A modified Camel and Cactus Test detects presymptomatic semantic impairment in genetic frontotemporal dementia within the GENFI cohort


ABSTRACT

Impaired semantic knowledge is a characteristic feature of some forms of frontotemporal dementia (FTD), particularly the sporadic disorder semantic dementia. Less is known about semantic cognition in the genetic forms of FTD caused by mutations in the genes MAPT, C9orf72, and GRN. We developed a modified version of the Camel and Cactus Test (mCCT) to investigate the presence of semantic difficulties in a large genetic FTD cohort from the Genetic FTD Initiative (GENFI) study. Six-hundred-forty-four participants were tested with the mCCT including 67 MAPT mutation carriers (15 symptomatic, and 52 in the presymptomatic period), 164 C9orf72 mutation carriers (33 symptomatic, 132 presymptomatic), and 162 GRN mutation carriers (56 symptomatic, 108 presymptomatic) and 248 mutation-negative members of FTD families who acted as a control group. The presymptomatic mutation carriers were further split into those early and late in the presymptomatic period (more than vs. within 10 years of expected symptom onset). Groups were compared using a linear regression model, adjusting for age and education, with bootstrapping. Performance on the mCCT had a weak negative correlation with age (rho = −0.20) and a weak positive correlation with education (rho = 0.13), with an overall abnormal score (below the 5th percentile of the control population) being below 27 out of a total of 32. All three of the symptomatic mutation groups scored significantly lower than controls: MAPT mean 22.3 (standard deviation 8.0), GRN 24.4 (7.2), C9orf72 23.6 (6.5) and controls 30.2 (1.6). However, in the presymptomatic groups, only the late MAPT and late C9orf72 mutation groups scored lower than controls (28.8 (2.2) and 28.9 (2.5) respectively). Performance on the mCCT correlated strongly with temporal lobe volume in the symptomatic MAPT mutation group (rho > 0.80). In the C9orf72 group, mCCT score correlated with both bilateral temporal lobe volume (rho > 0.31) and bilateral

KEYWORDS

C9orf72; frontotemporal dementia; genetics; MAPT; progranulin; semantic knowledge

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The Camel and Cactus Test (CCT) was designed as a way to assess semantic knowledge (Bozeat, Lambon Ralph, Patterson, Garrard, & Hodges, 2000). The task involves asking people to match a picture (or word) with a matching picture (or word) from a choice of four by their semantic association, for example, matching “camel” with “cactus” rather than “tree,” “sunflower” or “rose.” It was an extension of the Pyramids and Palm Trees Test (Howard & Patterson, 1992) in which people were asked to choose from only two pictures (or words); the CCT, with 64 items in total, was therefore expected to be more sensitive than its predecessor.

The CCT has been tested in a number of cohorts, but particularly in those with semantic dementia (SD, also known as semantic variant primary progressive aphasia), a subtype of frontotemporal dementia (FTD) (Adlam, Patterson, Bozeat, & Hodges, 2010; Bozeat et al., 2000; Garrard & Carroll, 2006; Jefferies & Lambon Ralph, 2006). Loss of semantic knowledge is the fundamental cognitive difficulty in these patients, and the CCT has been shown to sensitively and accurately identify the extent of the deficit. However, semantic impairment is not unique to SD in the FTD spectrum—it is seen in those with behavioral variant FTD (bvFTD) (Hardy et al., 2016), and in those with other forms of primary progressive aphasia (Rohrer, Rossor, & Warren, 2010c), albeit as a secondary cognitive deficit. Amongst these FTD variants, the group in which semantic deficits seem particularly prominent (often appearing in conjunction with, or shortly after behavioral impairment) is genetic FTD due to MAPT mutations (Hardy et al., 2016; Snowden et al., 2015), although this has not been studied in detail.

The Genetic FTD Initiative (GENFI) is an international genetic FTD cohort study aimed at developing novel markers of disease onset and progression (Rohrer et al., 2015). The difficulties of using the CCT in its original form in the GENFI study include firstly, the multiple languages (and cultures) that the study needs to be performed in, and secondly, the length that the test takes to administer, is approximately 20–30 min, is too time-consuming to be included in a battery of tests in which study participants are assessed in multiple cognitive domains as well as undertaking clinical, imaging and biofluid data collection.

We, therefore, developed a modified version of the CCT, usable across the different GENFI languages and short enough to be incorporated into a comprehensive neuropsychological battery. This new version of the CCT was subsequently tested in the GENFI cohort of presymptomatic and symptomatic carriers of mutations in the progranulin (GRN), chromosome 9 open reading frame 72 (C9orf72), and microtubule-associated protein tau (MAPT) genes, as well as a control dataset of non-mutation carriers from the same families.

**Methods**

**Development of the modified Camel and Cactus Test (mCCT)**

The development of the test was performed by the first author (KM) in conjunction with the GENFI Investigator Group. In order to ensure the same test was able to be used across multiple languages, the picture-picture matching version of the CCT was chosen, to avoid multiple translations of the words. The first modification that was made was to reduce the size of the test to 32 items: each of the original 64 test items were reviewed for the level of difficulty, confusability (whether any items could have potentially more than one answer that would be readily confused), and cultural appropriateness of individual items (whether participants in each country would recognize the stimuli adequately); we then chose 32 items that were of a spectrum of difficulty (in particular, removing easier items in an attempt to get more control participants off a ceiling score), and felt to be applicable within each of the countries of the GENFI study. The original version of the CCT used a combination of photographs and line drawings, and so the second modification the group decided to make was to develop a more modern photographic version of the test making use of available (labeled for reuse) images from Google Images, each of which was reviewed by the Investigator Group to ensure it was culturally appropriate. The final version of the mCCT is included as an Supplementary Appendix.

**Participants**

Participants were recruited from the 4th data freeze of the GENFI study including sites in the UK, Canada, Sweden, Netherlands, Belgium, Spain, Portugal, Italy, and Germany. Of the 680 participants in the data freeze, 644 undertook the mCCT: 248 mutation-negative controls, 67 MAPT mutation carriers, 165 GRN mutation carriers, and 164 C9orf72 mutation carriers (Table 1). Mutation carriers were either presymptomatic or symptomatic, with the latter group including the following diagnoses: MAPT mutation carriers, all bvFTD; GRN mutation carriers, 15 bvFTD, 17 PPA, 1 dementia-not otherwise specified; and C9orf72 mutation carriers, 40 bvFTD, 10 FTD with amyotrophic lateral sclerosis, 2 PPA, 1 progressive supranuclear palsy, 3 dementia-not otherwise specified. We split the presymptomatic mutation...
carriers based on their estimated age at onset, a measure calculated by the difference between the current age and the mean age at onset of symptoms within the family (Rohrer et al., 2015): those further than 10 years from estimated onset were called “early” presymptomatic mutation carriers, and those within 10 years of estimated onset were called “late” presymptomatic mutation carriers.

Imaging

The majority of mutation carriers had magnetic resonance imaging (MRI) on a 3T scanner as part of their assessment: 30/33 early presymptomatic, 17/19 late presymptomatic, 12/15 symptomatic MAPT mutation carriers; 76/79 early presymptomatic, 48/53 late presymptomatic, 31/33 symptomatic GRN mutation carriers; and 66/68 early presymptomatic, 35/40 late presymptomatic, 50/56 symptomatic C9orf72 mutation carriers. Volumetric T1 MRI brain scans were parcellated using the geodesic information flow (GIF) algorithm, which is based on atlas propagation and label fusion, with parcellations combined to create volumetric measures of frontal, temporal, parietal and occipital gray matter in both hemispheres (Rohrer et al., 2015).

Statistical analysis

In the control group, we explored the relationship of the mCCT score to age (Spearman rank correlation), sex (Mann–Whitney U test) and education (years in education—Spearman rank correlation).

Scores on the mCCT were compared between groups using a linear regression model in STATA (v.14; College Station, Texas) adjusting for age and education, with 95% bias-corrected bootstrapped CIs with 1000 repetitions.

Spearman rank correlation coefficients were calculated between mCCT scores and imaging measures in STATA.

Results

Healthy controls

Stratifying by decade, mean mCCT score was similar (29.5–30.5) in each age group within the controls (Table 2); however overall there was a weak but significant correlation of mCCT score with age (rho = −0.20, p = 0.001), that is, lower mCCT scores with higher age.

145 participants in the control group were female (58%) and 103 were male (42%). No significant differences in mCCT scores were seen between the groups (p = 0.441), with a mean (standard deviation) mCCT score of 30.2 (1.6) in females and 30.1 (1.6) in males.

Similar to age, when stratifying by education level, mean CCT score was similar (29.8–30.5) in each group within the controls (Table 3); however overall there was also a very weak but significant correlation of mCCT score with years of education (rho = 0.13, p = 0.037), that is, lower mCCT scores with fewer years of education.
Overall, controls scored between 25 and 32 out of a total possible score of 32 (mean score 30.2, standard deviation 1.6), with cumulative frequency shown in Table 4. In standard neuropsychological assessments, a score below the 5th percentile is commonly considered to be abnormal: for the mCCT a score of below 27 would, therefore, be considered outside the normal range. A score of 27 would be considered a borderline abnormal result.

**Mutation carriers**

All of the three symptomatic mutation carrier groups showed a significantly lower score than controls (Tables 1 and 5, Figure 1), with no significant difference between the different genetic groups: MAPT mean 22.3 (standard deviation 8.0), GRN 24.4 (7.2), and C9orf72 23.6 (6.5). Within each genetic group, scores were significantly lower in the symptomatic group compared with both the early and late presymptomatic groups (Tables 1 and 5, Figure 1).

No significant differences were seen between the early presymptomatic mutation carriers and controls. However a significantly lower score was seen in the late presymptomatic group compared with controls (and in the late compared with the early presymptomatic group) in both the MAPT and C9orf72 genetic groups but not the GRN group (Table 5, Figure 1): MAPT late presymptomatic 28.8 (2.2), early presymptomatic 30.9 (0.9); C9orf72 late presymptomatic 28.9 (2.5), early presymptomatic 30.4 (1.5); GRN late presymptomatic 29.8 (1.9), early presymptomatic 30.5 (1.3).
Imaging analyses revealed differences between the genetic groups in terms of the anatomical regions that were most significantly correlated with the mCCT score (Table 6). In the symptomatic MAPT group, the score was very strongly associated with bilateral temporal lobe atrophy (rho > 0.80 for both temporal lobes), with a borderline association with left temporal lobe atrophy in the late presymptomatic group (rho = 0.48). In the symptomatic C9orf72 group the score was also associated with bilateral temporal lobe atrophy (rho = 0.40 for right, and 0.31 for left), but also with bilateral frontal lobe atrophy (rho = 0.30 for right, and 0.29 for left).

In the late presymptomatic C9orf72 group, the only significant correlation was with left frontal lobe volume (rho = 0.33). In the symptomatic GRN group, the mCCT score was significantly correlated with left frontal lobe atrophy (rho = 0.48), but with quite widespread volume loss in the late presymptomatic group. No significant correlations were found with any of the regional volumes in the early presymptomatic groups.

**Discussion**

In this study, we have shown that a modified version of the Camel and Cactus Test is able to detect deficits within both symptomatic genetic FTD, and for MAPT and C9orf72 mutation carriers, the late presymptomatic period within 10 years of expected onset. Scores on the mCCT were correlated with atrophy in temporal regions for the symptomatic MAPT carriers, temporal and frontal areas for C9orf72 carriers, and frontal gray matter for GRN mutation carriers, suggesting different areas of a semantic association network are predominantly affected in the different groups.

By investigating a large control population consisting of mutation-negative members of genetic FTD families, we

**Figure 1.** Modified Camel and Cactus Test scores in each group—significant differences from controls and within each genetic group are starred.

**Table 6.** Spearman’s rank correlation coefficients (rho) of modified Camel and Cactus Test score with regional brain volumes in early and late presymptomatic (presymp) and symptomatic genetic groups.

<table>
<thead>
<tr>
<th>Region</th>
<th>MAPT early presymp</th>
<th>MAPT late presymp</th>
<th>MAPT symptomatic</th>
<th>GRN early presymp</th>
<th>GRN late presymp</th>
<th>GRN symptomatic</th>
<th>C9orf72 early presymp</th>
<th>C9orf72 late presymp</th>
<th>C9orf72 symptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right frontal</td>
<td>0.10</td>
<td>0.13</td>
<td>0.38</td>
<td>0.10</td>
<td>0.08</td>
<td>0.36</td>
<td>0.48</td>
<td>0.46</td>
<td>0.46</td>
</tr>
<tr>
<td>Left frontal</td>
<td>0.14</td>
<td>0.13</td>
<td>0.36</td>
<td>0.14</td>
<td>0.08</td>
<td>0.34</td>
<td>0.51</td>
<td>0.49</td>
<td>0.49</td>
</tr>
<tr>
<td>Right temporal</td>
<td>0.14</td>
<td>0.13</td>
<td>0.38</td>
<td>0.10</td>
<td>0.08</td>
<td>0.36</td>
<td>0.48</td>
<td>0.46</td>
<td>0.46</td>
</tr>
<tr>
<td>Left temporal</td>
<td>0.13</td>
<td>0.13</td>
<td>0.36</td>
<td>0.14</td>
<td>0.08</td>
<td>0.34</td>
<td>0.51</td>
<td>0.49</td>
<td>0.49</td>
</tr>
<tr>
<td>Right parietal</td>
<td>0.10</td>
<td>0.13</td>
<td>0.38</td>
<td>0.10</td>
<td>0.08</td>
<td>0.36</td>
<td>0.48</td>
<td>0.46</td>
<td>0.46</td>
</tr>
<tr>
<td>Left parietal</td>
<td>0.14</td>
<td>0.13</td>
<td>0.36</td>
<td>0.14</td>
<td>0.08</td>
<td>0.34</td>
<td>0.51</td>
<td>0.49</td>
<td>0.49</td>
</tr>
<tr>
<td>Right occipital</td>
<td>0.10</td>
<td>0.13</td>
<td>0.38</td>
<td>0.10</td>
<td>0.08</td>
<td>0.36</td>
<td>0.48</td>
<td>0.46</td>
<td>0.46</td>
</tr>
<tr>
<td>Left occipital</td>
<td>0.14</td>
<td>0.13</td>
<td>0.36</td>
<td>0.14</td>
<td>0.08</td>
<td>0.34</td>
<td>0.51</td>
<td>0.49</td>
<td>0.49</td>
</tr>
</tbody>
</table>

*p*-values are given in parentheses; significant values are in bold.
were able to explore the performance of the CCT in a much larger healthy group than previously. This allows determination of a percentile score and therefore an “abnormal” lower boundary. By making the test freely available, we hope that such healthy control data can be expanded and further validated, particularly in older populations, where there were limited numbers in this study.

Impairment of semantic knowledge has been described previously in people with MAPT mutations (Pickering-Brown et al., 2002, 2008) including very early in the illness: a single case report described a patient with only mild behavioral change who had evidence of semantic impairment on testing at that stage (including scoring only 35 out of 64 on the original visual version of the CCT: Garrard & Carroll, 2005). People with MAPT mutations commonly have focal atrophy of both temporal lobes in a pattern not dissimilar within each hemisphere as that seen in SD, that is, an anterior and inferior predominance of volume loss (Rohrer et al., 2010b; Whitwell et al., 2009). In SD it is felt that semantic impairment is caused by the breakdown of an anatomical network focused on the temporal pole with loss of connectivity to other temporal lobe structures in both hemispheres (Fletcher & Warren, 2011). It is therefore unsurprising that people with MAPT mutations also develop semantic impairment given the pattern of atrophy, and this is supported here by the strong association of performance on the mCCT with reduced bilateral temporal lobe volume. Such loss has been shown to occur presymptomatically (Cash et al., 2018; Rohrer et al., 2015), consistent with the finding in this study of semantic impairment before symptom onset.

Impairment on tasks of semantic knowledge has been investigated less in those with C9orf72 and GRN mutations. Whilst there are some case reports of patients with prominent early semantic deficits in these two groups (Abbate et al., 2014; Cerami et al., 2013; Jiskoot et al., 2018; Rohrer et al., 2010a), in one retrospective neuropsychological study comparing individuals with mutations in all three genes, impaired word comprehension was present at time of initial referral in only 24% of the C9orf72 group and 19% of the GRN group (compared with 86% in the MAPT group), and impaired object knowledge was only found in 16% of the C9orf72 group and 7% of the GRN group (compared with 80% in the MAPT group) (Snowden et al., 2015). One other explanation for poor performance on the mCCT might be the role of executive dysfunction, a common cognitive deficit in genetic FTD (found in 92% of MAPT, 93% of GRN and 84% of C9orf72 patients at initial referral in the same study discussed above: Snowden et al., 2015), and also known to be impaired presymptomatically (Jiskoot et al., 2018; Rohrer et al., 2015). The role of executive function in semantic tasks has been well-described (Jefferies & Lambon Ralph, 2006; Hoffman, Jefferies, & Lambon Ralph, 2010): it has been proposed that semantic cognition relies not just on a temporal lobe-based hub of semantic knowledge, but a second process of executive control required for computation and manipulation of semantic information (Jefferies & Lambon Ralph, 2006; Whitney, Kirk, O’Sullivan, Lambon Ralph, & Jefferies, 2012), located in the ventrolateral prefrontal cortex (Hoffman et al., 2010; Whitney et al., 2012).

This would be consistent in this study with the association of performance on the mCCT with the frontal lobe in both symptomatic GRN and C9orf72 carriers. Interestingly, performance in symptomatic C9orf72 carriers showed an association with both frontal and temporal lobe atrophy, suggesting that both systems may be impaired in this group.

In summary, the mCCT appears to be a useful test of semantic knowledge, able to detect impairment of semantic cognition in both the symptomatic and late presymptomatic periods of genetic FTD. In comparison with the original CCT it is shorter and contains only visual stimuli, making it practical for use in international trials. Future longitudinal studies will be important to investigate the rate of change over time and to understand further the time period before symptom onset when such changes can be detected.

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