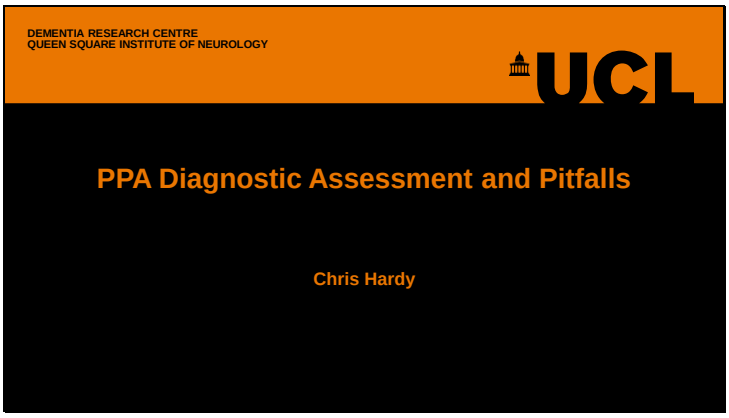
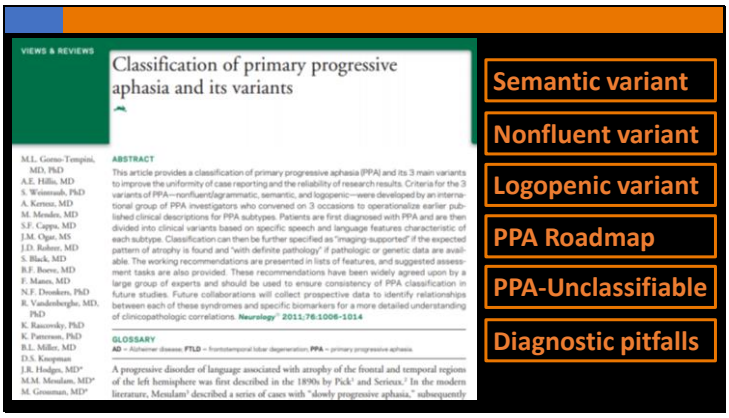
Slide 1


DEMENTIA RESEARCH CENTRE
QUEEN SQUARE INSTITUTE OF NEUROLOGY
UCL
PPA Diagnostic Assessment and Pitfalls
Chris Hardy

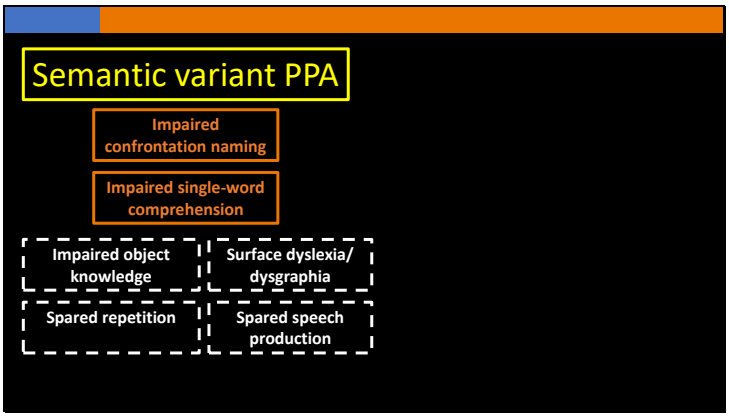
Slide 2



So, over the next thirty minutes or so I'll talk about assessing patients with PPA, and I'll do this with reference to the 2011 consensus criteria pictured here. These have been cited nearly 2,000 times according to google scholar and really are the gold-standard for how we currently understand phenotypic variation in PPA.

I'll go through each of the major PPA syndromes, namely semantic variant, nonfluent variant and logopenic variant PPA referring to the consensus criteria in each case, and also adding some new observations that we have made based on the UCL cohort for each syndrome. I'll then present a roadmap that we've developed at UCL showing a way to classify patients into one of the three major variants based on their speech output, before talking briefly about those cases who don't meet those criteria for semantic, nonfluent or logopenic PPA. And finally, I'll talk about some diagnostic pitfalls.

Slide 3



So turning first of all to arguably the most well-defined of the three major PPA phenotypes, semantic variant PPA, aka ‘semantic dementia’.

Here I’ve transcribed the current consensus criteria for a diagnosis of semantic variant PPA. These stipulate that the patient must have both of these elements in orange here – impaired confrontation naming and impaired single-word comprehension, and three of the four elements in white – impaired object knowledge (particularly for low frequency/ low familiarity items); surface dyslexia or dysgraphia; spared repetition; and spared speech production in terms of grammar and motor speech.

And really what these criteria boil down to is that this is a pervasive disorder of semantic memory – it affects a person’s knowledge of objects in every modality – they will have trouble naming objects, recognising objects, using objects, identifying sounds, identifying smells. The person slowly loses their knowledge of everything that they have learned about the world.

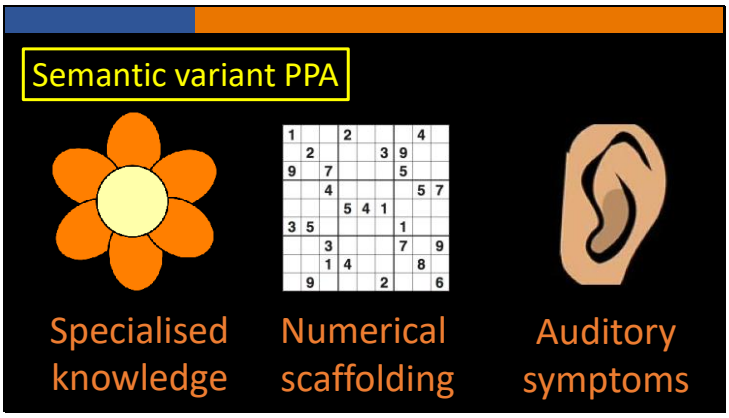
Slide 4

Despite this loss of semantic memory, the speech of somebody with svPPA is remarkably fluent – and I've got a video here of one of our patients talking to a former colleague, Charles Marshall about the difficulties she has when she tries to go shopping.

[Play video]

And I think that's a nice video for a few reasons – it shows just how fluently somebody with svPPA talks, despite the loss of vocabulary, it shows her intact prosody – the rise and fall of her voice, and she described this frequency effect really nicely, whereby less common items are harder for her to identify and locate than common things like "onions".

Slide 5

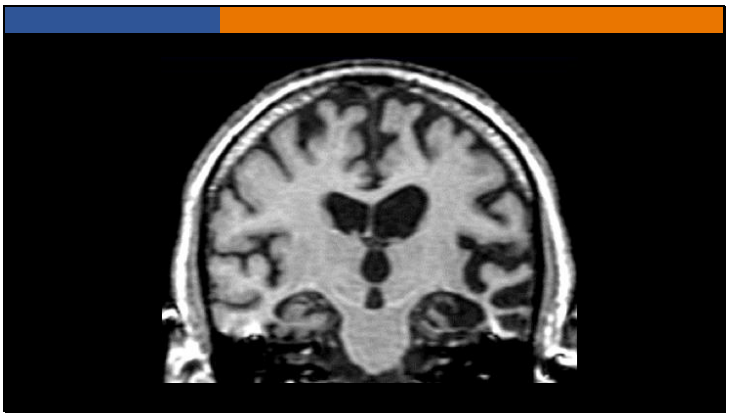


Actually, this frequency effect can be really telling even at very early stages of the disease. Quite often, we'll see people who say that they first noticed something was wrong when they struggled to remember words in a highly specialist vocabulary, so for example, the gardener who started to forget the Latin names for flowers, the ornithologist who struggled with rare bird names, the osteopath who couldn't remember the names of bones.
By contrast, numerical representations seem to be relatively well-preserved in svPPA, presumably because they're stored posteriorly to the core damage of the anterior temporal lobe. A really good clue to a patient's diagnosis can be whether or not they take enjoyment from number puzzles like Sudoku – not many patients with lvPPA or nfvPPA will manage these as their disease progresses, but this can become an obsession for somebody with svPPA as they desperately hold onto that isolated window of ability.

Something else that we've noticed is that patients' conversations can be 'scaffolded' around these intact representations – have a listen to this 30-second speech sample and count how many times this gentlemen says a numb [play clip]

And finally we've noted that auditory symptoms are often prevalent in svPPA – many patients will complain of unexplained ringing in their ears "tinnitus" and can display a bivalent response to certain sounds – the same patient can become 'musicophilic' and obsessed with specific bands or artists, whilst showing increased aversion to particular environmental sounds.

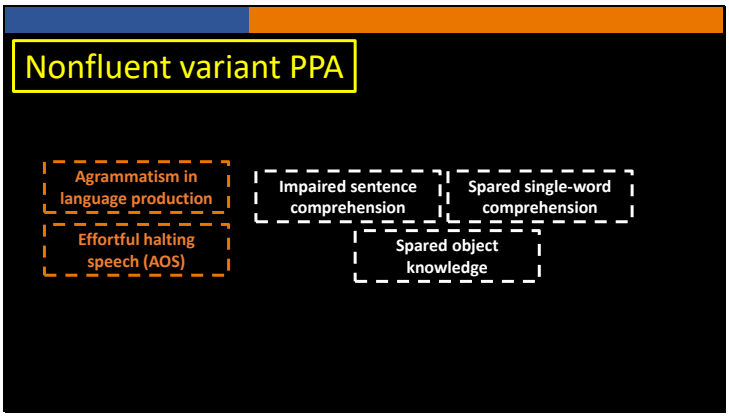
Slide 6



Now, the main focus of this talk is on the clinical presentation of people with PPA so I won't dwell on this slide, but just to emphasise, the vast majority of patients with svPPA will have a scan that looks like this – with a cored out left anterior temporal lobe that is very asymmetrical L>R.

I think one important thing to note is that by the time somebody comes to clinic, their scan can already look dramatically affected, meaning that these underlying changes are happening years and years before symptom onset. I think that has important corollaries for potential pharmacological therapies – how can you stratify somebody into a trial for a potential drug if the people you need to recruit don't know that they have anything wrong with them? svPPA is extremely rarely genetic so we don't have the same opportunity for drug therapies as we do in familial FTD. I think the highlights the importance of cognitive and behavioural rehabilitation strategies – these are likely to make real, tangible differences to the lives of people directly and indirectly affected by svPPA.

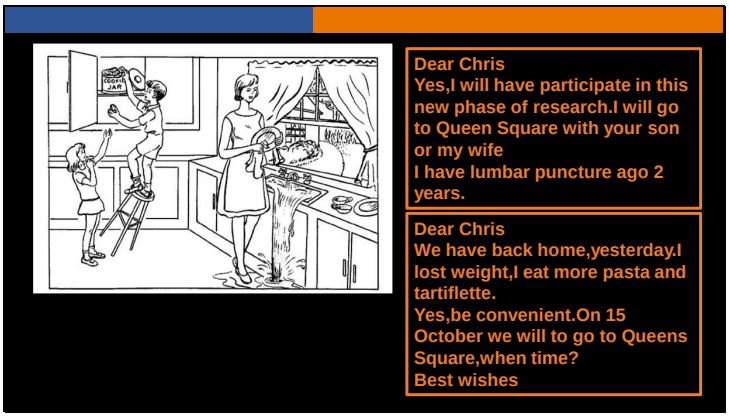
Slide 7



Moving on now to the nonfluent variant of PPA, the 2011 criteria stipulate that the person should have EITHER agrammatism in their language production, OR effortful, halting speech with inconsistent speech sound errors and distortions, or apraxia of speech.

If one of these is present, then they need two of the three white boxes for a diagnosis of nfvPPA, so i) impaired comprehension of syntactically complicated sentences; spared single-word comprehension; iii) spared object knowledge

Slide 8

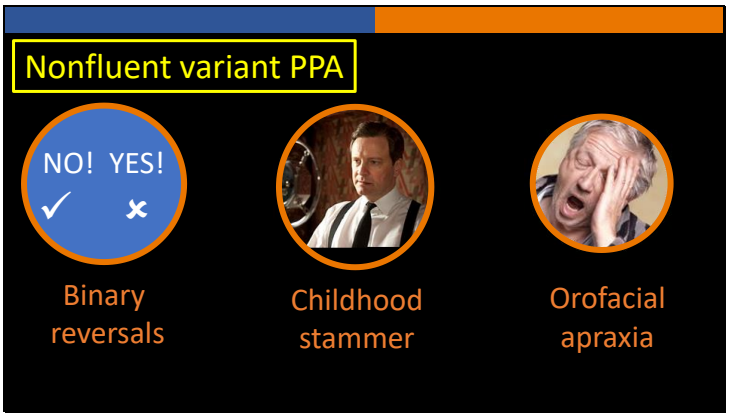


I just wanted to give a quick example of a very apraxic speech phenotype, so here I've got the famous cookie theft picture, and a speech sample of a man with nfvPPA – and I want you to listen to how effortful and difficult his speech is here.

So hopefully you could all hear how difficult that was. I'll always remember this gentleman very well because despite his aphasia, he never lost the will to tell jokes – I'll never forget walking into the waiting room in our centre to see him mid-joke with everyone else paying rapt attention to him.

Now in cases like this where speech can be very apraxic and effortful, it can be really hard to tell if someone is agrammatic – so a nice window into this can be to look at a person's written speech. Here I've got two emails from a different gentleman which highlight agrammatism in PPA:

Slide 9

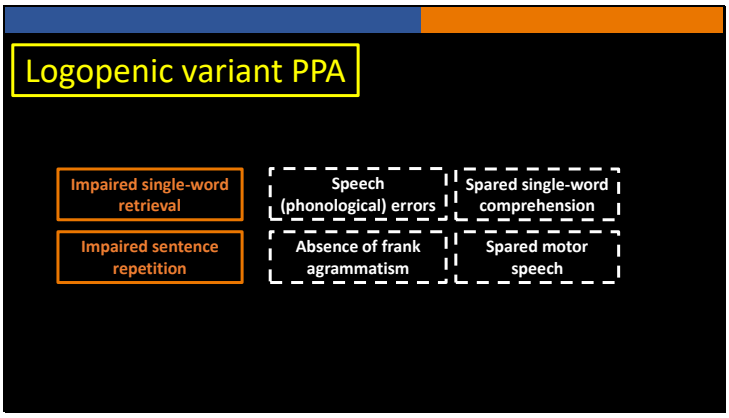


Now to focus on some clinical aspects of nfvPPA that aren't emphasised in the current criteria. First, we've noticed that binary reversals occur in up to 50% of the patients we see, whereby the person will get binary response options confused. This most often manifests in yes/no confusion but can occur with e.g. hot/cold, left/right. It isn't just limited to the verbal domain either – a patient will frequently nod their head when they mean to shake it, or put their thumb up when they mean to point it down. It can be incredibly confusing and frustrating for the person and the patient, and it means that we try to avoid closed-response questions with our patients. I should say that work was led by Harri Sivasathiaseelan, Jason Warren and Martin Rossor in London.

We've also noticed that several of our patients with nfvPPA will mention a childhood stammer, corrected in early adulthood but that re-emerges in nfvPPA in later life. I think this is an interesting observation, but we need to investigate it further – it might simply reflect a kind of 'response bias' – but equally it might tie in with some of the nice work from UCSF suggesting that childhood developmental disorders might signal specific network vulnerabilities that are selectively targeted by proteinopathies in later life.

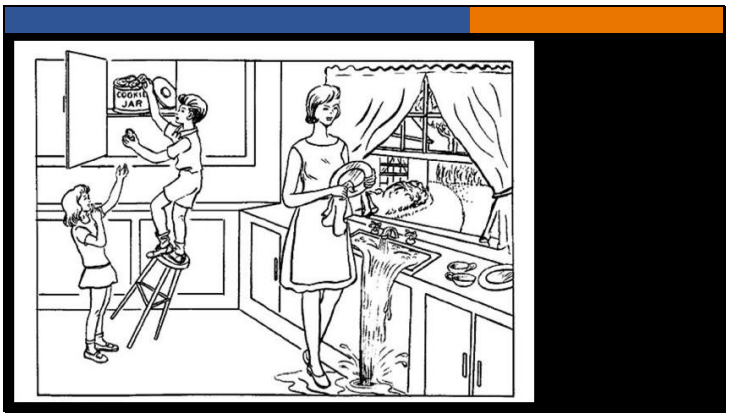
nfvPPA is often associated with orofacial apraxia, dysphagia, and overlap with Parkinsonism. These neurological features might give clues to the underlying proteinopathies – we think that neurological features of apraxia of speech and Parkinsonism are likely to signal a tauopathy whilst agrammatism might herald TDP-43.

Slide 10



So turning now to the most recently described PPA syndrome we have logopenic aphasia, which was only put on record in 2004. In the current criteria, both of the core features in orange are required – impaired single-word retrieval in spontaneous speech and naming; and impaired repetition of sentences and phrases. Three of the features in white are required for a diagnosis of lvPPA: i) speech (phonologic) errors in spontaneous speech and naming; ii) spared single-word comprehension and object knowledge; iii) spared motor speech; iv) absence of frank agrammatism.

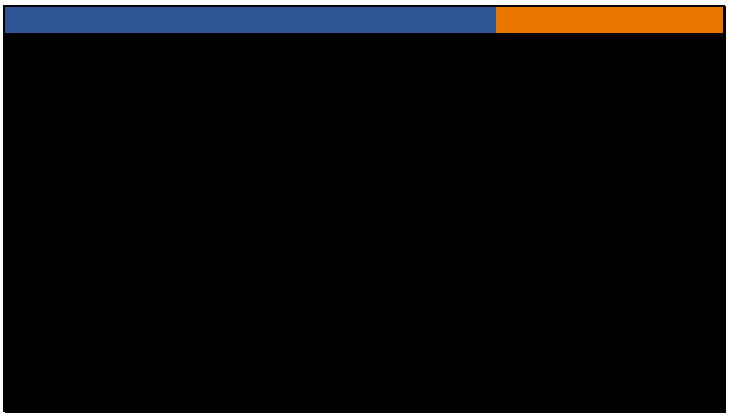
Slide 11



I think that of the three major PPA syndromes, lvPPA is the one that we understand least; we have this very strange constellation of symptoms with short-term memory problems, phonemic speech errors, word-retrieval problems, and to me these symptoms don't seem as coordinated as those seen in svPPA and nfvPPA.

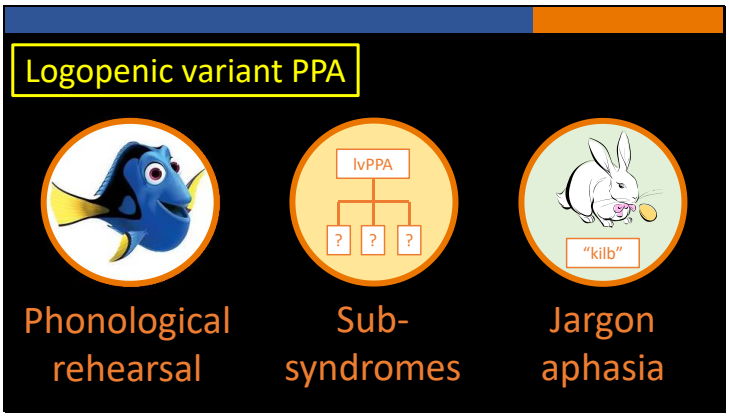
So first of all I wanted to play you this clip of a gentleman who really struggles with word-finding difficulties – and in particular I want you to note the difference in his speech to somebody with svPPA.

Slide 12



Next I want to show you a video of somebody we saw recently with lvPPA – this is Charles Marshall demonstrating the importance of testing repetition in somebody with PPA. This is a task that somebody with svPPA would be able to manage quite easily – and just look at what happens as the thing to remember gets longer and longer.

Slide 13

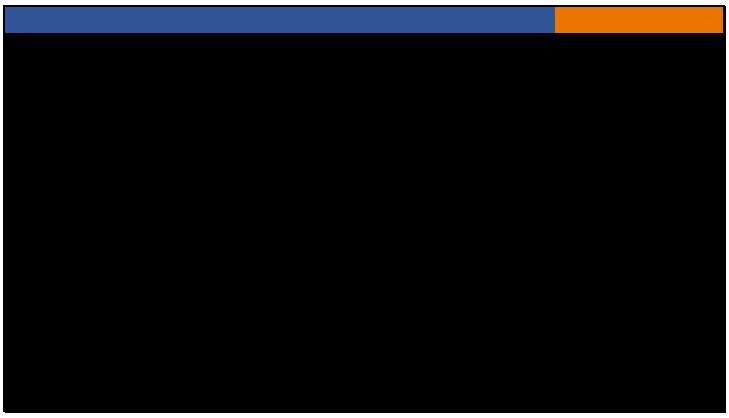


I hope that clip emphasises what we believe to be critically vulnerable in the logopenic variant – a breakdown of his 'phonological loop' – meaning that he is able to repeat short words, but struggles when more demand is placed on that system. Something else I think is interesting is that it's almost 'leaky' – when he's trying to remember the item he's just been asked, part of the previous item often comes to the fore.

So I do think that we need to do more and better research to fully understand the nature of lvPPA. With that said, there has been some amazing work done around the world, and I think the UCSF and Sydney groups are leading the way here. Christian Leyton in particular has done some nice work in suggesting that there might be multiple sub-systems of lvPPA:

Pure anomia
Pure anomia plus mild single-word comprehension deficits
Anoma, mild single-word comprehension deficits and repetition deficits
Something we've noticed is that our patients with lvPPA can develop prominent jargon – neologisms in speech and writing that they themselves are ostensibly unaware of – and this appears to be related to the integrity of the temporo parietal junction in the dominant language hemisphere.

Slide 14



So, having been through the three major phenotypes, how do we reach accurate diagnosis? There have been several attempts to do this – and Marsel Mesulam and Rik Vandenberghe have produced ‘diagnostic roadmaps’ for PPA that help us to apply these consensus criteria in a meaningful way that helps us distinguish between the subtypes. We’ve recently made our own as well.

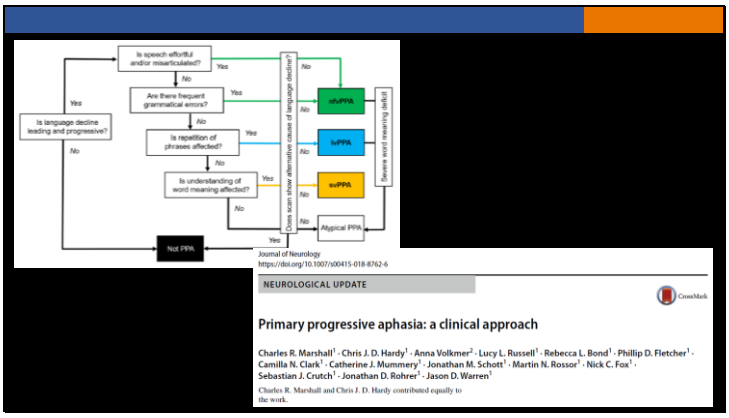
So, for a diagnosis of PPA, language dysfunction must be the first, and the most salient clinical complaint.

If it is, we ask if speech is effortful and misarticulated OR if there are frequent grammatical errors. If there are then the diagnosis is nfvPPA.

If it’s not, then we can ask our next question – is repetition of phrases affected? If so, then we can point toward lvPPA. If not, then we ask our final question – is understanding of word meaning affected. And if so, we might suspect svPPA.

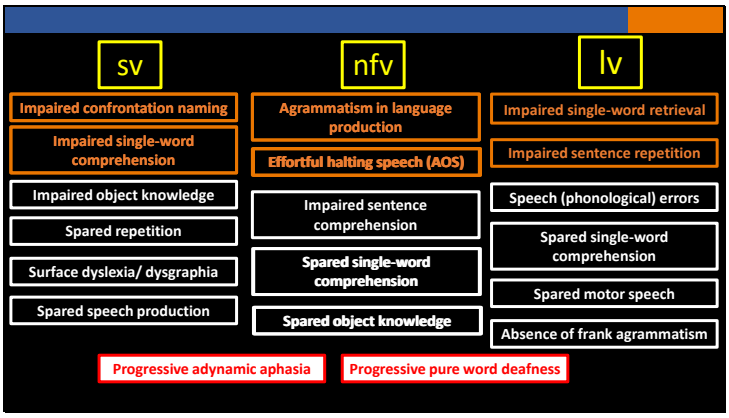
In all cases, for a clinical diagnosis we would check to see if the scan shows an alternative cause of language decline.

Slide 15



Just to say a more formal presentation of this roadmap is here, and you can find it in our recent paper here.

Slide 16



However, as everyone in this room can attest, it's not always that easy, and the patients we see don't always fit nicely into our nice categories. The exact number of patients who don't meet the consensus criteria for one of the three syndromes varies significantly across series; a really nice paper produced by the UCSF group last year showed that only 4 out of 69 of their patients didn't meet criteria for one of the three major syndromes; whilst the Cambridge group have published saying that more than 40% of their cohort didn't meet criteria for one of the major PPA phenotypes we've talked about here.

My own impression, for what it's worth is that around 2 in every 10 patients do not neatly fit into the criteria I've displayed here. We've already talked about primary progressive apraxia of speech as perhaps representing a specific disease entity – something propounded by Keith Josephs at the Mayo Clinic.

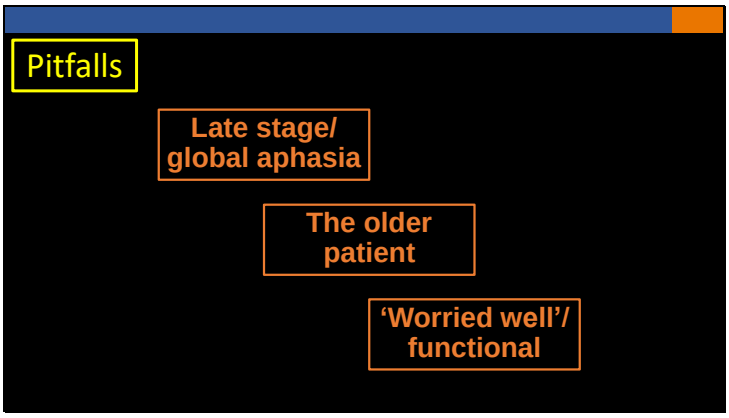
Something else we see not uncommonly is the patient with the core features of nfvPPA, but who also has a significant semantic comprehension deficit – so-called "mixed PPA".

We also see something like a progressive pure anomia whereby the leading presentation is with problems naming, seemingly in the absence of any semantic deficit. In our experience, these cases tend to develop a semantic impairment later in the course of the disease, but I would argue that there is a significant difference between the patient whose disease starts with an insidious anomic deficit and the patient who presents with a semantic deficit that underlies their anomia.

There are many other specific syndromes that fall within the PPA umbrella but that we can't capture very well with these criteria – 'progressive adynamic aphasia', where a patient will present with a paucity of verbal output with minimal other language, cognitive or behavioural deficits; or 'progressive pure word deafness', where the patient will present with a selective agnosia for spoken words, in the context of intact processing of environmental sounds and comprehension of written words.

Now all of that is not meant to be bashing the consensus criteria – I think they're incredibly important and have really unified international PPA research in a way that just wasn't possible prior to 2011. But I do think it's worth bearing in mind that if you've seen one person with PPA, you've seen one person with PPA. These criteria are fantastic tools for clinicians and people working with PPA, but every person we see will have a phenotype that is specific to them, their backgrounds and their experiences – which is something important to bear in mind when thinking about designing rehabilitation strategies.

Slide 17



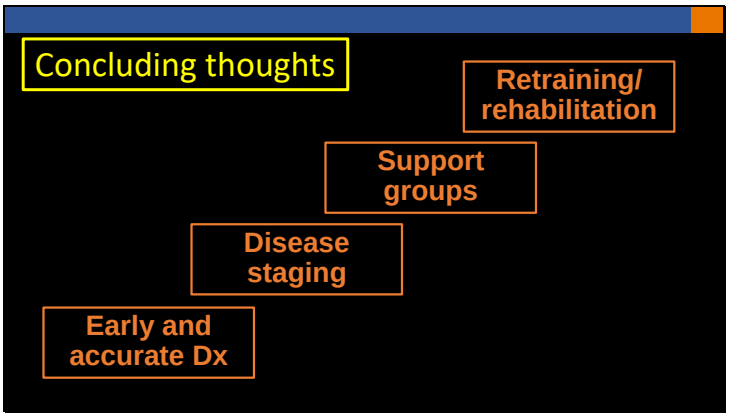
On the last slide, I talked about 'mixed' aphasia – but actually what we see in late stage PPA is mutism or sparse, stereotyped utterances and widespread cognitive decline. A corollary of this is that diagnosis at later stages of PPA may be better informed by neurological rather than linguistic features; Parkinsonism, for instance, might signal nfvPPA.

I've mainly focused on clinical presentation here – but for the nonfluent and logopenic variants, neuroanatomical changes on MRI scans can be subtle.

We tend to think of PPA as young-onset but there is definitely a cluster of older patients, in whom it is likely that PPA is underdiagnosed. I think we see this most commonly in the nonfluent variant where people can develop speech problems in their mid to late eighties

And finally, it's worth noting that word-finding difficulties are very common complaints in patients attending memory clinics. For many people this will reflect normal ageing and stress; but we have also seen rare cases of people presenting with speech problems that are excessively deliberate and apparently have no organic cause.

Slide 18



So I've just got 4 final points to wrap up with.

Early and accurate diagnosis is possible, and important. Ultimately, effective pharmacological treatment of PPA will depend on this.

We need to get better at disease staging. When somebody receives a diagnosis, we get asked so often, "what is going to happen to me?" "how long do I have?" and at the moment, all we can say is that "every person is different". And that's true, but not helpful. So there's a lot of work to be done on using baseline data to predict rates of decline and outcomes. What we would like to have is to be able to take an individual patient and say, "this is what we think is likely to happen to you". Unfortunately, it's just so noisy that we can't do this yet – but we need to be able to.

I don't think we can understate the importance of support groups. PPA is very rare and most people will never have heard of it before their diagnosis. It can feel incredibly isolating, especially if you're lumped into services focused on people with typical Alzheimer's disease. Being able to talk to somebody who knows how it feels is really important and I think support groups are desperately needed. I help run a PPA support group in London in the UK and we have around 75 people coming to see us, sometimes from hundreds of miles away.

And finally, and hopefully to set the scene for what's going to come next, we need evidence-based retraining and rehabilitation interventions to help people living with the disease. Far too often we hear stories of people being told that they received a diagnosis of PPA and were told that there's nothing to be done – it's degenerative – there's no point in speech and language therapy or cognitive rehabilitation. This is fundamentally inaccurate and I'm delighted and excited to hear about some of the amazing work done by my colleagues around the world in the next three sessions.

Slide 19

Thank you