josephs *et al.* [47] reported a 22% prevalence of visual hallucinations in a group of 59 PCA patients who presented also with parkinsonism and rapid eye movement (REM) sleep disorder. Neuroimaging on these individuals identified atrophy in the primary visual cortex, thalamus, basal ganglia and midbrain compared with healthy controls, and atrophy in the thalamus and bilateral globus pallidus compared with PCA individuals without hallucinations [47]. In our experience, many patients with PCA will develop delusions or hallucinations, but late in the course of the disease.

The use of a structured scale, such as the Neuropsychiatric Inventory [48,49], Geriatric Depression Scale [50] or the Cambridge Behavioral Inventory [51], at initial evaluation and at 3–6 month intervals is recommended for assessing and monitoring of symptoms over the course of the disease.

Clinical formulation through consensus

In some settings, a single clinician obtains the history and performs the examinations necessary for the comprehensive evaluation of a patient suspected of having PCA. We take a multidisciplinary consensus approach in our clinical research program to refine our diagnostic conceptualization. Type and severity of symptoms the patient is experiencing are rated based on data from structured interviews of the patient and informant conducted separately. Ratings of deficits on neuropsychological testing and on the neurological exam (and in some cases, the speech-language pathology assessment) are used to grade type and severity of signs observed by clinicians in the office. Information gathered from each source then is integrated into an overall set of ratings of type and severity of impairment using the Clinical Dementia Rating and extensions of the Clinical Dementia Rating currently under development. Since its implementation and over the course of this process in our program, it has become clear that performance-based testing and symptoms reported by reliable observers can be inconsistent with each other; thus, their integration likely allows for the most balanced assessment of the relative severity of impairments across cognitive, behavioral-psychiatric, and sensorimotor domains. Through this integrative and comparative process, we hope to continually improve the accuracy of diagnosis and subtyping of PCA and other complex neurodegenerative conditions.

Imaging & other biomarkers for diagnostic assessment

If our assessment is consistent with a core PCA clinical phenotype as described in previous sections, we then consider all of the aforementioned information in order to gauge primary suspected etiology (the third step of our three-step diagnostic formulation in Figure 1). Diagnostic testing begins with a brain MRI (or CT with 3D reformatting in patients with contraindications to MRI). Regional brain atrophy provides supportive evidence for the localization of atrophy consistent with posterior cortical neurodegeneration. MRI scan protocols typically include a high-resolution 3D T1-weighted sequence, T2/FLAIR, T2* gradient echo or susceptibility-weighted imaging and diffusion-weighted imaging sequences. These sequences provide valuable information regarding focal atrophy (which usually is apparent in patients with PCA), the burden of microvascular ischemic changes and the presence or absence of microhemorrhage(s) and/or superficial siderosis potentially suggesting cerebral amyloid angiopathy. This type of MRI protocol will rule out other pathologies such as inflammation, demyelination, or tumor. In the rare case of PCA that is caused by a prion disease such as Creutzfeldt–Jakob Disease, diffusion-weighted imaging can identify cortical or deep gray restricted diffusion consistent with this etiology. Most cases of PCA are characterized by grossly visible atrophy of the posterior parietal and occipital cortices bilaterally and relative sparing of medial temporal lobe structures (when compared with typical AD dementia), findings corroborated by quantitative morphometric studies of cortical volume and thickness (Figure 3) [38,52].

In some cases, visual inspection of MRI images may not reveal regional atrophy in which the viewer can be confident. Here, FDG-PET can provide more sensitive, supportive evidence for the localization of hypometabolism consistent with posterior neurodegenerative pathology. FDG-PET may or may not be readily accessible depending on the practice setting; in some settings, SPECT may be more readily accessible as a functional neuroimaging modality. These functional imaging methods are valuable in providing evidence of likely neurodegeneration with a posterior localization consistent with PCA (Figure 4B).

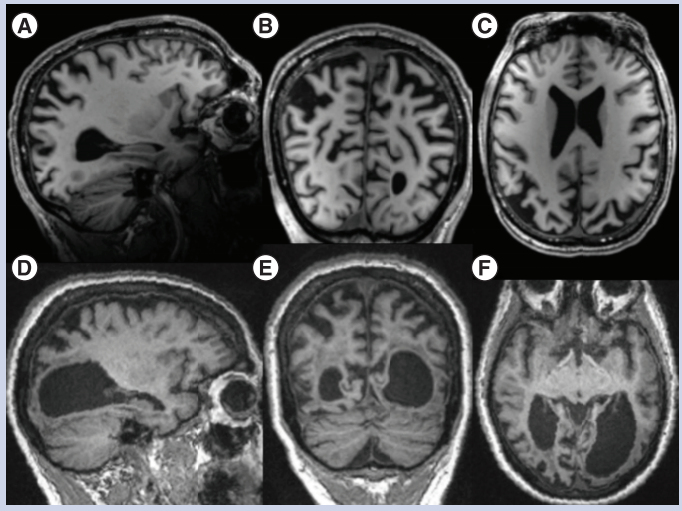

Figure 3. Atrophy patterns in posterior cortical atrophy. The PCA patient in the top row presented with symptoms and signs consistent with the biparietal (dorsal) variant of PCA, which fits with the focal atrophy pattern seen in the parietal lobes in the sagittal **(A)**, coronal **(B)** and axial **(C)** T1-weighted MRI images. The PCA patient in the bottom row presented with the occipital variant with subsequent involvement of parietal cortex, as seen by the striking occipital atrophy in sagittal **(D)**, coronal **(E)** and axial **(F)** T1-weighted MRI images. In addition to the prominent gray matter atrophy, the white matter near the areas of atrophy shows abnormal signal consistent with degenerative pathology. This patient was cortically blind at the time of the scan.
PCA: Posterior cortical atrophy.

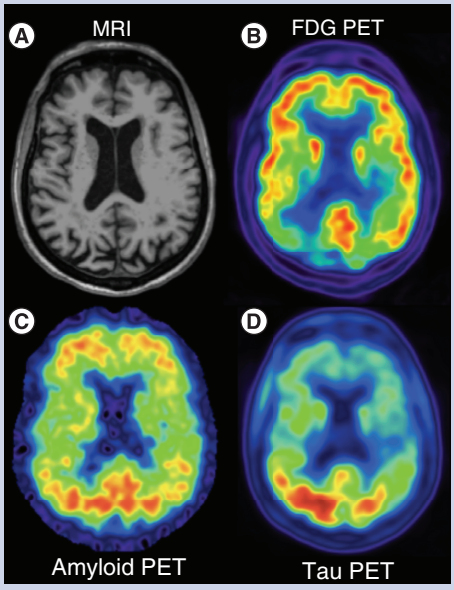

Figure 4. This posterior cortical atrophy patient presented with prosopagnosia and simultanagnosia. T1-weighted MRI scan shows subtle parietal atrophy; **(A)** FDG-PET scan shows right>left biparietal cortical hypometabolism; **(B)** amyloid (C11-PiB) PET shows elevated signal in bilateral frontal and parietal cortical regions; **(C)** tau (F18-AV1451) PET shows elevated signal in right>left biparietal cortex, strongly overlapping with areas of loss of metabolism.

Once we have determined that a patient with the PCA syndrome has posterior neurodegeneration, we attempt to rule in or out particular etiologies with the addition of specific molecular biomarkers to our overall clinical assessment. For the most part, molecular biomarker tests in PCA aim to evaluate the presence or absence of AD pathology, since this is the most common underlying neurodegenerative pathology in patients with PCA and is the pathology for which the most robust biomarkers exist at present. Cerebrospinal fluid (CSF) can be analyzed for a profile consistent with AD where Aβ protein is abnormally low and both total tau and hyperphosphorylated tau are

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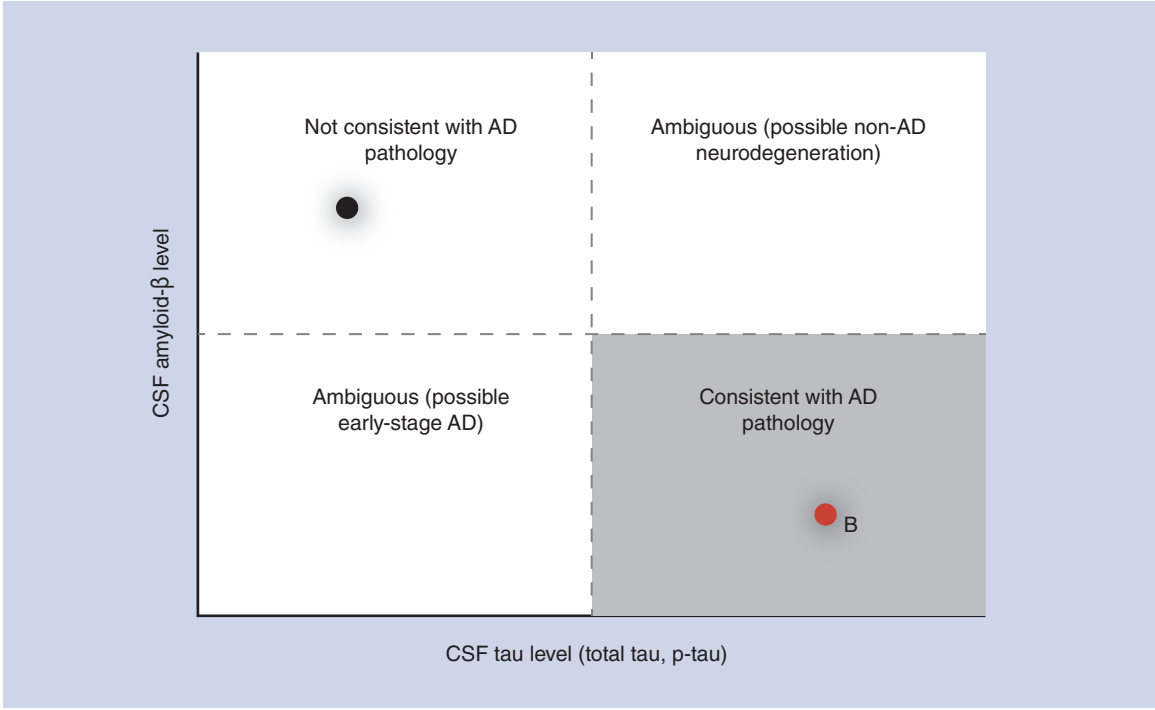

Figure 5. Cerebrospinal fluid measures of amyloid-b and tau are useful in determining whether the likely underlying neuropathology is or is not Alzheimer's disease. Levels of these proteins in the upper left quadrant are consistent with the absence of cerebral neuritic plaques and neurofibrillary tangles. The presence of cerebral amyloid neuritic plaques and tau-related neurofibrillary tangles is indicated by reduced amyloid levels and elevated total and hyperphosphorylated tau levels. Levels of these proteins in the upper right and lower left quadrants are indeterminant. Elevated tau in the absence of abnormal amyloid may suggest non-AD neurodegeneration or another lesion. Reduced amyloid in the absence of elevated tau may suggest cerebral amyloidosis, which may represent early-stage AD.
AD: Alzheimer's disease; CSF: Cerebrospinal fluid.

abnormally high (Figure 5) [53]. Recent studies suggest neurogranin concentrations in CSF may also help distinguish between typical and atypical presentations of AD (such as PCA), with neurogranin and total-tau concentrations being higher in typical AD compared with PCA patients [54]. Other studies have found that atypical AD is heterogeneous with evidence for subtle differences in amyloid processing and neurodegeneration across clinical syndromes (i.e., PCA being associated with lowest T-tau, P-tau, T-tau/Aβ1-42, Aβx-40/X-42 ratio compared with other syndromes with presumed similar AD pathology) [55]. In some patients, results are indeterminate, and in rare cases, CSF may provide evidence of other pathologies such as prion disease.

Multiple amyloid PET tracers are now available and US FDA approved for clinical use but not yet reimbursed by insurance except in the context of select research studies. Appropriate use criteria for amyloid imaging [56] would usually support the potential value of amyloid PET imaging in the assessment of a patient with PCA. In our practice, we attempt to obtain amyloid PET imaging through whatever means possible, often under research protocols given the complexities of insurance reimbursement (Figure 4C). We are also now studying the use of tau PET tracers as a diagnostic biomarker in PCA; at some point in the future, this may become a valuable imaging modality in the workup of suspected PCA (Figure 4D).

Monitoring progression of posterior cortical atrophy

Monitoring overall clinical status

As patients with PCA are followed longitudinally, the most critical element of the clinical assessment is overall clinical status (Figure 6). Visual symptoms typically continue to be the most pronounced impairments over the course of the disease. With disease progression, patients develop impairments in memory, language and somatosensory or motor function, contributing to loss of independent function; at this stage, they are considered to have dementia (PCA dementia syndrome). A repeat structured clinical interview that includes questions regarding activities of daily

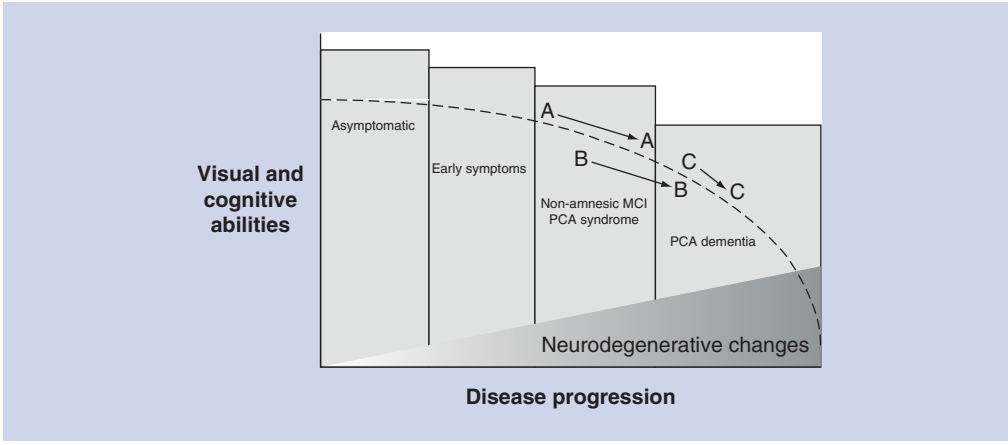

Figure 6. The natural history of posterior cortical atrophy. As neurodegenerative changes within the brain accumulate, early symptoms develop and at some point, become recognizable as a nonamnesic MCI presentation with a clinical syndrome consistent with PCA. Eventually, symptoms progress such that independent function is lost at which point the condition can be considered PCA dementia. Some patients **(A)** have a slow progression of symptoms and maintain largely independent function, some patients **(B)** have a similarly slow progression but lose independent function and some patients **(C)** have a relatively more rapid progression with loss of independent function.
MCI: Mild cognitive impairment; PCA: Posterior cortical atrophy.

living will reveal these symptoms. Worsening of existing mood symptoms can occur, while behavioral/psychiatric symptoms, including agitation, delusions, hallucinations or sleep disturbances, can emerge and warrant close monitoring and symptomatic treatment. As functional losses related to declining visual abilities or hand–eye coordination problems increase, additional supports through occupational or physical therapy are critical. A home safety evaluation by occupational therapy (OT) or physical therapy (PT) can be invaluable. As other cognitive or behavioral symptoms emerge, the kinds of support and assistance that help patients with dementia and their caregivers is increasingly needed. In the USA, the Alzheimer's Association is often an excellent starting point and a valuable resource.

Monitoring progression of neurologic impairments

Serial neurological examinations in patients with PCA are imperative for tracking signs that correspond with worsening functional impairments in day-to-day activities. Within the domain of visuospatial functioning, patients frequently demonstrate progressive simultanagnosia, oculomotor apraxia and optic ataxia (elements of Balint syndrome) as well as visual and/or multimodal left hemineglect. The neurological examination is useful likewise to assess for other parietal-localizing signs such as limb apraxia, cortical sensory loss, left–right confusion, finger agnosia and more generalized disruptions in body schema that interfere with a patient's ability to form an accurate internal representation of body position in space. Coupled with a disrupted representation of visual space (and frequently, executive dysfunction), disruptions in body schema and limb apraxia can lead to an accelerated loss of function in instrumental and basic activities of daily living in PCA compared with amnesic dementias such as typical AD.

Longitudinal neurological assessment is similarly required to ascertain if a patient has elements of a secondary neurodegenerative syndrome, leading to the distinction of 'PCA-pure' versus 'PCA-plus', put forth by the PCA consensus classification criteria [9]. PCA-plus applies to cases in which core clinical criteria for at least one other neurodegenerative syndrome (such as dementia with Lewy bodies or corticobasal syndrome) are fulfilled. More commonly, one might see relatively symmetrical parkinsonism as occurs in dementia with Lewy bodies; less commonly asymmetric rigidity/akinesia, myoclonus and/or dystonia as occur in corticobasal syndrome; and rarely, myoclonus, pyramidal, extrapyramidal and/or cerebellar signs as occur in prion disease. These additional symptoms and signs may be present at initial presentation or may develop as the illness progresses, and thus should be considered at every follow-up neurological visit.

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Monitoring neuropsychiatric symptoms

Neuropsychiatric symptoms in PCA can contribute substantially to caregiver burden and distress; thus, assessing mood and behavioral changes through scales such as the Neuropsychiatric Inventory or Geriatric Depression Scale at regular intervals can be important for identifying appropriate psychopharmacologic and behavioral interventions for patients, and psychosocial support and education for caregivers.

Monitoring progression of general cognitive impairment: similarities/differences from typical Alzheimer's disease

Progression of cognitive impairments may be difficult to track depending on the subjective report of cognitive changes early in the course of the disease. Kennedy *et al.* [57] identified a healthy individual who presented with subjective memory complaints, but whose initial neuropsychological testing revealed deficits only in visual scanning (trail-making tests) and visual memory, and to a lesser extent, in object perception; verbal memory, visual reasoning and language were normal. Over the course of 4 years, deficits remained circumscribed to the visuospatial/visuoperceptual domain and continued to deteriorate, with the disorder progressing to include dyscalculia, dyslexia and dysgraphia; notably, performance on verbal memory measures remained stable and well within normal limits. This case highlights the importance of monitoring progression through serial neurocognitive investigation, in addition to attempting to obtain patient and informant reports of difficulties experienced in daily life.

With progression of the disease and development of dysfunction in cognitive domains other than visuospatial, patients with PCA increasingly resemble those with typical AD dementia albeit still with disproportionate impairment in the visuospatial domain. Compared with PCA patients, patients with typical AD dementia often show a far greater decline in short-term memory, executive functioning and language, with relative preservation of visuoperceptual abilities even well into the course of the disease. Comportment and behavior in typical AD may also deteriorate with disease progression. In the case of PCA, a patient can develop full-blown Balint or Gerstmann syndromes with progression of the disease, and experience a significant degree of visual impairment to be considered cortically blind. With a decline in sensorimotor function, PCA patients become increasingly dependent with respect to navigating their immediate environments and managing activities of daily living, including dressing and eating. Typical AD patients in more advanced stages usually retain procedural activities around dressing and eating, but may need increased cueing to complete the tasks due to lapses in memory or executive functioning.

Imaging & other biomarkers for monitoring progression of disease

We usually focus on repeating MRI scans (or CT with 3D reformatting in cases of MRI contraindications) to monitor progression of the brain disease causing a patient's PCA. Lehmann *et al.* [58] longitudinal investigation of atrophy patterns in PCA compared with tAD demonstrated the progression to a more diffuse pattern of atrophy from the initial, focal presentation. This pattern of widespread atrophy over the course of disease progression typically mirrors the deterioration in memory, language and executive functioning skills despite preservation in earlier stages of PCA. Although we are currently investigating the value of FDG-PET, amyloid PET, tau PET and CSF as longitudinal biomarkers of disease progression, we do not advocate for their use longitudinally in clinical practice. At some point, it may become clear that they are useful for monitoring progression and the effects of treatments if disease-modifying interventions become available.

Current & future treatments for posterior cortical atrophy

As is the case for all neurodegenerative dementias, once the diagnosis of PCA is made, the discussion must turn to the fact that, at present, there are no disease-modifying therapies and few symptomatic therapies for PCA, none with strong evidence for their efficacy. PCA patients can, however, be registered as legally blind/handicapped and access services and resources available for the blind or partially sighted despite demonstrating normal acuity as seen early in the course of the disease. In general, cognitive and behavioral symptoms of PCA can be addressed, optimally by a multidisciplinary team of specialists [59]. Treatment includes pharmacologic and nonpharmacologic management of symptoms, management of co-morbid conditions, psychosocial support, and education of the patient and family [60].

Pharmacological treatment

Currently, there is no medication known to be effective in stopping or slowing the progression of PCA, as is the case for all neurodegenerative dementias today. To date, there has been one clinical trial examining the efficacy of donepezil in treating symptoms of PCA [61], which unfortunately failed to demonstrate any impact on neuropsychological outcomes.

Treatment is typically symptom-focused, and usually includes cholinesterase inhibitors traditionally used in AD. These medications may help some symptoms including memory loss or attention and concentration. Trials of levodopa or carbidopa can be introduced to address movement or gait disturbances should they develop over the course of the disease.

Few studies focusing on the management of neuropsychiatric symptoms in PCA exist. The empirical treatment approach resembles that of other forms of dementia. Depression, anxiety and mild agitation may be responsive to treatment with serotonin reuptake inhibitors or other related medications [62]. Sleep disturbance is an important symptom to treat in patients experiencing it, and may be addressed with melatonin or trazodone. For severe agitation, a low-dose atypical antipsychotic (usually quetiapine) can be helpful [63] as can low-dose valproate [64], but the risk of increased all-cause mortality should be balanced against possible benefits [65]. Psychosis will often respond to low-dose atypical antipsychotics such as risperidone [66].

Rehabilitative treatment

Neuropsychological rehabilitative programs have been reported in single case studies in PCA (e.g., [67,68]) but with minimal or no lasting improvements. The current standard of care for PCA patients involves referral to an occupational therapist who works with the patient and caregiver on learning and implementing compensatory strategies that support activities of daily livings/instrumental activities of daily livings. Strategies focus on ways to negotiate the household, functioning in the community, and adapting the work environment.

The OT evaluation begins with an assessment of an individual's strengths and limitations while performing functional tasks. Through this assessment, a client-centered treatment plan that maximizes safety and independence for the patient is developed and executed with the patient and involving a caregiver. Standardized assessments may include tests such as the clock drawing test [69] the motor free visual perceptual test [70] and functional performance-based assessments such as the kettle test [71] and the multiple errands test [72]. In addition to standardized assessments, the OT evaluation obtains an occupational profile. This profile records what activities the patient has engaged in, the patient's values and what professional, familial and communal roles the patient has played. It identifies among these activities those which the patient is unable to do or perform at the level of independence they once did. Interventions then focus on training strategies to compensate for limitations. Strategies include using senses other than vision, promoting use of intact cognitive skills and implementing environmental modifications (e.g., high contrast colors to help with item identification, increasing ambient lighting, placing Velcro on doorknobs to identify important rooms such as the bathroom). Use of visual cues to aid visually guided navigation has also shown some promise as an environmental adaptation [73]. Yong *et al.* [74] have also identified potential interventions targeting reading through the strategy of restricting visual field (through single- vs double-word presentations), which minimized spatial and oculomotor demands of text reading, and an intervention that involved moving words into a fixation box, which assisted in localization of words within sentences, reducing the tendency for visual disorientation, excessive crowding and fixation instability.

Education is provided to the patient and caregiver to increase awareness of the patient's deficits and how they impact day-to-day functioning. Patients often benefit from having caregivers present during all or part of the evaluation and treatment to help ensure that strategies learned in therapy can be carried over into the home environment successfully [75,76].

Psychosocial treatment

Support groups for both patients and caregivers can be helpful for reducing isolation, validating individual experiences and assimilating coping strategies and advice generated by peers. Psychoeducation helps patients and families manage expectations of functioning in daily life and understand medical prognoses. Cognitive–behavioral therapy has also been found effective in addressing neuropsychiatric problems that often develop in PCA [43].

PCA patients may withdraw from activities due to visuoperceptual problems that limit safe and consistent participation. This behavior can exacerbate the negative psychological impact that often already accompanies the disorder. It is critical, therefore, to ensure that the patient remains active as much as his/her visuoperceptual abilities

Box 2. Posterior cortical atrophy: a caregiver's perspective.

"In my wife Judy's case, there were no bright line markers for the onset of PCA. Instead, we spent 5 or 6 years trying to get a proper eyeglass prescription starting in 2004. Her complaint was that she could not see, but she could pass the eye test at 20:20 with glasses. In addition, there were increasing episodes of forgetfulness and depression. Her driving was impaired. In retrospect, my wife clearly knew that something was not right and she very cleverly hid the symptoms, as best she could from me and herself. Our daughter Marie, living in California, clearly saw her mothers' decline and insisted that we do something more to help her mother. In October of 2007, the three of us traveled to Jacksonville, Florida, for appointments at the Mayo Clinic. As a result of four days of exams, we learned that Judy's eye problem was not her eyes but her brain. Their diagnosis was that Judy had PCA, a diagnosis that had not been on any of our radar screens. It was a relief to have a diagnosis, even though the prognosis was unfavorable. Judy bravely confronted her diagnosis. She was an evangelist for the local Alzheimer's Association. She described early-onset dementia to a number of audiences. She continued her daily walks with her dog and healthy eating habits. We continued her care at home, until it was too much. She moved into a memory care unit in March of 2011 where she died in March of 2018. As caregivers, we tried to provide for her in the best possible way."
– Fontaine Richardson

PCA: Posterior cortical atrophy.

and physical environment permits. Continued participation in meaningful activities is one way to avoid exacerbation of depression and anxiety. We typically encourage caregivers to identify and engage patients in structured and regular activities, such as those provided in day programs. Given the impediments to participating in visually mediated activities at day programs, incorporating therapies that involve use of other sensory modalities (as is the case in reminiscence therapy) may be particularly important to integrate into activities for PCA patients. Reminiscence therapy [77] can be helpful for stimulating recall of remote personal events, and will be particularly helpful once memory impairments become prominent in the PCA profile. PCA patients may also be well suited for music-based interventions involving exposure to familiar music or singing, which have become increasingly popular and being included in day-program activities.

Patient engagement in care planning

When a diagnosis of PCA is first made, many patients are still able to participate in care-planning activities, as reasoning, judgment, memory and communication skills are relatively preserved early in the course of the disorder. Although most patients appear to retain a fair degree of independence having spontaneously implemented compensatory strategies for reading, writing, navigation and finding personal effects, they have nonetheless begun to have difficulty functioning at their previous levels. We believe it is essential to engage each patient and family member in these discussions soon after diagnosis, typically focusing on adapting to the cognitive, physical and emotional challenges associated with PCA, and how best to plan for the coming years that will likely involve worsening of existing symptoms. Identifying new or worsening symptoms as well as areas of stability at each clinic follow-up are crucial in ongoing planning and care management. At some point, it may be helpful to 'step back' and engage in discussions of longer-term care planning while the patient is able to participate. The clinician(s) should clarify the patient's and family's knowledge of, experience with, and preferences regarding dementia care planning. In some cases, discussions may be conducted in the context of patient/family meetings. In other cases, it may be optimal to have these conversations with the patient separate from the family or other caregivers. The involvement of an experienced clinician (e.g., clinical social worker or occupational therapist) with dementia care planning skills is invaluable for these purposes. The Alzheimer's Association may offer local resources to assist with this fundamentally important process.

Neuropathology & genetics of posterior cortical atrophy

The neuropathology of PCA is usually AD. However, there are barely any clinicopathologic studies of PCA with more than five cases. Available studies suggest that AD neuropathology may account for 65 [6], 77 [5], to 100% [10] of cases. PCA may also be caused by pathology associated with corticobasal degeneration, Lewy body disease or rarely other neurodegenerative diseases [5]. We previously reported a case of frontotemporal lobar degeneration pathology presenting as PCA [11]. In patients with PCA due to AD, it is not yet clear why the localization of neuropathology is different than the typical localization in AD.

While PCA is rarely related to an autosomal dominant-inherited condition [11], it is important nonetheless to take a comprehensive family history, as complex genetic factors may play a role in PCA. For example, mutations in *PSEN1* [78] and the *HTT* gene [79] have been described in suspected cases of PCA, along with a report of familial prion disease associated with a 5-octapeptide insertion in the prion protein (5-OPRI) [80]. Mutations in two of the three most common known genetic causes of frontotemporal lobar degeneration – microtubule associated protein tau (*MAPT*) [81] and progranulin (*GRN*) [12] – have been identified recently in PCA patients, although both reported cases lacked neuropathologic confirmation. Our reported case of frontotemporal lobar degeneration pathology presenting as PCA was found to have a *GRN* gene mutation [11]. Here, the patient's father reportedly had an AD-like illness, although the clinical phenotype was not reported in detail. Thus, although patients with autosomal-dominant neurodegenerative dementias may present with a PCA syndrome, to the best of our knowledge there have been no reports of multiple family members exhibiting PCA.

Some investigators have begun studying why some patients with AD neuropathology develop atypical clinical syndromes like PCA, rather than the memory-predominant dementia that is typical of AD. Genome-wide association studies and whole-genome sequencing studies are in progress to attempt to identify genetic variants (or combinations of genetic variants) that might predispose a person to develop AD pathology in visual systems of the brain rather than memory systems. One such study identified risk associated with polymorphisms near genes not previously associated with neurodegenerative conditions – *CNTNAP5, FAM46A* and *SEMA3C* – as well as risk associated with polymorphisms in or near *APOE, CR1, ABCA7* and *BIN1* previously associated with AD [82]

We are only beginning to understand the interplay of genetic factors in PCA, something that is outside the scope of routine clinical practice. Ideally, the field needs large multicenter studies of patients who meet Crutch *et al.*'s [9] diagnostic criteria for PCA due to AD in order to identify genetic or other factors that influence the atypical localization of AD pathology in patients with this syndrome.

Conclusion

PCA is a complex clinicopathological syndrome. Diagnosis is challenging due to heterogeneity of presenting symptoms, terminology and classification systems, although there have been considerable recent advances in these areas, thanks to the sustained efforts of an international consensus group. At present, we are still far from understanding the factors that lead to the development of neuropathology in patients with PCA, as is the case for most neurodegenerative diseases but – also even more importantly – the factors that influence the localization of neuropathology in the poster cortical regions. Efforts to develop efficacious treatments are partly hampered by lack of standardized methods to monitor the progression of illness. As such, PCA presents unique challenges for clinicians in identifying treatment options and providing counseling and psychoeducation on clinical status and prognosis. For researchers, a lack of consensus around staging and diagnostic criteria undermines efforts to develop clinical trials for patients with PCA or to include patients with PCA due to AD in AD clinical trials. To the best of our knowledge, no current clinical trial focusing on PCA exists; however, there are increasing efforts to improve PCA treatment targeting symptoms or brain pathologies such as amyloid or tau. Given evidence that neurodegenerative pathophysiology is complex and multifactorial yet respects large-scale network architecture in the brain [83,84], PCA could provide a model for discovering and targeting specific pathogenic factors in individuals or select groups, in other words, along the lines of 'precision medicine' in neurodegeneration.

Future perspective

We believe that key future directions include the development of tools sensitive and specific enough to capture the full range of cognitive and behavioral abnormalities exhibited in PCA and enable fine-grained monitoring of disease progression. There exists also a need and an opportunity for identifying genetic or proteomic markers that could help clarify why patients with PCA due to AD pathology develop pathology localized to posterior regions of the brain and that is not typically seen in typical AD. Beyond existing scales, domain-specific scales of impairment equivalent to those created for disorders such as primary progressive aphasia (e.g., the PASS [85]) are needed. Also needed is further refinement of existing cognitive batteries that better characterize areas of visuoperception, such as motion detection. Extension of these batteries to monitoring systems that capture variability in PCA as exhibited in daily life could facilitate both diagnosis and treatment, as well as longitudinal studies of the natural evolution of the disease. Partnerships with public and private funding agencies will be critical in identifying better diagnostic and treatment tools to reduce patient and caregiver burden. The clinical and research goals laid out in the current review can only be accomplished through a unified effort within the international community of researchers focused

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on PCA and related diseases, an effort that must include vigorous sharing of data and diagnostic and therapeutic innovations. It is our hope that the current review will serve as a stepping-stone toward standards for improved research and clinical care in PCA.

Acknowledgments

The authors express special appreciation to the participants in our PCA program and their families for their valuable contributions.

Financial & competing interests disclosure

This work was supported by grants from the NIA R21-AG051987, P50-AG005134 and R01-DC014296 and philanthropic funding to the MGH FTD Unit including the Mooney Family Fund. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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