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DEMENTIA

Thames Valley practice recommendations for the diagnosis of the Fronto-temporal Dementias

Purpose of document:

This has been written to help clinicians in memory clinics when a diagnosis of Fronto-temporal Dementia (FTD) is being considered. It aims to clarify essential parts of the diagnosis process and indicate various options for patients post-diagnosis.

Key Points:

- It is important for patients and families that FTD is diagnosed accurately and in a timely manner
- The condition impacts greatly on the welfare of the patient and family
- To optimise diagnosis, a neurology review, expert neuropsychological and/or speech and language assessment, and brain imaging are essential
- A significant proportion of patients may be appropriate for genetic counselling, dementia advisor support and research participation

Background:

The Fronto-temporal Dementias (FTD) are uncommon disorders but they pose a significant challenge to patients and carers and can be difficult to diagnose.

The Prime Minister's challenge on dementia 2020 **(Department of Health, 2015: https://www.gov.uk/government/publications/prime-ministers-challenge-on-dementia-2020)** emphasises the importance of a timely and accurate diagnosis.

NICE guidance (**https://www.nice.org.uk/guidance/cg42?unlid=190152663201512282286)** state that memory assessment services should be a single point of referral for all people with a possible diagnosis of dementia. In view of the unusual presentation of FTD, patients can present in a variety of settings including general adult psychiatric services. NICE suggests that MRI is the preferred modality to assist with early diagnosis of dementia, although CT could be used. NICE guidance also states that HMPAOSPECT or FDG-PET should be considered to help differentiate Alzheimer's disease, Dementia with Lewy Bodies and FTD if the diagnosis is in doubt. NICE also states that EEG should be considered if FTD is

suspected and recommends Lund-Manchester (1994) and NINDS Criteria for FTD , although both of these recommendations are now probably outdated.

What are the FTDs?

For the purpose of this document we have used International Consensus Criteria for behavioural variant (bvFTD) and expert consensus for primary progressive aphasia (PPA) which is currently best described as three subtypes:

There are possible and probable behavioural variant FTD (FTDC) criteria (**ref1**)
http://www.ncbi.nlm.nih.gov/pubmed/?term=K+Rascovsky+et+al+%2CBrain+2011%3A+134%3B+2456-2477

There are also criteria for three subtypes of primary progressive aphasia, but this is likely to be revisited as more evidence emerges (**ref 2**) The three main subtypes are Progressive non-fluent aphasia (PNFA) in which patients have deficits of speech sound production and grammar; logopenic variant PPA (LP) in which patients have slowed speech but few speech errors; and semantic dementia (SD).

Correct diagnosis of subtype has implications for not only prognosis, but also pathology (**ref 3**)
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3059138/

With regards to the genetic defects that have been found, repeat expansion in the C9orf72 gene, defects in the GRN and MAPT genes are also associated fronto-temporal dementia. #genes **(ref 4)**

This paper aims to pull together information about variation in practice in the Thames Valley, including Milton Keynes and to suggest guidance based on consensus agreement about good practice where evidence is unclear. There has previously been uncertainty about what constitutes best practice with regard to diagnosing and initial management of patients with FTD.

There have been two meetings aiming to bring together professionals from the counties that make up the Thames Valley. The group represented psychology, psychiatry and neurology.

In order to gather information about local variations in practice a survey monkey questionnaire was sent out across the AHSN area. The information gathered has been used to inform this guidance and to highlight areas that are under-resourced in some localities.

A range of basic bedside tests which are useful in differentiating FTD from other dementias have been included in the appendix to facilitate use in memory clinics.

Thames Valley FTD practice survey

There were 31 responses to an electronic survey of memory clinic clinicians across the Thames Valley in March 2016 (responses as follows: 4 from Milton Keynes, 3 from Buckinghamshire, 9 from Berkshire, 14 from Oxfordshire).

A wide range of clinical staff responded including 5 psychologists, 13 psychiatrists, and 11 other memory clinic clinicians.

Several themes emerged and the most prominent was the range of access to sophisticated scanning, skilled neuroradiology reports, and speech and language therapy. There was scope to increase confidence in skills amongst some memory clinic clinicians with regard to specialist neuropsychological testing and discussion of complex cases with specialist neurologists.

50% did not have access to scan interpretation by specialist neuro-radiologists. 30% never used EEGs, 50% never used EMGs. In some areas CT scans were carried out despite requests for MRIs. 21% of respondents always organised a neurology review and 39% sometimes did. Only 14% had specialist neuropsychologists in their own clinic and free comments included the wish to have access to other executive and language tests.

There was a range of screening tests used, 78% used the MOCA, 39% used the ACE, 30 used an MMSE and 40% also used a carer rated Frontal Behavioural Scale.

Use of speech and language therapists was variable, 50% never used them for diagnosis and only 42% ever used them for rehabilitation work.

When asked who usually makes the diagnosis, 13 responded old age psychiatrists and 10 neurologists in this sample.

Apparently regarding genetic testing practice, 10% refer via neurology, 42% directly to clinical genetics and 47% do not refer at all.

This survey shows some discrepancies in practice and this guidance aims to help reduce unnecessary variation and improve best practice.

Memory Clinic Pathway strategy for FTD:

There is often a significant delay between onset of symptoms and diagnosis for people with FTD because their symptoms do not fit the prototypic amnestic picture of dementia expected by the general public and many generalist clinicians. Accurate diagnosis of FTD in the early stages will usually require not only an interview with the client, collateral evidence and scan data, but also onwards referral for neuropsychology, and/or specialist speech and language assessment if available/appropriate and neurological screening to exclude conditions such as MND.

When a possible case reaches specialist Memory Clinics, the goal should therefore be to determine the index of suspicion in favour of false positives and further specialist assessment, rather than the incorrect exclusion (or indeed diagnosis) of FTD and no further assessment. MRIs, neuropsychological assessment and neurological assessment not only provide data for accurate diagnosis, but can also provide baseline data for those cases where diagnosis may require follow up over time.

The Thames Valley FTD pathway therefore recommends the following as a basis on which to detect possible FTD cases to refer on for further assessment:

When to consider FTD diagnosis in Memory Clinic

- Informant reports personality and behavioural changes
- Often an absence of concern in the patient and little evidence of memory deficits
- Evidence of linguistic changes
- Gradual onset, often over years with no alternative explanation such as head injury
- Young age of onset (often under 65 years)
- Family history of neurodegenerative disorders, especially young onset dementia
- Family history of Motor Neurone Disease
- Physical examination indicative of wasting, muscle fasciculation, increased reflexes, dysarthria, dysphagia, parkinsonism or eye movement abnormalities in the context of behavioural/language changes

Summary of useful bedside tests when FTD is suspected

	Addenbrookes Cognitive Examination third version	Montreal Cognitive Assessment MOCA	Frontal assessment battery	Frontal behavioural scale(for informant use)	Cognitive estimates	Complex picture	Mini Mental State Examination (MMSE)
bvFTD	✓	✓	✓	✓	✓	✓	x
PNFA	✓	✓	x	x	x	✓	x
LP	✓	✓	x	x	x	✓	x
SD	✓	x	x	x	✓	✓	x

Initial CORE bedside tests :

- Addenbrookes Cognitive Examination third version (ACE III) **#tips**
- Montreal Cognitive Assessment (MOCA)

MOCA or ACE III : Either of these should be used as standard screening assessments with all patients in Memory Clinic instead of the MMSE because they are copyright free and assess a broader range of domains. Their capacity to assess executive function is particularly important with FTD. If there is only time for one, the ACE III may be preferable where a linguistic FTD is suspected as it is more comprehensive.

Addenbrookes Cognitive Examination III (Hodges) (ref 5) : This takes about 10-15 minutes and was developed to help differentiate between FTDs and AD. It has a section to screen for nominal aphasia, surface dyslexia for irregularly pronounced words (can be an issue in Semantic Dementia), and agrammatism and comprehension of syntax and grammar.

MOCA (ref 6): this takes about 5 minutes to complete. There is a section that detects perseveration, difficulty with sentence repetition and executive dysfunction.

Additional simple bedside tests (included in the appendices)

1) **Frontal Assessment Battery (FAB) (ref 7 and ref 8)** #FAB has helpful validated cut off scores. It includes tests of similarities, lexical fluency, motor series (Luria), conflicting instructions, inhibitory control and prehension behaviour. Dysfunction of dorsolateral prefrontal cortex is often picked up by commonly used 'frontal lobe tests' from the Frontal Assessment Battery eg abstraction, response inhibition and set shifting.
2) **Cognitive estimates test (ref 9)** #CET
3) **Simple arithmetic calculation tasks** after checking that they can read and write numbers (usually preserved in SD but lost early in AD and CBD)*(some examples in Appendix 1)*
4) Use of a **picture to describe a complex scene** may be helpful to pick up:
    a. Abnormal rate of speech
    b. Dysarthria
    c. Phonological and semantic error
    d. Word finding pauses
    e. Grammatical errors

    See picture from The Queen's Square Screening Test for Cognitive Deficits (with kind permission from Prof Elizabeth Warrington) *(Appendix 2)*

5) **Use of validated brief informant questionnaire** – such as the Fronto-temporal Behavioural Scale #FBS **(ref 10)**

    This is brief with four subdomains relating to difficulties with self-control, physical neglect compared with previous habits, difficulties with mood, signs of loss of interest.

Please note these do not replace the need for expert neuropsychological or speech and language assessment

Actions needed after initial memory clinic assessment:

1. A referral for a neurology opinion
2. A referral for in depth neuropsychological testing or speech and language therapist assessment
3. A referral for a brain scan, ideally an MRI in the first instance

When a diagnosis of FTD is likely please consider the following:

1. Genetic counselling by a specialist neurologist or geneticist
2. Discussion about research participation
3. A referral to a specialist dementia support service such as the Young Dementia UK or YPWD (Berkshire) if onset before 65 years and local Dementia Advisors if later onset

Recommendations for future optimisation of whole Thames Valley pathway:

1. Improved access to detailed scanning such as MRI rather than CT head
2. Improved access to specialist neuro-radiology reporting
3. Improved access to specialist speech and language therapy for diagnosis and management of FTDs across whole Thames Valley
4. Increased networking opportunities across the Thames Valley to upskill with regard to memory clinician skills and specialist neuropsychology

References

(1) Rascovsky,K et al., Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia, Brain 2011: 134; 2456-2477

(2) Mesulum, M and Weintraub, S.,Is it time to revisit the classification guidelines for primary progressive aphasia? Neurology 2014;82:1108-1109

(3) Gorno-Tempini, ML et al., Classification of primary progressive aphasia and its variants. Neurology 2011; 76: 1006-14

(4) Van der Zee, J; Van Broeckhoven, C., "Dementia in 2013: Frontotemporal lobar degeneration – building on breakthroughs". Nature Reviews Neurology 2014. **10** (2): 70–72. doi:10.1038/nrneurol.2013.270. PMID 24394289

(5) Elamin M et al., The Utility of the Addenbrooke's Cognitive Examination Version Three in Early-Onset Dementia. Dement Geriatr Cogn Disord 2016;41 (1-2): 9-15

(6) Nasreddine ZS et al., The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005 Apr; 53 (4): 695-9

(7) Dubois, B. ; Litvan, I.; The FAB: A frontal assessment battery at bedside. Neurology. 55(11): 1621-1626, 2000

(8) Slachevsky, A; Dubois, B. Frontal Assessment Battery and Differential Diagnosis of Frontotemporal Dementia and Alzheimer Disease. Archives of Neurology. 61(7): 1104-1107, 2004

(9) Cognitive estimates test (Shallice and Evans), modified into a 10 item test by John Hodges (in Cognitive Assessment for Clinicians, John R Hodges, second edition,2007)

(10) Lebert F et al., Frontotemporal –Behavioural Scale (#FBS) Frontotemporal behavioural scale. *Alz Dis Assoc Disorder* 1998;12:335-339

(11) Howard D and Patterson K. The Pyramid and Palms Tree Test, Thames Valley Test Company (1992)

Appendix 1 – Brief clinic based tests for Fronto-temporal Dementias

FRONTOTEMPORAL BEHAVIOURAL SCALE (FBS) - TOTAL SCORE = .../4
For each category score = 1 if at least 1 of the symptoms are present
score = 0 if no symptoms are present

Lebert F, Pasquier F, Souliez L, Petit H. Frontotemporal behavioural scale.
Alz Dis Assoc Disorder 1998;12:335-339

SURNAME/FIRST NAME : DATE *:*
1 – Difficulties with self-control: score = ../1
- Have you noticed any changes in your close relation's eating patterns? yes no
- Has he or she developed any new preferences for sugary foods or for certain salty foods? yes no
- Does he or she eat very quickly? yes no
- Does he or she place any non-food items in his/her mouth? yes no
- Has he or she developed a new taste for alcoholic drinks? yes no
- Does he or she ever say anything uncalled-for, out-of-place or dishonest, or does he or she seem less tactful than before? yes no
- Does he or she display any uninhibited behaviour or has he or she ever done things that are normally not done in public? yes no
- Is he or she more easily irritated without good reason? yes no
- Is he or she easy to anger? yes no
- Does he or she ever laugh or cry for no reason, regardless of the context? yes no
- Is he or she continually moving or does he or she have difficulty with staying in the same place for a certain amount of time?
yes no

2 – Physical neglect compared with previous habits: score = ../1
- Has he or she become insensitive to cleanliness and hygiene? Has he or she become indifferent about stains on his/her clothing?
yes no
- Has he or she lost the ability to match his/her clothing? Does he or she neglect washing him/herself if not encouraged to do so?
yes no

3 – Difficulties with mood: score = ../1
- Is he or she happy and smiling, no matter what the situation? yes no 2
- Has he or she become apparently sad in a permanent manner, regardless of the situation? yes no
- Has he or she become indifferent to familiar events, to his/her close relations, to their health and how they are feeling?
yes no
- Does he or she have a tendency to cry easily when faced with an annoyance or when he/she cannot do something? yes no
- or when his/her close relations show him/her any sympathy? yes no
- or when there is someone unusual present ? yes no
- or when he/she listens to music ? yes no

4 – Signs of a loss of interest: score = ../1
- Does he or she have less activities than before? Does he or she need to be stimulated for all activities? yes no
- Does he or she have a tendency to hide in his/her bed when there is no stimulation? yes no
- Does he or she now have fixed ideas? Has he or she become anxious about certain things, for example, money, food or meal times? Does he or she always ask the same question? yes no
- Does he or she complain repeatedly about a part of his/her body (stomach, head etc.) yes no
- Has he or she become disinterested about his/her environment, local news, fashion? yes no

Frontal Assessment Battery

Purpose
The FAB is a brief tool that can be used at the bedside or in a clinic setting to assist in discriminating between dementias with a frontal dysexecutive phenotype and Dementia of Alzheimer's Type (DAT). The FAB has validity in distinguishing Fronto-temporal type dementia from DAT in mildly demented patients (MMSE > 24). Total score is from a maximum of 18, higher scores indicating better performance.

1. Similarities (conceptualization)
"In what way are they alike?"

- A banana and an orange

(In the event of total failure: "they are not alike" or partial failure: "both have peel," help the patient by saying: "both a banana and an orange are fruit"; but credit 0 for the item; do not help the patient for the two following items)

- A table and a chair
- A tulip, a rose and a daisy

Score (only category responses [fruits, furniture, flowers] are considered correct)

Three correct: 3 Two correct: 2 One correct: 1 None correct: 0

2. Lexical fluency (mental flexibility)
"Say as many words as you can beginning with the letter 'S,' any words except surnames or proper nouns."

If the patient gives no response during the first 5 seconds, say: "for instance, snake." If the patient pauses 10 seconds, stimulate him by saying: "any word beginning with the letter 'S.' The time allowed is 60 seconds.

Score (word repetitions or variations [shoe, shoemaker], surnames, or proper nouns are not counted as correct responses)

> 9 words: 3 6 -9 words: 2 3 -5 words: 1 < 3 words: 0

3. Motor series "Luria" test (programming)
"Look carefully at what I'm doing."

The examiner, seated in front of the patient, performs alone three times with his left hand the series of "fist–edge–palm."
"Now, with your right hand do the same series, first with me, then alone."
The examiner performs the series three times with the patient, then says to him/her:
"Now, do it on your own."

Score

Patient performs six correct consecutive series alone: 3
Patient performs at least three correct consecutive series alone: 2
Patient fails alone, but performs three correct consecutive series with the examiner: 1
Patient cannot perform three correct consecutive series even with the examiner: 0

4. Conflicting instructions (sensitivity to interference)
"Tap twice when I tap once."
To ensure that the patient has understood the instruction, a series of 3 trials is run: 1-1-1.

"Tap once when I tap twice."
To ensure that the patient has understood the instruction, a series of 3 trials is run: 2-2-2.

The examiner then performs the following series: 1-1-2-1-2-2-2-1-1-2.

Score No errors: 3 1 -2 errors: 2 > 2 errors: 1
Patient taps like the examiner at least four consecutive times: 0

5. Go–No Go (inhibitory control)
"Tap once when I tap once."
To ensure that the patient has understood the instruction, a series of 3 trials is run: 1-1-1.

"Do not tap when I tap twice."
To ensure that the patient has understood the instruction, a series of 3 trials is run: 2-2-2.

The examiner then performs the following series: 1-1-2-1-2-2-2-1-1-2.

Score No errors: 3 1 -2 errors: 2 > 2 errors: 1
Patient taps like the examiner at least four consecutive times: 0

6. Prehension behaviour (environmental autonomy)

"Do not take my hands."

The examiner is seated in front of the patient. Place the patient's hands palm up on his knees. Without saying anything or looking at the patient, the examiner brings his own hands close to the patient's hands and touches the palms of both the patient's hands, to see if he will spontaneously take them. If the patient takes the examiner's hands, try again after asking the patient: "Now, do not take my hands."

Score

Patient does not take the examiner's hands: 3
Patient hesitates and asks what he/she has to do: 2
Patient takes the hands without hesitation: 1
Patient takes the examiner's hand even after he/she has been told not to do so: 0

Interpreting results
A cut off score of 12 on the FAB has a sensitivity of 77% and specificity of 87% in differentiating between frontal dysexecutive type dementias and DAT

ReferenceS
Dubois, B. ; Litvan, I.; The FAB: A frontal assessment battery at bedside. Neurology. 55(11): 1621-1626, 2000.

Slachevsky, A; Dubois, B. Frontal Assessment Battery and Differential Diagnosis of Frontotemporal Dementia and Alzheimer Disease. Archives of Neurology. 61(7): 1104-1107, 2004.

Cognitive Estimates Test

In this task derived by Shallice and Evans the questions cannot be derived from general knowledge. Patients with frontal lobe disorders give bizarre answers which are not often modified by asking the patient to reconsider their answers. The specificity and sensitivity have not been well studied but there are no good alternatives. This is a modification of the original test reproduced with kind permission from Cognitive Assessment for Clinicians (2007) by John R Hodges.

The test is introduced by saying ***"I'd like you to make the best guess you can in answer to these questions. Almost certainly you wont know the correct answer, but just make your best guess."***

Each answer is scored for usualness or extremeness. Answers in the correct range score 0. Some answers have to be interpolated, but scores below are a guide.

Controls obtain a mean score of 4.0 (+/- 2.0)

Questions and error scores				**correct range**
1) **What is the height of the BT tower?**				100-800 feet (I foot=0.3metres)
>1500	3	<60	3	
=1500	2	=60	2	
>800	1	<100	1	
2) **How fast do racehorses gallop?**				15-40mph
>50	3	<9	3	
=50	2	<15	2	
<40	1			
3) **What is the best paid job in Britain?**				Queen/pop/film star
Manual worker	3			
Blue-collar worker		2		
Professionals	1			
4) **What is the age of the oldest person in Britain today?**				104-113years
>115	3	<103	3	
=115	2	=113	1	
=114	1			
5) **What is the length of the average man's spine?**				1'7" – 3'11"
>5'0"	3	<1'6"	3	
>4'0"	2	=1.6	2	
=4"0	1			
6) **How tall is the average English woman?**				5'3"- 5'8"
>6.0	3	<5'2"	3	
=5'11", 6'0"	2	=5'2"	1	
=5'11", 5'10"	2			
7) **What is the population of Britain?**				20-60 million
>1000 million	3	<2 million	3	
>500 million	2	<5 million	2	
=500 million	1	<20 million	1	
8) **How heavy is a pint of milk?**				1-3 lb
>3lb	3	<1lb	3	
=3lb	1	=1lb	1	
9) **What is the largest object normally found in a house?**				bed, bath etc.
<carpet	3			
Carpet	3			
Piano,sofa etc	1			
10) **How many camels are there in Holland?**				1-50
Very large number	3			
None		1		

Calculation Assessment

(reproduced with kind permission from Cognitive Assessment for Clinicians (2007) by John R Hodges)

1) Number reading and writing

Number reading and writing should be assessed before arithmetical abilities by asking the patient to do the following:

1) Read a series of simple (7,2,9 etc.) and complex (27,93,107,1226,etc.) numbers written by the examiner
2) Write numbers to dictation
3) If there are errors then it is helpful to examine the patient's ability to copy and point to numbers on command.

2) Arithmetic operations:

Only after reading/writing has been assessed should the patient's ability to understand arithmetic operations be assessed as follows:

1) Calculation skills should be tested by asking the patient to perform oral arithmetic calculations that sample the four basic operations ie addition, subtraction, division and multiplication
2) Written calculations should then be examined

Extra tips: Addenbrookes Cognitive Examination R screening test (Hodges):

A similar test is the ACE-R which has been replaced by the ACE III to avoid the copyright issues when using an integrated MMSE.

With the ACE-R a useful ratio to help determine if FTD or AD is more likely is the VLOM (verbal fluency and language score/orientation and memory score ratio). The data has been collected for the ACE R which was slightly modified to the ACE III (to remove the MMSE for copyright reasons).

VLOM Score > 3.2 AD more likely than FTD with a 74% sensitivity and a 85% specificity

VLOM Score < 2.2 is highly suggestive of FTD with a 58% sensitivity and a 95% specificity

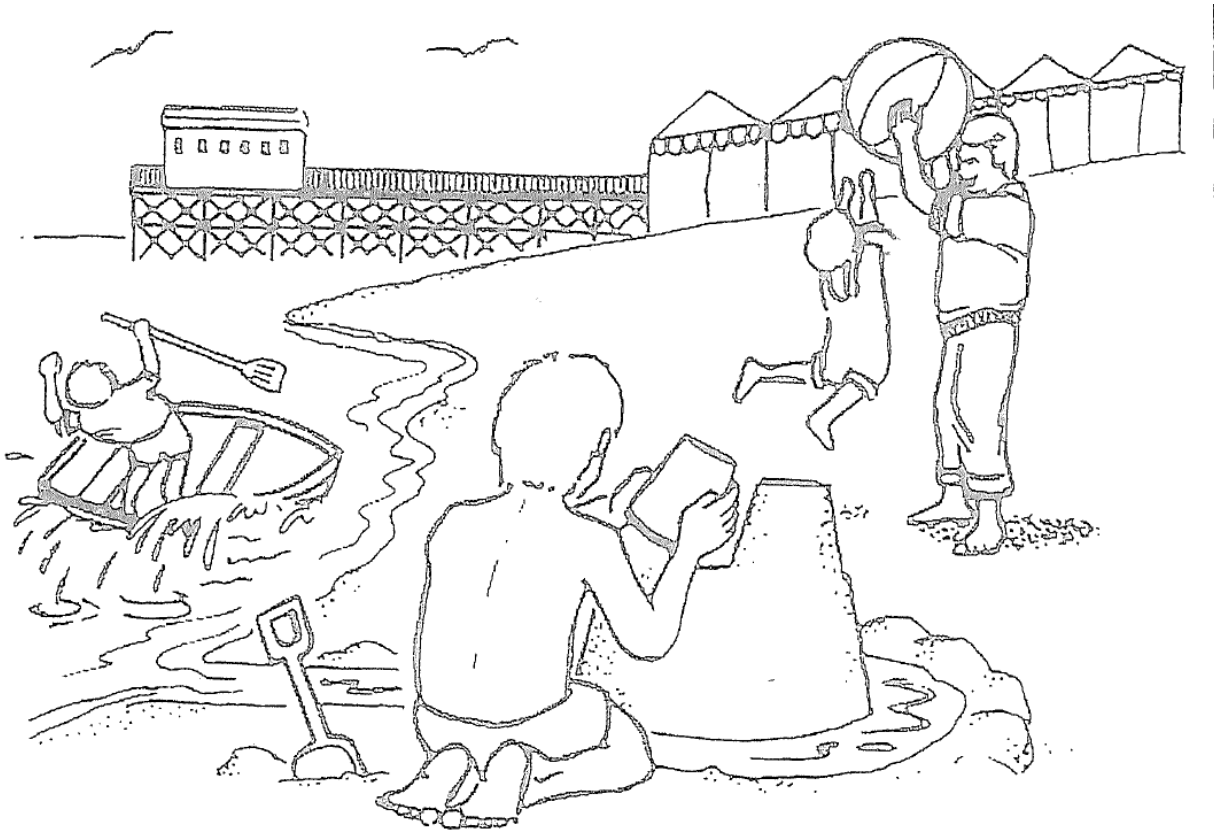
For the word naming tests in the ACE if the client is also asked to define the words it can help differentiate SD and phonological processing issues. In SD the patient can repeat the word or name objects but gives a vague definition. There may also be surface dyslexia. If the patient only has phonological process issues then he/she may not be able to repeat the word but can convey the meaning.

PPA there is an impairment of repetition of words but understanding of the meaning is good. The Pyramids and Palms test (**ref 11**) may help with this but will involve specialist neuropsychology testing. PPA patients may find it harder to repeat sentences that have no meaning.

Of note patients with language deficits may struggle with verbally based cognitive assessment for obvious reasons. If this seems to be the case, you may wish to ask them to describe a picture as below in appendix 2. Nonetheless if there is a clinical suspicion the patient must be referred for specialist neuropsychological assessment, which will include assessment of language domains and non-verbal abilities. In some areas, specialist speech and language assessment for linguistic FTD is available as an appropriate alternative to neuropsychological testing.

The ACE is also available as a free app for the iPad, which provides a summary of results that can be appended to reports as an appendix.

Appendix 2 - Picture from The Queen's Square Screening Test for Cognitive Deficits (with kind permission from Prof Elizabeth Warrington)



This is an example of a complex interactive scene for use in eliciting spontaneous language.