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Neuropsychiatric symptoms in primary progressive aphasia: phenomenology, pathophysiology, and approach to assessment and treatment

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SUMMARY

Primary progressive aphasia (PPA) is a neurodegenerative syndrome characterized by insidious and progressive loss of language. Current diagnostic criteria require symptoms to be largely restricted to language dysfunction for at least the first 2 years of the syndrome. However, as the disorder progresses – and sometimes even in the early stages – patients with PPA may exhibit neuropsychiatric symptoms. In this article, we review the phenomenology and frequency of neuropsychiatric symptoms in PPA. Among the few studies of this topic that have been performed, there is consistent agreement that neuropsychiatric symptoms are not uncommon among PPA patients. In some cases, particularly the semantic variant of PPA, symptoms are similar to those found in the behavioral variant of frontotemporal dementia. We further review the approach to assessment of behavioral symptoms in PPA and their possible management strategies, and speculate regarding their potential neurobiological substrates.

Primary progressive aphasia (PPA) is a neurodegenerative syndrome characterized by the insidiously progressive loss of language abilities [1]. According to contemporary diagnostic criteria, the diagnosis of PPA requires that aphasia must be the most salient symptom and the major cause of impaired daily living activities for approximately the first 2 years of the clinical syndrome [1–3]. PPA is usually viewed as one major clinical form of the frontotemporal lobar degeneration (FTLD) spectrum of neurodegenerative diseases [4]. Depending on the type of language problem, PPA is further sub-categorized into a nonfluent/agrammatic variant (PPA-G, known previously as progressive nonfluent aphasia [PNFA]) involving effortful and agrammatic speech, a semantic variant (PPA-S, also known as semantic dementia [SD]) involving impaired single-word comprehension and a logopenic

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variant (PPA-L, also known as logopenic progressive aphasia) involving impaired word retrieval and repetition [2].

The presence of prominent early neuropsychiatric or behavioral symptoms is generally considered exclusionary for PPA. Patients with a neurodegenerative syndrome in which these symptoms are the earliest feature may fit criteria for the behavioral variant of frontotemporal dementia (bvFTD) [5]. In spite of this distinction, which is particularly important for clinical research on these disorders, some patients whose diagnosis fits the criteria for PPA have prominent early neuropsychiatric or behavioral symptoms (a point discussed briefly in the new diagnostic criteria) [2]. Many others have relatively mild but notable symptoms in these domains, particularly as PPA progresses to involve abilities beyond language.

In this article, we review the existing medical literature that has investigated the neuropsychiatric symptoms in patients with PPA. We discuss the phenomenology and clinical features of these symptoms and speculate regarding their neurobiological substrates, highlighting relevant studies when considering the approach to treatment.

Review of the literature on neuropsychiatric symptoms in PPA

A systematic search for papers reporting studies of neuropsychiatric symptoms in PPA was conducted. The following MeSH search terms 'primary progressive aphasia', 'neuropsychiatric', 'psychiatric', 'behavioral', 'neuroanatomy' and 'neuroimaging' were used. Subsequently, each subcategory of PPA ('semantic dementia', 'progressive non-fluent' or 'agrammatic aphasia' and 'logopenic' PPA) was combined with the other search terms and were searched for separately. The studies were identified from the following databases: Pubmed (Medline); Embase; PsychInfo; and Cochrane. The references of all the identified articles were reviewed and relevant references were added to the review list. Finally, we entered each of the review list articles into the Science Citation Index of the Institute for Scientific Information Web of Science, and articles citing those in the review list were reviewed and relevant primary research articles were added to the list. Research and review articles were restricted to the English language from 1949 to present were included. We identified multiple studies reporting on the spectrum of neuropsychiatric symptoms in PPA, eight studies reporting investigations of specific neuropsychiatric symptoms and two case reports.

Studies of the spectrum of neuropsychiatric symptoms in PPA

The studies varied in patient selection and comparison groups. In some studies, patients with PPA were analyzed as one group, whereas other studies employed subtype categories. The majority of studies used the Neuropsychiatric Inventory (NPI) to measure the frequency or severity of neuropsychiatric symptoms. A few studies used the Frontal Behavioral Inventory (FBI) or the behavioral domain of the Clinician Dementia Rating Scale (CDR). Except for two longitudinal studies, the rest were either cross-sectional studies or retrospective chart reviews. Table 1 summarizes the studies that investigated the spectrum of neuropsychiatric symptoms in PPA using the NPI, FBI or CDR.

In addition to the studies that used behavioral scales to measure neuropsychiatric symptoms, Snowden *et al.* evaluated the behavior of 30 bvFTD and 11 SD patients using a newly created semi-structured interview conducted with caregivers [6]. With regard to basic emotions, all patients were impaired in their capacity to show basic emotions, but SD patients were less impaired than bvFTD patients in their capacity to express anger, sadness and disgust. They did, however, commonly show impairments in the expression of fear. In the bvFTD group, changes in primary emotions were largely characterized by a reduction in

expression of emotion, whereas some SD patients exhibited exaggerated emotional displays, while others showed diminished emotional responses. With regard to social emotions, both groups showed reduced demonstrations of empathy or embarrassment, and increased selfishness. As for interest in social interactions, patients with SD and bvFTD showed an opposite pattern: bvFTD patients were more likely to avoid social contact, whereas SD patients were more likely to seek social contact (in contrast to Bozeat *et al.*'s findings [7]). Eating behaviors were altered in both groups, but with different patterns. bvFTD patients, especially those with prominent disinhibited behavior, showed increased eating and were indiscriminate in the type of food they ingested, whereas SD patients had food fads and were more selective in their food consumption. Complex repetitive behaviors, including hoarding, verbal stereotypies and obsessive-compulsive symptoms, were prevalent in SD, similar to the findings of Bozeat *et al.* [7].

Two studies have investigated the neuroanatomic correlates of neuropsychiatric symptoms in PPA. In the first, NPI scores were compared between 27 SD patients, 24 bvFTD patients and 22 patients with either Alzheimer's disease (AD) or mild cognitive impairment [8]. Principal component analysis in all patients showed that the presence of disinhibition was associated with decreased volume in the right anterior temporal, right ventromedial prefrontal cortex and right amygdala. Depression was associated with decreased volume in the right amygdala and right anterior temporal cortex and eating disorders were associated with decreased volume in the right frontal cortex and right ventromedial prefrontal cortex.

Rohrer and Warren recently investigated the neuroanatomic correlates of neuropsychiatric symptoms in PPA subtypes using the NPI and voxel-based morphometry [9]. Anxiety, apathy, irritability/lability and abnormal appetite/eating disorders correlated with reduced gray matter density in the right lateral orbitofrontal cortex, while disinhibition correlated with reduced gray matter density in the left lateral orbitofrontal cortex. Other correlations were found between apathy and atrophy in the right dorsolateral prefrontal cortex, irritability/lability and atrophy in the right anterior cingulate cortex, and disinhibition and atrophy in the left anterior superior temporal gyrus and entorhinal cortex.

Studies of a single neuropsychiatric symptom in PPA

A number of investigations have been performed on a single neuropsychiatric symptom in PPA. With the idea that a relatively isolated language difficulty in a person who is otherwise healthy could make them vulnerable to depression and social withdrawal, Medina and Weintraub examined Geriatric Depression Scale (GDS) scores and found that a group of 61 PPA patients had higher GDS scores than the controls, although on average not in the 'depressed' range [10]. Interestingly, the depressed group was much more likely (43%) than the nondepressed group (15%) to have had a premorbid history of depression.

In two studies, Banks and Weintraub investigated the lack of insight in patients with PPA, bvFTD and AD [11,12]. They asked both the patients and caregivers to rate the FBI and the responses were compared. PPA patients tended to underestimate their own behavioral changes relative to caregiver estimates, although not as prominently as bvFTD or AD patients.

In another study of insight, Eslinger *et al.* asked patients with bvFTD, PNFA, SD and AD to estimate their performance on tasks and also compared their own ratings on symptom scales to caregivers' ratings [13]. They found that fronto-temporal dementia (FTD) patients significantly underestimated their apathy, meaning that they viewed themselves as much more motivated than their caregivers did. This was also true within the PPA subgroups. Empathic concern was overestimated in both PNFA and SD, as was self-monitoring in the SD subtype.

One study investigated the prevalence of misidentification syndrome among people with different types of dementia [14]. AD and Lewy body dementia groups had the highest prevalence of this syndrome (~15%). Approximately 8% of patients with SD (n = 24) also endorsed some kind of misidentification symptoms (either by themselves or reported by their caregivers). These symptoms were not present in other PPA subtypes (n = 101) or bvFTD (n = 119).

Sollberger *et al.* longitudinally studied interpersonal traits in a group of patients with AD, bvFTD and SD by having patients' caregivers fill out the Interpersonal Adjective Scales (IAS) [15]. They found that SD was associated with prominent changes in personality trait characteristics. Dominance and warmth scores became abnormally low at the moderate-to-severe disease stage, although both showed an early drop from premorbid levels. The extraversion score already showed a significant drop to an abnormally low level at the very mild disease stage.

Studies of neuropsychiatric syndromes in single cases

One case report described a 75-year-old female without any remarkable medical or psychiatric history who developed a full blown panic disorder with agoraphobia at 71 years of age [16]. A year after the panic disorder, the patient exhibited a decline in linguistic fluency, word-finding difficulties, effortful speech and hesitant utterances with frequent pauses, phonemic paraphasias and transpositional errors. Approximately 2 years after the onset of aphasia, she was reported to have developed cognitive decline substantial enough to be consistent with dementia. Neuroimaging highlighted left temporal and inferior frontal abnormalities. Although the neuroimaging abnormalities in this case are consistent with those of PPA-S, the clinical description of language characteristics is inconsistent with this diagnosis, thus leaving the subtype unclear.

The second case was a 57-year-old woman who had received a diagnosis of PPA by her neurologist 6 years earlier [17]. Initially, she developed gradual but progressive difficulties in word finding and object naming with intact comprehension. As PPA advanced, her speech output and understanding of language became compromised. However, she continued to maintain her social activities. Computed tomography was reportedly unremarkable. Her medical history was significant for hypertension. There was no personal or family history of psychiatric illness. Later during the course of PPA, she started to disengage herself from family and social activities, eat poorly and neglect her appearance. Her family interpreted these symptoms as a result of worsening language problems. She then developed restlessness and episodes of crying. She was admitted to the hospital after she attempted suicide by running into traffic. She was treated with venlafaxine, and was engaged in art, group exercise and pet therapy. She showed improvements in self-care, appetite and nonverbal interactions after receiving treatment; thus, her mood appeared to improve. In our opinion, this case description is consistent with the PPA-S and illustrates the types of neuropsychiatric symptoms described quantitatively in the studies above.

General synthesis of literature on specific neuropsychiatric symptoms

The review of the existing literature indicates that, even when measured using a general screening instrument, such as the NPI, neuropsychiatric symptoms are not infrequent in patients with PPA. As this instrument has been used so frequently, we performed a synthesis of the literature reviewed above, focusing on each individual neuropsychiatric symptom construct using the NPI as a framework. In addition, at the end of this section we highlight a few other symptom constructs relevant to PPA that are not captured by the NPI. Table 2 demonstrates the frequency range of each neuropsychiatric symptom reported in PPA.

Delusions & hallucinations

Psychotic symptoms in PPA are either rare or absent [18–20]. The study by Rohrer and Warren reported a higher rate of psychotic symptoms in PPA-L and PPA-S (14 and 11%, respectively), which could be related to longer duration or more severe illness [9].

Agitation/aggression

Agitation/aggression is more frequent in PPA patients than in controls (11 vs 1%) and increases over time [21]. It is present in all types of PPA [9,18]; however, it is less severe than in bvFTD [19]. In one study, agitation/aggression was reported in up to 50% of patients with PPA [9].

Depression/dysphoria

Depression/dysphoria are consistently reported and appear to be the most prevalent psychiatric symptoms across all types of PPA [9,20,22]. In fact, one of the case reports described a PPA patient who gradually became depressed and attempted suicide, but she eventually responded to treatment [17]. We have observed a similar case in our practice. Nevertheless, only a subset of patients with these symptoms meet formal diagnostic criteria for clinical depression [10].

Anxiety

Anxiety is reported as frequently as depression in PPA [9,22]. It is observed in up to 70% of PPA-L patients [9]. Anxiety can be an isolated symptom or a cluster of symptoms severe enough to form an anxiety disorder. In one case report, a patient with no previous anxiety disorder developed a classic panic disorder with agoraphobia, fulfilling DSM criteria, 1 year before the symptoms of PPA slowly emerged [16].

Elation/euphoria

Mood elation/euphoria is not as common as depression in PPA, although it is similarly prevalent in bvFTD and in PPA [22], its frequency in the studies ranged between 5 and 20% [9,20,22].

Apathy/indifference

Apathy is one of the most common symptoms in PPA patients [9,22] and compared with controls, the frequency of apathy is significantly higher in PPA [20] and increases over time [21]. In pathologically confirmed PPA cases, apathy was one of the clinical features that suggested FTLD rather than AD pathology [23].

Disinhibition

Disinhibition is less frequent and less severe in PPA than in bvFTD [19,22]; however, its frequency increases over time [22]. In one study, up to 70% of PPA-S patients exhibited disinhibition [9]. In PPA, disinhibition is one of the distinguishing features that points toward FTLD pathology rather than AD pathology [23].

Irritability

Banks and Weintraub reported a similar proportion of mood symptoms including irritability in PPA and in bvFTD [22]. Irritability is more frequent in PPA when compared with controls [20], and is one of the most frequent symptoms reported in all types of PPA [9].

Aberrant motor behaviors

Aberrant motor behaviors are present in PPA, although they appear to be less frequent than other neuropsychiatric symptoms [9,20,22] and less severe than similar symptoms in bvFTD [18] (except one study that did not find any difference in the frequency between PPA and bvFTD [22]).

Night-time behaviors

PPA patients seem to have a relatively low frequency of night-time behaviors (in one study the frequency was similar to that of controls) [20], although the frequency increases over time [22].

Appetite/eating behaviors

Compared with controls, changes in eating behaviors are more evident in PPA patients [20]. Over 3 years of longitudinal follow-up, hyper-orality significantly increased over time in PPA patients [21]. This symptom (sweet food preference) was also highly associated with FTL D pathology rather than AD pathology in PPA [23].

Insight

PPA patients are better than bvFTD and AD patients at estimating their ability to perform tasks such as memory tasks. However, relative to other general or physical characteristics, such as weight or eyesight, their estimation of behavioral symptoms is less accurate [11,12,24]. For example, PPA patients may lack insight into loss of empathic concern and apathy [13].

Obsessive–compulsive spectrum symptoms

Compulsive and repetitive behaviors are quite common in the PPA-S subtype of PPA. In fact, the study by Snowden *et al.* showed that simple motor stereotypies such as lip smacking, hand rubbing and foot tapping were as common in PPA-S as those in bvFTD, and complex routines, verbal stereotypies and repetitive themes were more frequent in PPA-S than bvFTD patients [6]. In the same study, more than 90% of PPA-S patients exhibited some form of repetitive theme and more than 70% of them were reported to have verbal stereotypies. Furthermore, PPA-S patients exhibited obsessive and compulsive symptoms, such as excessive worrying and performing the same tasks again and again, more frequently than bvFTD patients. Similar observations were reported by Bozeat *et al.* [7].

Loss of empathy

Loss of empathy, selfishness and no sense of embarrassment were ubiquitously found in PPA-S patients [6].

Personality changes

Personality changes are a classic symptom early in the course of bvFTD. By contrast, to fulfill diagnostic criteria for PPA, a patient must be largely free of these symptoms during the first 2 years of the disease [1]. However, one recent study demonstrated that PPA-S is accompanied by subtle or overt changes in personality (dominance, warmth and extraversion) even during the early stages [15]. Other symptoms common in PPA-S, such as selfishness, lack of empathy and disinhibition, may also be viewed as personality changes [6].

Neuropsychiatric symptoms across PPA subtypes

Taken together, the literature suggests that PPA-S patients commonly exhibit neuropsychiatric symptoms, often relatively early and in a fairly stereotypical fashion. Many of these symptoms are similar to those of bvFTD, including loss of empathy, changes in eating behavior, compulsive behavior and disinhibition. Although these symptoms are highly consistent with FTD, depending on when they begin and how they are reported by informants, it may be difficult for the clinician to be confident in assigning a subtype diagnosis (i.e., bvFTD vs PPA-S vs SD). In fact, in the Neary *et al.* diagnostic criteria for FTD, features considered supportive of a diagnosis of SD included loss of sympathy or empathy and narrowed preoccupations (mental rigidity) [25]. Aberrant motor behavior is also commonly reported in some studies; in our experience this often includes elaborate movements related to repetitive or compulsive behaviors, although there has been little focused study of this topic. Depression is also reported as common in PPA-S in some studies; in our experience, however, at least some patients say certain phrases repetitively (i.e., catchphrases) that appear to express negative emotion (e.g., “I feel so stupid” or “I used to know that and now I just don't know anything”), but with minimal affective behavior consistent with depression, and a structured interview with some of these patients' caregivers reveals little behavior in daily life that appears consistent with a diagnosis of depression.

In PPA-G, neuropsychiatric symptoms are less frequent initially, but as the illness progresses it becomes increasingly common to see apathy, depression or irritability. In some cases these symptoms are present early in the illness, which may lead to misdiagnosis as a primary psychiatric disorder (commonly depression).

In PPA-L, neuropsychiatric symptoms are relatively infrequent early on, but increase as the illness progresses and include agitation, anxiety, irritability and apathy. In many cases the clinical phenomenology of neuropsychiatric symptoms appears similar to that seen in AD.

Neuroanatomic substrates of neuropsychiatric symptoms in PPA

A predominantly right-sided distribution of frontal and temporal areas has been implicated in the pathogenesis of many behavioral symptoms in FTD, such as apathy, disinhibition and abnormal eating behavior [26–29]. Right anterior temporal lobe atrophy is correlated with disinhibition and depression [8]. Right orbitofrontal, insular and striatal atrophy is correlated with eating disorders [30] and right ventromedial prefrontal cortex with aberrant motor behaviors, eating disorders and disinhibition [8,26]. In the study by Rohrer and Warren, anxiety, apathy, irritability and appetite changes were correlated with right hemisphere atrophy in PPA [9]. In PPA-S, atrophy is usually reported to be predominant in the left temporal pole and ventral left temporal lobe, but many patients exhibit subtle atrophy or hypometabolism in orbital and ventromedial prefrontal regions, as well as the ventral anterior insula and striatum; furthermore, a lesser but nontrivial degree of right hemisphere involvement is common [31,32]. Right frontal abnormalities have also been observed in nonfluent aphasia [33–35]. In our experience, there is often at least subtle atrophy in homologous regions of the right hemisphere in PPA at baseline assessment; right hemisphere structures commonly become involved as the condition progresses (Figure 1).

Management of neuropsychiatric symptoms in PPA

Given the heterogeneity of the underlying pathology in FTD, and the wide range of clinical phenotypes involving behavioral/psychiatric, cognitive and motor symptoms, clinical trials with a homogeneous group of patients are sparse [36]. The selection of outcome measures is also challenging. General behavioral rating scales such as the Comprehensive Psychiatric Rating Scale (CPRS) do not capture all the behavioral abnormalities of FTD. While the NPI

[37], the NPI-questionnaire and the Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) [38] scales are aimed at a general dementia population rather than specifically at the FTD spectrum, they have been employed as outcome measures in some trials in FTD. Symptoms that commonly present in FTD, such as obsessive-compulsive spectrum behaviors, personality changes and lack of empathy, are not captured by these scales. The FBI and Cambridge Behavioral Inventory (CBI) were developed to more specifically capture the behavioral features of FTD [7,39,40], but to date they have only been used in a handful of trials. Table 3 lists some instruments that are used to measure behavioral/psychiatric symptoms in patients with dementia. Knopman *et al.* studied the validity of different cognitive and behavioral tests as outcome measures in a population of patients with FTD [41]. They found that while the Modified CDR and Clinical Global Impression of Change scale demonstrated decline in the majority of patients, almost a third of patients improved on behavioral scales (NPI and FBI), suggesting that these instruments may not be ideal for use as outcome measures in FTD. Nevertheless, they may be of use in trials of interventions targeting specific types of symptoms, particularly if such trials recruit patients with more prominent neuropsychiatric symptoms at baseline.

In clinical practice, neuropsychiatric symptoms do not often resolve completely, yet over time, their frequency or severity may intensify or attenuate. It is critical to try to use valid scales to monitor these symptoms over time, particularly if empirical management strategies are attempted. The management of symptoms should be tailored to individual patients and caregivers. Education of caregivers (as well as patients if possible) about the safety issues and the nature of the neuropsychiatric symptoms is an important first step in management. Referral of families to the Association for Frontotemporal Degeneration and the Alzheimer's Association will provide further information and help families connect with the existing support groups. One reasonable strategy for prioritizing the goals of management is to choose one symptom at a time to focus on (usually the most disabling symptom). A multidisciplinary care plan involving a psychiatrist or neurologist, or geriatrician specializing in these symptoms, a social worker, and, if possible, a nurse practitioner or psychologist can assist families in developing behavioral strategies and providing psychosocial support [42]. Most symptoms are best managed by behavioral interventions. However, if the response is inadequate or symptoms are prominent, empirical pharmacological treatments can be tried.

To date, no published studies report on clinical trials attempting to treat neuropsychiatric symptoms specifically in a PPA sample. However, as is apparent from this literature review, these symptoms are not uncommon in PPA and despite the lack of adequate research-based evidence, we need to manage the neuropsychiatric symptoms of these patients in day-to-day clinical practice. Therefore, we must look to studies in bvFTD patients, mixed samples of FTD or other dementia patients for guidance. Below we summarize the results of clinical trials that have measured behavioral or psychiatric symptoms as outcomes in patients with FTD, organized by the type of pharmacological agent tested.

Antidepressants

A randomized double-blind study in 26 subjects with bvFTD using trazodone demonstrated a decrease in NPI scores by improvement of irritability, agitation, depression and eating disorders [43]. Data regarding paroxetine are conflicting; while one study did not find any improvement in the NPI or CBI of patients with bvFTD ($n = 10$) [44], two others showed an improvement in behavioral symptoms [45,46]. In one randomized study, eight bvFTD patients per group received 20 mg paroxetine or 1200 mg piracetam for 14 months. Patients treated with paroxetine showed an improvement in behavioral symptoms reflected by a reduction of caregivers' distress [45]. In another study, 11 patients with bvFTD were treated with fluoxetine, sertraline or paroxetine for 3 months. After treatment, disinhibition,

depressive symptoms, carbohydrate craving and compulsions all showed improvement in at least half of the subjects in whom they had been present [46]. In four PPA-S patients with hostile behavior, sertraline reduced aggressive behaviors and total NPI questionnaire scores [47].

Two case series studied the efficacy of moclobemide and selegiline in managing behavioral symptoms in FTD. Six patients with bvFTD treated with moclobemide for 14 days showed variable improvement in depression, aggressive symptoms, irritability, distractibility, mental rigidity, and stereotypy of speech and perseveration [48]. In three bvFTD patients, selegiline improved NPI scores and demonstrated some benefit on cognition by reducing errors on the Stroop and Paced Auditory Serial Addition Task [49].

Cognitive enhancers

An open-label study of 21 bvFTD, 13 PPA-S and nine PPA patients using memantine for 26 weeks caused a transient improvement in NPI scores predominantly in the bvFTD group [50,51]. In another case series, memantine improved total NPI scores in three bvFTD subjects with specific improvement in scores of apathy, agitation and anxiety [51]. However, in a different study, 16-week treatment of bvFTD patients with memantine did not change the NPI or the FBI scores [52]. Unfortunately, the data from the most recent clinical trial of memantine in FTD do not look encouraging with regard to NPI or other outcome measures [Boxer A, Pers. Comm.]. Rivastigmine reduced caregiver burden as well as NPI, BEHAVE-AD and Cornell Depression Scale scores, when given to bvFTD patients (n = 20) for 12 months [53]. On the other hand, donepezil worsened bvFTD patients' (n = 12) scores on a novel scale called the FTD Inventory and increased disinhibition and compulsivity [54].

Atypical antipsychotics

In a case report, risperidone improved agitation, delusions and hallucinations in bvFTD [55]. Another case study demonstrated that aripiprazole partially restored frontal glucose metabolism in a bvFTD patient, which the authors interpret as suggesting a beneficial role in frontal functions [56]. Czarnecki *et al.* reported that three patients with bvFTD developed extrapyramidal symptoms and tardive antecollis after treatment with olanzapine, risperidone or quetiapine [57]. It is not clear from this report whether there was any benefit in any of these cases.

Miscellaneous agents

In a single case of bvFTD, quantitative EEG demonstrated profound greater left than right bi-frontotemporal slowing, which partially normalized after methylphenidate administration [58]. In a randomized double-blind trial, methylphenidate reduced risk betting in the Cambridge Gambling Task in bvFTD patients (n = 8) but had no effect on any other measures [59]. In a case report, topiramate reduced alcohol abuse in bvFTD but not other obsessive-compulsive tendencies [60]. A very recent study of oxytocin in bvFTD demonstrated preliminary data showing a beneficial effect on the NPI [61].

In summary, while it is helpful to have this small amount of literature, the small sample sizes (less than 20 participants), heterogeneity of participants and variability in outcome measures leave many questions about the utility of existing agents in the management of neuropsychiatric symptoms in FTD. At present, the treatment of these symptoms in FTD continues to be challenging and largely reliant on individualized empirical approaches. Figure 2 displays a diagram of our usual approach to the assessment and management of neuropsychiatric symptoms in FTD, with the caveat that 'one size does not fit all' in this or any other dementia.

Conclusion & future perspective

Although much of the scientific and clinical literature on PPA focuses on the canonical language impairments, as the illness progresses and extends beyond brain language networks neuropsychiatric symptoms become more common. Furthermore, it is not infrequent for neuropsychiatric symptoms to be present during the early stages of PPA. In the PPA-S subtype, in particular, behavioral symptoms are very common and similar to those in bvFTD. On the other hand, PPA-G and PPA-L exhibit fewer behavioral symptoms that some have characterized, at least in some patients, as more reminiscent of those observed in AD [18].

While existing instruments are valuable, it is worth considering the development of new instruments for the measurement of neuropsychiatric symptoms tailored toward PPA. It might be useful for studies of putative disease-modifying therapies to measure neuropsychiatric symptoms, in addition to language, as an indicator that an intervention can slow progression of or otherwise ameliorate PPA. Ultimately, clinical trials of potential treatments aimed at improving the lives of PPA patients and their families need to focus not only on language and general cognitive function but also on neuropsychiatric symptoms.

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Practice Points

- Primary progressive aphasia is typically conceptualized as a disorder primarily affecting language, but clinical practice and a review of the literature indicates that neuropsychiatric symptoms are common.
- Very little is known about the biological basis of neuropsychiatric symptoms in primary progressive aphasia, but a few studies suggest that neurodegeneration in particular brain regions or circuits may underlie some of these symptoms.
- There is relatively little systematic research on the clinical characteristics of neuropsychiatric symptoms in primary progressive aphasia, and no evidence-based literature on their management.

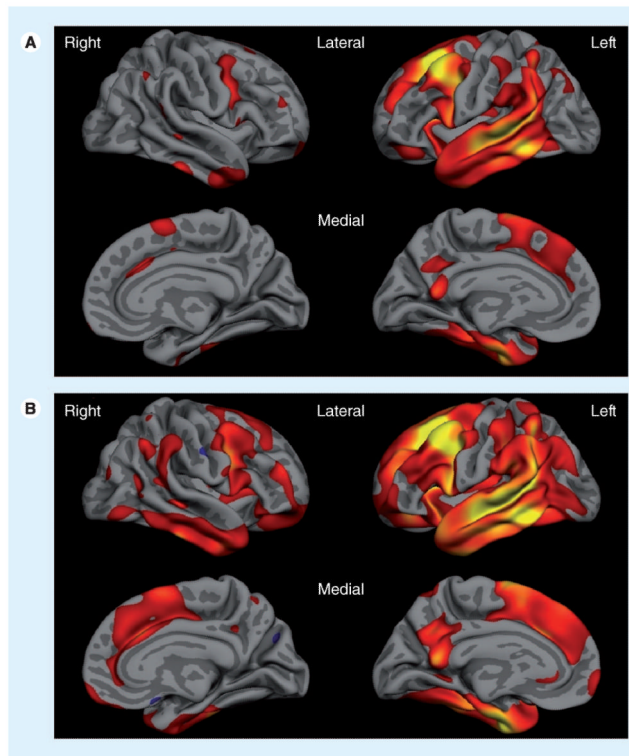


Figure 1. Cortical atrophy in a mixed sample of patients with primary progressive aphasia (A) Baseline cortical atrophy and (B) progression of atrophy after 2 years, illustrating not only the spread within the left hemisphere, but also the increasing degree of atrophy within right hemisphere structures. Red–yellow indicate localization of thinner cortex in the group of primary progressive aphasia patients compared with the matched control group.

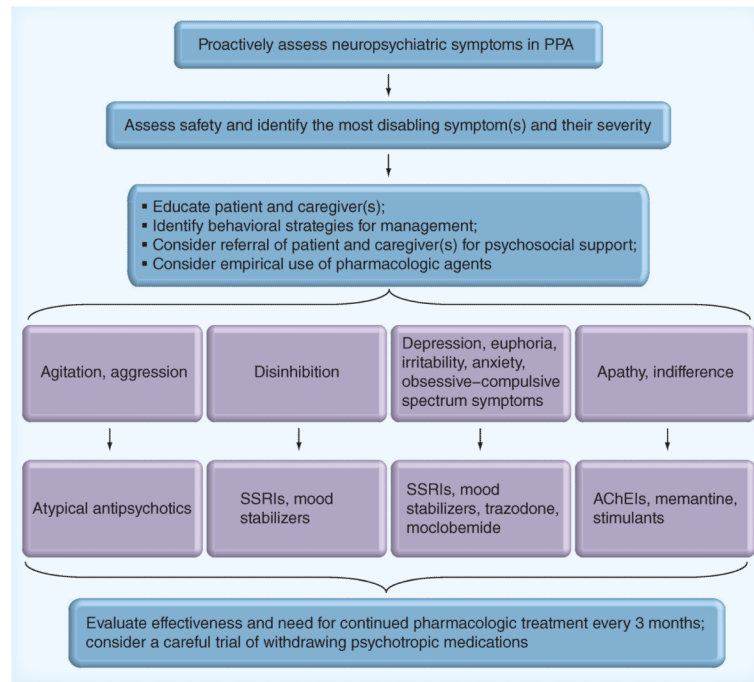


Figure 2. Clinical algorithm for empirical assessment and management of behavioral and neuropsychiatric symptoms in primary progressive aphasia
 AChEIs: Acetylcholinesterase inhibitors; PPA: Primary progressive aphasia; SSRI: Selective serotonin reuptake inhibitor.

Table 1

Summary of studies of the spectrum of neuropsychiatric symptoms in primary progressive aphasia.

Study (year)	Type of study	Patients (n)	Scale	Outcome measure	Major results	Additional notes	Ref.
Rosen <i>et al.</i> (2006)	Cross-sectional	PPA-S (33), PPA-G (17), PPA-L (17), bvFTD (50) and AD (119)	NPI	Total NPI score, FTD-specific NPI score	bvFTD > PPA-S > PPA-L ≈ PPA-G ≈ AD	–	[18]
Marra <i>et al.</i> (2007)	Cross-sectional	PPA-G (10), bvFTD (22) and AD (20)	NPI	Mean severity score	bvFTD > PPA-G ≈ AD	No PPA-G with delusions, hallucinations or aberrant motor behaviors	[19]
Banks and Weintraub (2008)	Cross-sectional	PPA (42) (not subtyped) and bvFTD (28)	NPI	NPI severity score, number of symptoms	bvFTD > PPA Number of symptoms in long-duration PPA (>5 years) ≈ bvFTD	Mood, agitation, nightmare symptoms, apathy and appetite symptoms common in PPA	[22]
Fatemi <i>et al.</i> (2011)	Cross-sectional	PPA (55) (not subtyped), CTL (111)	NPI	Frequency of symptoms	PPA > CTL (apathy, depression, appetite, motor symptoms, anxiety and irritability) PPA ≈ CTL (sleep-related/night-time symptoms)	Delusions, euphoria and hallucinations were rare or absent in PPA	[20]
Liu <i>et al.</i> (2004)	Cross-sectional	SD (27), bvFTD (24) and AD or mild cognitive impairment (22)	NPI	Frequency of symptoms	Elation/euphoria, disinhibition, aberrant motor behaviors: bvFTD ≈ SD > AD Sleep disorders: SD > bvFTD and AD Apathy: bvFTD > SD	–	[8]
Rohrer and Warren (2010)	Cross-sectional	PPA-S (9), PPA-G (14), PPA-L (7) and PPA associated with mutations in the <i>GRN</i> -PPA (3)	NPI	Frequency of symptoms	Frequency >50% in all PPA subtypes: agitation/aggression, depression, anxiety, apathy, disinhibition, irritability/lability and abnormal appetite/eating disorders Frequency >50% in PPA-S: depression, anxiety,	No relationship between total score and either duration of disease or MMSE score	[9]

Study (year)	Type of study	Patients (n)	Scale	Outcome measure	Major results	Additional notes	Ref.
					irritability, disinhibition and abnormal appetite/eating symptoms Frequency >50% in PPA-G: agitation, depression and apathy Frequency >50% in PPA-L: agitation, anxiety, irritability and apathy		
Xiong <i>et al.</i> (2011)	Retrospective chart review	PPA with AD spectrum pathology (13) and PPA with FTLN spectrum pathology (20)	NPI	Frequency of symptoms	Eating disorders, disinhibition, apathy had highest specificity for FTLN spectrum pathology	The absence of depression not useful in predicting FTLN pathology	[23]
Knopman <i>et al.</i> (2008)	Longitudinal (1 year)	PPA-S (26), PPA-G (25), PPA-L (9) and bvFTD (47)	NPI and FBI	Frequency of symptoms	bvFTD and PPA-S > PPA-G > PPA-L After 12 months, on the NPI and FBI, the PPA-S patients showed greater worsening than the other three subtypes	Hallucinations and delusions were infrequent, but all other symptoms reported in PPA	[41]
Knopman <i>et al.</i> (2011)	Cross-sectional	Probable AD (2550), DLB (281), VaD(88), bvFTD (234) and PPA(137)	CDR supplemental 'behavioral' and 'language' domains	Frequency of symptoms	PPA-S > PPA-G likely to have abnormal rating in behavioral domain Most PPAs had nonzero rating on behavioral domain	–	[62]
Kertesz <i>et al.</i> (2000)	Cross-sectional	PPA(11),bvFTD (26), AD (38), VaD (16)and depressive disorders (17)	FBI	Mean FBI score	bvFTD > PPA ≈ AD Vascular dementia > PPA The main symptoms exhibited by PPA were apathy, irritability and, to a lesser extent, inappropriate behavior	–	[40]

Study (year)	Type of study	Patients (n)	Scale	Outcome measure	Major results	Additional notes	Ref.
Marczinski <i>et al.</i> (2004)	Longitudinal (3 years)	bvFTD (12) and PPA (14)	FBI	Mean FBI score	FBI scores in PPA rose in the third year to >27 FBI scores in bvFTD rose in the second year and reached a plateau in the third year	Apathy, aspontaneity, personal neglect, disorganization, inattention, logopenia, poor judgment, inappropriateness, restlessness, aggression and hyperorality items increased over time in PPA patients	[21]
Bozeat <i>et al.</i> (2000)	Cross-sectional	bvFTD(13), SD (20) and probable AD (37)	CBI	Frequency of symptoms	Mood symptoms: bvFTD ≈ SD ≈ AD Mental rigidity: SD > bvFTD > AD Stereotypic behaviors: SD > bvFTD > AD Social withdrawal: bvFTD > SD > AD Apathy: bvFTD > SD > AD	Psychotic symptoms were less frequent in the temporal variant. Stereotypic and eating behaviors were the strongest factors differentiating FTD from AD	[7]

AD: Alzheimer's disease; bvFTD: Behavioral variant of frontotemporal dementia; CBI: Cambridge Behavioral Inventory; CDR: Clinician Dementia Rating Scale; CTL: Control; DLB: Lewy body dementia; FBI: Frontal Behavioral Inventory; FTD: Frontotemporal dementia; FTLD: Frontotemporal lobar degeneration; MMSE: Mini Mental State Examination; NPI: Neuropsychiatry Inventory; PPA: Primary progressive aphasia; PPA-G: Primary progressive aphasia nonfluent/agrammatic variant; PPA-L: Primary progressive aphasia logopenic variant; PPA-S: Primary progressive aphasia semantic variant; SD: Semantic dementia; VaD: Vascular dementia.

Table 2

Frequency ranges of neuropsychiatric symptoms in primary progressive aphasia.

Symptom	All PPAs (%)	PPA-S (%)	PPA-G (%)	PPA-L (%)	Ref.
Delusions	2–9	5–19	0–7	14	[7–9,19,20,22]
Hallucinations	0–6	0–11	0	14	[7–9,19,20,22]
Agitation/aggression	20–50	30–64	50	57	[6,7,9,20,22]
Depression/dysphoria	38–56	44–78	57	29	[7–9,20,22]
Anxiety	15–50	41–56	36	71	[8,9,20,22]
Elation/euphoria	8–19	22–37	14	14	[8,9,20,22]
Apathy/indifference	32–56	33–65	64	57	[7–9,20,22]
Disinhibition	12–38	36–74	14	43	[6,8,9,20,22]
Irritability	18–56	33–82	29	71	[6–9,20,22]
Aberrant motor behavior	4–24	22–52	0–21	29	[7–9,19,20,22]
Night-time behaviors	22–30	44–52	21	14	[8,9,20,22]
Appetite/eating behaviors	26–50	35–67	43	43	[7–9,20,22]
Mental rigidity	–	80	–	–	[7]
Stereotypies/rituals/compulsions	–	35–91	–	–	[6,7]
Distractibility	–	90	–	–	[7]
Decrease in self-care	–	64–65	–	–	[6,7]
Poor judgment	–	65	–	–	[7]
Social withdrawal	–	18–60	–	–	[6,7]
Lack of empathy/selfishness	–	75–91	–	–	[6,7]

PPA: Primary progressive aphasia; PPA-G: Primary progressive aphasia nonfluent/agrammatic variant; PPA-L: Primary progressive aphasia logopenic variant; PPA-S: Primary progressive aphasia semantic variant.

Table 3

Neuropsychiatric and behavioral scales used in dementia.

Scales	Symptoms measured	Ref.
NPI and NPI-Q	Delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability, aberrant motor behavior, night-time behaviors and eating/appetite behaviors (NPI is a caregiver/informant interview; NPI-Q is a self-administered questionnaire with written instructions)	[37,63]
FBI	Apathy, asponaneity, indifference/emotional flatness, inflexibility, disorganization, inattention, personal neglect, loss of insight, preservation, obsession (stereotypy), hoarding, inappropriateness, poor judgment and impulsivity, restlessness/roaming, irritability, aggression, hyperorality/food fads, hypersexuality and utilization behavior	[39]
FRS	Lack of interest, lack of normal affection, confusion in unusual surroundings, restlessness, impulsivity and lack of judgment	[12]
CBI	Challenging behaviors (uncooperative, threatens to harm self/others), disinhibition, eating habits, sleep, stereotypic and motor behaviors, motivation and insight/awareness	[7]
BEHAVE-AD	Paranoid and delusional ideation, hallucinations, activity disturbances, aggressiveness, diurnal rhythm disturbances, affective disturbances, anxieties and phobias	[4]
NPI-C	Delusions, hallucinations, agitation, aggression [†] , dysphoria, anxiety, elation/euphoria, apathy, disinhibition, irritability/labality, motor disorders, sleep disorders, appetite and eating disorders, and aberrant vocalization	[8]
FTD Inventory	Behavioral disinhibition, violation of social norms, apathy, hypomania-like behaviors, loss of interpersonal warmth or empathy, loss of insight, decline in personal hygiene and grooming, mental rigidity and inflexibility, distractibility and impersistence, hyperorality and dietary changes, compulsive and stereotyped behavior, and environmental dependency	[64]
GDS (short form)	Satisfaction with life, dropping activities or interests, feeling life is empty, getting bored, being in good spirits, being afraid that something bad is going to happen, feeling happy, feeling helpless, preference to stay at home, having problems with memory, thinking it is wonderful to be alive, feeling worthless, feeling full of energy, feeling hopeless and thinking most people are better off than they are	[59]

BEHAVE-AD: Behavioral Pathology in Alzheimer's Disease; CBI: Cambridge Behavioral Inventory; FBI: Frontal Behavioral Inventory; FRS: Frontotemporal Dementia Rating Scale; FTD: Frontotemporal dementia; GDS: Geriatric Depression Scale; NPI: Neuropsychiatry Inventory; NPI-C: Neuropsychiatric Inventory-Clinician Rating Scale; NPI-Q: Neuropsychiatry Inventory Questionnaire.

[†]Note that aggression has been separated from agitation.