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ORIGINAL COMMUNICATION

The Addenbrooke's Cognitive Examination-Revised accurately detects cognitive decline in Huntington's disease

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Abstract Cognitive features, which begin before manifestation of the motor features, are an integral part of Huntington's disease and profoundly affect quality of life. A number of neuropsychological batteries have been used to assess this aspect of the condition, many of which are difficult to administer and time consuming, especially in advanced disease. We, therefore, investigated a simple and practical way to monitor cognition using the Addenbrooke's Cognitive Examination-Revised (ACE-R) in 126 manifest Huntington's disease patients, 28 premanifest gene carriers and 21 controls. Using this test, we demonstrated a selective decrease in phonemic, but not semantic, fluency in premanifest participants Cognitive decline in manifest Huntington's disease varied according to disease severity with extensive cognitive decline observed in early-stage Huntington's disease patients, indicating that this would be an optimal stage for interventions designed to halt cognitive decline, and lesser changes in the advanced cases. We next examined cognitive performance in patients prescribed antidopaminergic drugs as these drugs are known to decrease cognition when administered to healthy volunteers. We paradoxically found that these drugs may be beneficial, as early-stage Huntington's disease participants in receipt of them had improved attention and Mini-Mental State Examination scores. In conclusion, this is the first study to test the usefulness of the ACE-R in a Huntington's disease population and demonstrates that this is a brief, inexpensive and practical way to measure global cognitive performance in clinical practice with potential use in clinical trials.

Keywords Huntington's disease · Cognition · Addenbrooke's Cognitive Examination · Screening · Dementia

Introduction

In addition to motor and psychiatric features, Huntington's disease (HD) is characterised by cognitive decline which begins up to 15–20 years prior to disease onset and progresses to profound global dementia in the advanced stages of the disease [20, 29]. Since the cognitive features of the disease profoundly affect quality of life [8], it is crucial that these are targeted in potential clinical trials using simple robust tests. In the two largest studies to investigate this (PREDICT-HD and TRACK-HD), large lengthy neuropsychological batteries have been used. However, such assessments are not only difficult and time-consuming to administer but are too tiring for patients, particularly those with advanced disease, leading to reduced rates of compliance. A simple and practical tool to monitor cognitive decline starting from the premanifest stages through to the more advanced stages is thus required and would be useful

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in routine clinical practice as well as in disease modifying trials.

The Addenbrooke's Cognitive Examination-Revised (ACE-R) is a brief cognitive screening battery which assesses five neuropsychological domains (orientation and attention, memory, verbal fluency, language and visuospatial function) [19], incorporates the Mini-Mental State Examination (MMSE) [3] and has been used in a number of neurodegenerative disorders [2, 7]. It has many advantages in that it is quick and easy to administer and requires little or no training. In addition, normative data for this test has been extensively described [19]. The purpose of this study was, therefore, to investigate the usefulness of the ACE-R in HD and to determine whether it is valuable for detective cognitive decline through the entire disease course. Using this test, we found a selective decline in the fluency subdomain of the ACE-R in premanifest HD gene carriers (preHD) when compared to controls which was due to a specific impairment in phonemic, rather than semantic, fluency. We further demonstrated that patients in the early stages of manifest HD (early HD), exhibit worse performance in a number of subdomains whilst retaining functional measurements, such as the ability to work, which has implications for trials designed to prevent further cognitive decline. We also showed that longitudinal data from this cohort collected over a short period of time (6–18 months) was stable despite disease progression, as judged by a decline in measures of function [15, 24]. Finally, we investigated concerns that antidopaminergic medication, often used as symptomatic treatment in HD, may have a detrimental effect on patients' cognition [9] as has been found previously in healthy volunteers [16–18]. Interestingly, early HD patients receiving antidopaminergic medication had increased MMSE and attention scores whilst no cognitive differences were detected in moderate and advanced HD patients receiving such medications.

In summary, we present data showing that a simple cognitive assessment tool can easily be used to detect specific deficits in both premanifest and manifest HD participants including those in the advanced stages of the disease. As such, this test is an easy and practical way to monitor cognitive decline in all stages of HD and may be useful for clinical practice as well as in any cognitive enhancing and disease modifying trials.

Method

Participants

Retrospective data was collected from HD participants and premanifest gene carriers who had undergone cognitive testing using the ACE-R as a result of attending the HD clinic in the John van Geest Centre for Brain Repair, Cambridge, UK between 2009 and 2012 or through participation in related studies derived from that clinic and approved by the local research ethics committee in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. For participants who attended the clinic or research studies multiple times, only data from their first visit was used for cross-sectional comparisons and subsequent visits were used for longitudinal measures.

Both manifest and premanifest participants had a positive genetic test for the HD mutation. All participants were assessed using the Unified Huntington's Disease Rating Scale (UHDRS). The UHDRS Total Motor Score (TMS) is used to quantify the presence of motor features and can range from 0 (no motor features detected) to a maximum score of 124. A score $\geq$5 on the TMS on the UHDRS was used to define manifest disease and participants who scored less than 5 were deemed to be premanifest gene carriers (preHD). The UHDRS Total Functional Capacity (TFC) score [14] was used to divide manifest patients according to their disease stage. Patients in the early stages of the disease had a TFC score between 11 and 13, patients with moderate disease had a TFC score between 7 and 10 and those in the advanced stages of the disease had a TFC score less than 6.

Age-matched control participants were recruited from patients' partners and from the local community via advertisement. Inclusion criteria were (1) no family history of HD or negative genetic test for HD and (2) absence of any known neurologic or psychiatric disorder.

ACE-R administration

The ACE-R takes approximately 20 min to administer and comprises five cognitive domains; attention (18 points), memory (26 points), fluency (14 points), language (26 points) and visuospatial (16 points) leading to a maximum total of 100 points. The ACE-R also encompasses the MMSE score (30 points) which was extracted and used as a comparison measure in this study.

Statistical analysis

Statistical analysis was performed using IBM SPSS software version 21.0 with any missing data excluded from the analysis. Normality for all the variables was tested using one-sample Kolmogorov–Smirnov tests. Variables which followed the normal distribution were analysed using one-way ANOVA followed by post hoc comparisons where significance was present. Variables which did not follow a normal distribution, which included most cognitive tests, were tested using Mann–Whitney U tests for cross-sectional analyses and Wilcoxon tests for repeated measures.

Scores for the individual cognitive domains of the ACE-R and the MMSE are expressed as percentages of the total score in order to facilitate comparisons of performance. Graphs were created using graphPad prism version 5.0 and are presented as mean ± SEM unless otherwise stated. Level of statistical significance was set at 0.05.

Results

Participant demographics

A total of 175 participants were tested in this study and were divided into controls, preHD and HD patients at various stages of their disease. PreHD participants had a lower CAG repeat than the manifest groups ($p = 0.003$). As would be expected, all groups differed in terms of the motor (TMS), functional measures (FA and TFC) and age which signify disease progression ($p < 0.05$, Table 1).

Selective decline in fluency in preHD participants

Cognitive decline in HD is thought to begin before the onset of the motor features, which are classically used to give a definitive diagnosis of manifest disease. In order to investigate whether such a decline could be detected using a cognitive screening test, we compared performance in ACE-R subdomains and the MMSE score in preHD and age-matched controls. We found a selective decline in the fluency subdomain of the ACE-R ($p = 0.035$, Fig. 1a), a difference which is not assessed by the MMSE.

Verbal fluency score was further separated into phonemic and semantic fluency. We found that preHD participants were selectively impaired in phonemic ($p = 0.016$), rather than semantic fluency (Fig. 1b).

We analysed this further to assess whether performance in this test could predict time to disease onset. Estimated years to diagnosis and probability of diagnosis within the next 5 years were calculated using the Langbehn equation [10] and the median (14.7 years to diagnosis) was used to divide the preHD group into those who are far (preHD far, $n = 11$) and close to onset (preHD close, $n = 10$). Although preHD close participants had lower fluency scores than preHD far, this difference was not statistically significant (Fig. 1c) and there were no significant correlations between fluency performance and estimated years to diagnosis or probability of diagnosis within the next 5 years (Fig. 1d), most likely due to the small sample size.

Extensive cognitive decline in manifest HD

In the early stages of the disease, HD participants showed extensive cognitive decline compared to preHD participants. They had significantly lower ACE-R scores ($p < 0.001$) due to a further decline in fluency ($p < 0.001$) as well as in the memory ($p < 0.001$) and visuospatial domains ($p = 0.003$, Fig. 2a, Table 2). Semantic fluency also became affected ($p < 0.001$) at this stage in addition to worsening phonemic fluency relative to preHD ($p = 0.021$). Cognitive decline could also now be detected for the first time using the MMSE where early manifest HD participants had significantly lower scores ($p = 0.001$). Attention and language were not significantly lower in early stage HD when compared to preHD participants but were significantly lower when early HD patients were compared to controls ($p < 0.01$). There was further cognitive decline with disease progression as moderate HD patients showed substantially lower scores in every domain when compared to early HD patients ($p < 0.05$) (Fig. 2b, Table 2). In the advanced disease stages, there was a further reduction in visuospatial scores ($p = 0.029$) but no further cognitive decline in other domains (Fig. 2b; Table 2).

In order to assess whether cognitive decline occurs over a short time period in manifest HD patients, performance in these tasks was examined in a number of early ($n = 20$), moderate ($n = 20$) and advanced ($n = 12$) HD participants who had attended the clinic for a follow up visit at least

Table 1 Participant demographics

	Controls	preHD (UHDRS <5)	Manifest HD (UHDRS ≥5)		
			Early (TFC 11–13)	Moderate (TFC 7–10)	Advanced (TFC 0–6)
N	21	28	49	40	37
Age (years)	51.1 (±2.96)	46.8 (±2.14)	53.8 (±1.77)	53.6 (±2.14)	57.2 (±1.82)
CAG	–	40.6 (±0.388)	43.4 (±0.592)	44.1 (±0.830)	42.7 (±0.445)
TMS	–	1.29 (±0.271)	14.8 (±1.17)	23.5 (±1.68)	27.8 (±2.01)
FA	–	24.7 (±0.144)	23.7 (±0.281)	19.8 (±0.332)	15.2 (±0.605)
TFC	–	12.8 (±0.094)	12.3 (±0.130)	8.58 (±0.192)	4.49 (±0.247)

Table shows mean ± S.E.M.

TMS total motor score, *FA* functional assessment, *TFC* total functional capacity

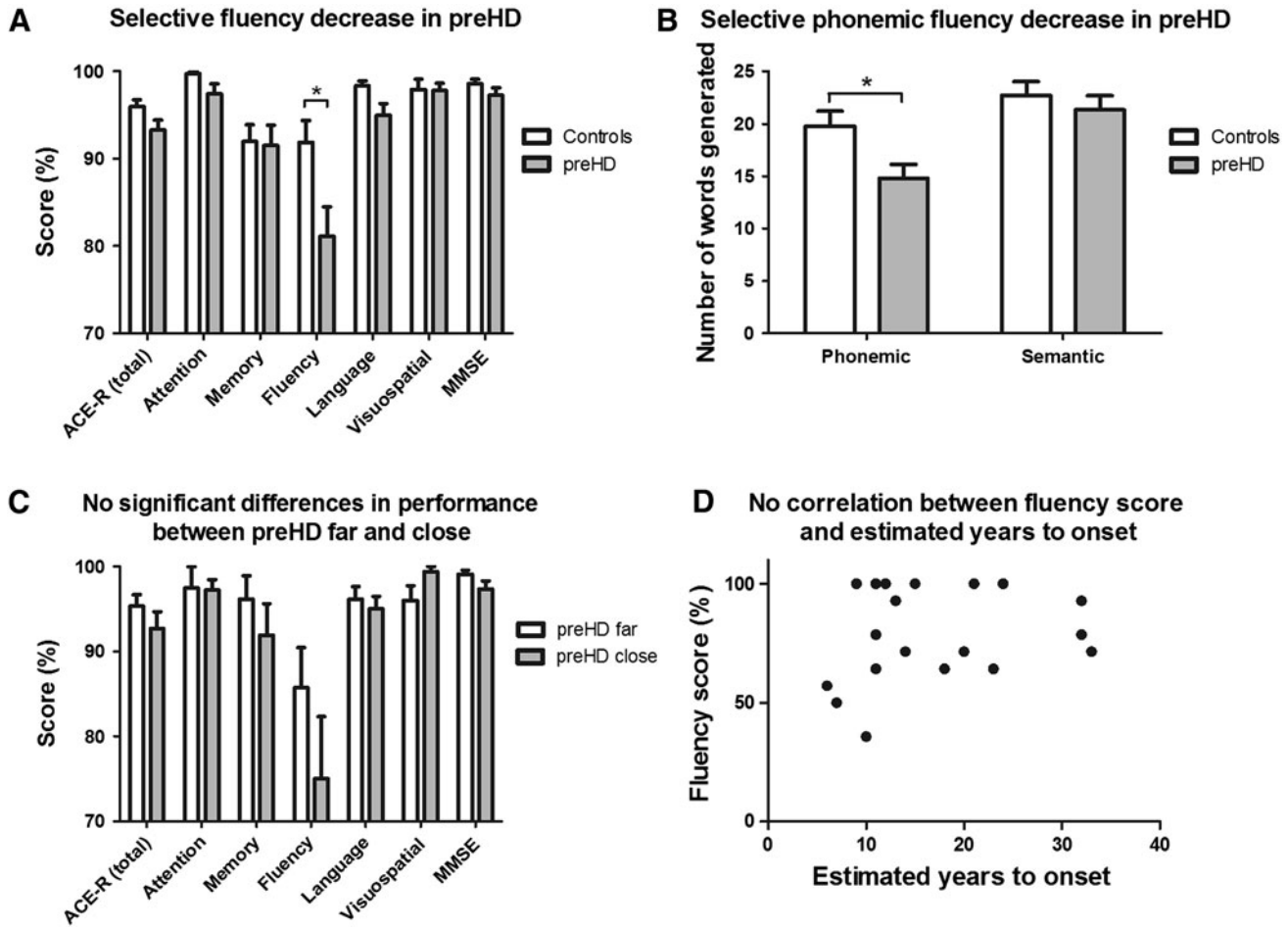

Fig. 1 Selective decline in fluency scores in preHD participants. **a** preHD participants have lower fluency scores relative to controls **b** and this is due to a selective decrease in phonemic, rather than semantic, fluency. **c** Although lower fluency performance is observed in preHD participants closer to onset, this difference is not significant and **d** does not correlate with estimated years to disease onset

6 months after their original visit. During the follow up visit participants had lower FA and TFC scores ($p = 0.041$, $p = 0.025$ respectively) with a trend towards higher TMS scores ($p = 0.062$, Fig. 2c). However, we found that the total ACE-R score, including the subdomains, and the MMSE were unchanged during the follow up visit (Fig. 2d, supplementary table 1). This is in contrast to the cross-sectional data presented and is most likely as a result of the small number of patients that attended a follow up visit and the short time period between the two visits.

Diagnosis of cognitive impairment using the ACE-R

Since these screening tests can be used to diagnose cognitive impairment or dementia, we next examined the proportions of participants that, according to these screening tests, would be defined as having cognitive impairment. Two total ACE-R cut-offs were previously identified based on calculations of sensitivity, specificity and positive predictive values at different prevalence rates [19]. The higher cut-off (88) has a better sensitivity (0.94) but lower specificity (0.89) and a lower positive predictive value (<0.68) at low prevalence rates, i.e. less than 20 %. The lower cut-off (82) has an excellent specificity (1.00) and a higher positive predictive value (1.0), even at low prevalence rates of 5 %, at the expense of sensitivity (0.84) [19]. Cut-offs for the individual domains, which define those who differ by more than two standard deviations from control data, have also been described previously [19]. For the MMSE, a score of less than 24 is most frequently used to diagnose dementia.

The proportion of participants that fell under the specified cut-offs for the total ACE-R score, the individual cognitive domains and the MMSE are provided in Table 3. A substantial number of manifest participants scored below 82 on the ACE-R even in the early stages of the disease (24 %), and this number increased significantly in the moderate (67 %) and advanced (74 %) stages of the disease. Interestingly, a proportion of patients even with advanced HD are not demented. In comparison the

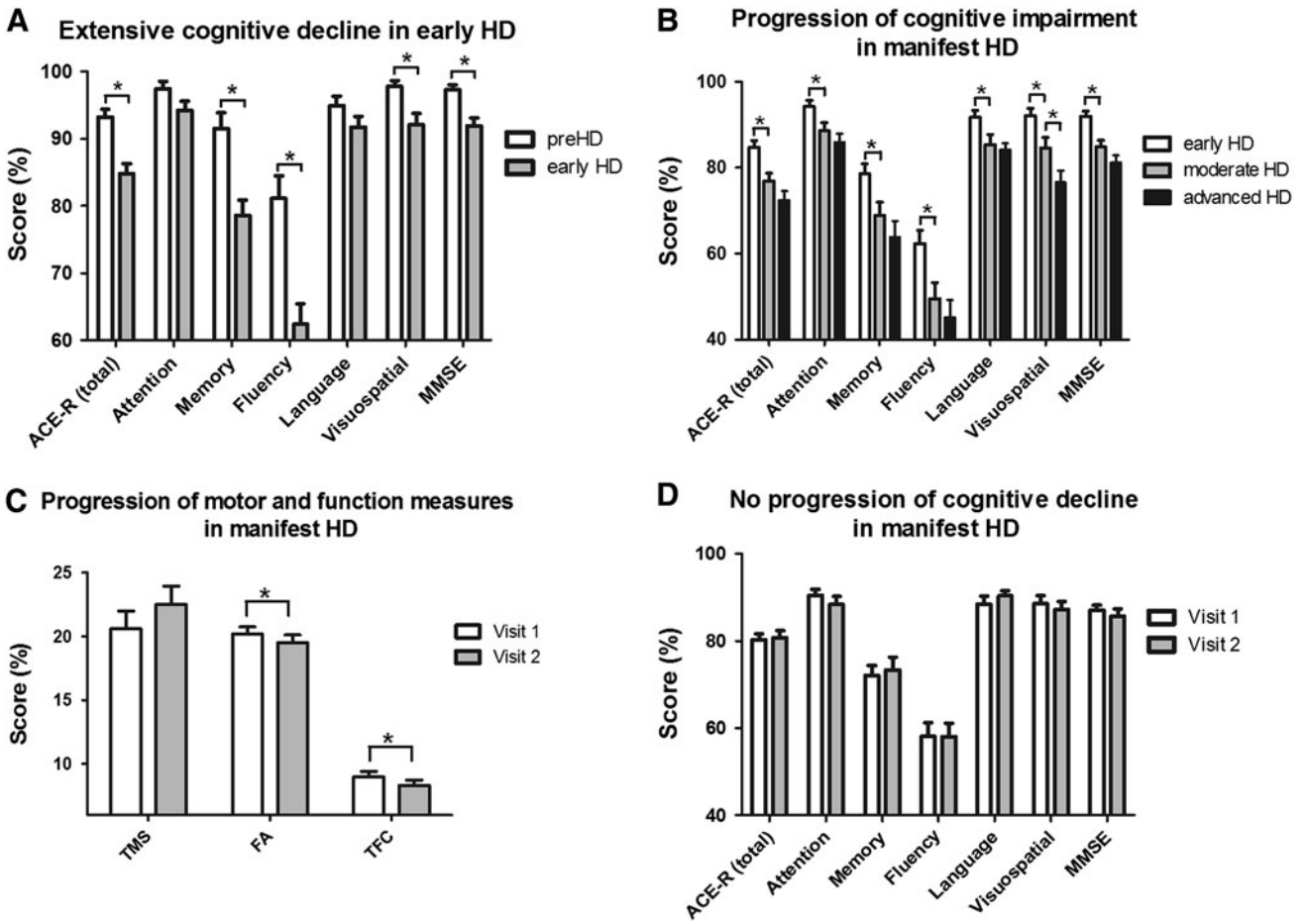

Fig. 2 Extensive cognitive decline in manifest HD. **a** Early manifest HD patients showed global cognitive decline with lower scores in a number of subdomains when compared to preHD. **b** Additional cognitive decline was observed in the moderate stages of the disease which, apart from the visuospatial domain, did not decline further in the advanced stages. **c** Longitudinal data (mean 1.35 years) showed progression of the disease as detected by reduced functional measures during a follow up visit. **d** However, cognitive decline could not be detected over the same time

Table 2 Overall cognitive performance in stages of HD

Cognitive performance					
Test	Controls	preHD	Manifest HD		
			Early	Moderate	Advanced
ACE-R	96.0	93.3	84.8*	76.9**	72.4
Attention	99.7	97.4	94.2	88.6**	85.8
Memory	91.9	91.5	78.6*	68.8*	63.8
Fluency	91.8	81.1*	62.4*	49.5*	49.5
Language	98.4	94.9	91.7	85.4**	85.4
Visuospatial	97.9	97.8	92.1*	84.5**	76.5*
MMSE	98.6	97.3	91.9*	84.8**	81.2

Table shows mean performance on ACE-R, the individual cognitive domains and the MMSE expressed as percent of maximum score to facilitate comparisons

*$p < 0.05$ and **$p < 0.01$ when compared to the previous group

Table 3 Detection of cognitive impairment

Detection of cognitive impairment in HD (%)						
Test	Cut-off	Control	preHD	Manifest HD		
				Early	Moderate	Advanced
ACE-R	<82	0	4	24	67	73
	<88	0	21	45	88	86
Attention	17	0	11	24	55	59
Memory	18	0	11	20	43	49
Fluency	9	0	11	41	70	73
Language	24	0	14	24	55	73
Visuospatial	15	14	14	29	55	76
MMSE	<24	0	0	6	20	41

Table shows the percentage of controls, preHD and manifest patients at different disease stages that performed below the suggested cut-offs for dementia the ACE-R and the MMSE

numbers of demented patients were underestimated by the MMSE where only a small number (6 %) of participants in the early stages performed under the cut-off.

The effect of antidopaminergic drugs on cognition

Since dopamine is known to be important in cognition and antidopaminergic medication, particularly dopamine D2 receptor antagonists, are used to treat chorea and mood swings in HD, we examined the effect of such medication on cognition. Overall, the majority of patients (63.5 %) were not taking antidopaminergic drugs. Of those taking antidopaminergic drugs (36.5 %), the most commonly prescribed was olanzapine (23.8 %) which is in agreement with a previous study showing that this is the most commonly prescribed drug in the UK [21]. Other drugs prescribed in this population included tetrabenazine (4 %), risperidone (3.2 %), sulpiride (2.4 %) or a combination of these drugs (2.4 %).

Overall, participants receiving antidopaminergic medication had lower fluency ($p = 0.016$) leading to a trend towards a lower total ACE-R score ($p = 0.069$) which may imply that antidopaminergic drug treatment causes cognitive decline. However, such data is confounded because participants receiving such treatment were in more advanced stages of the disease as shown by their worse motor ($p < 0.001$) and functional scores ($p < 0.001$). In order to minimise such confounds we compared the effect of antidopaminergic drugs within the different subgroups of manifest disease, as determined by TFC, meaning that participants were mostly matched in terms of motor and functional scores. Interestingly, when divided according to disease stage, early stage HD patients who received dopaminergic drugs had significantly higher MMSE ($p = 0.015$) and attention ($p = 0.026$) scores with a trend towards better total ACE-R score ($p = 0.067$) and performance in the memory domain ($p = 0.066$, Fig. 3a, supplementary table 2). There were no differences in cognition between patients in the moderate (Fig. 3b) or advanced (Fig. 3c) stages of HD who received antidopaminergic drug treatment compared to those who did not (supplementary table 2).

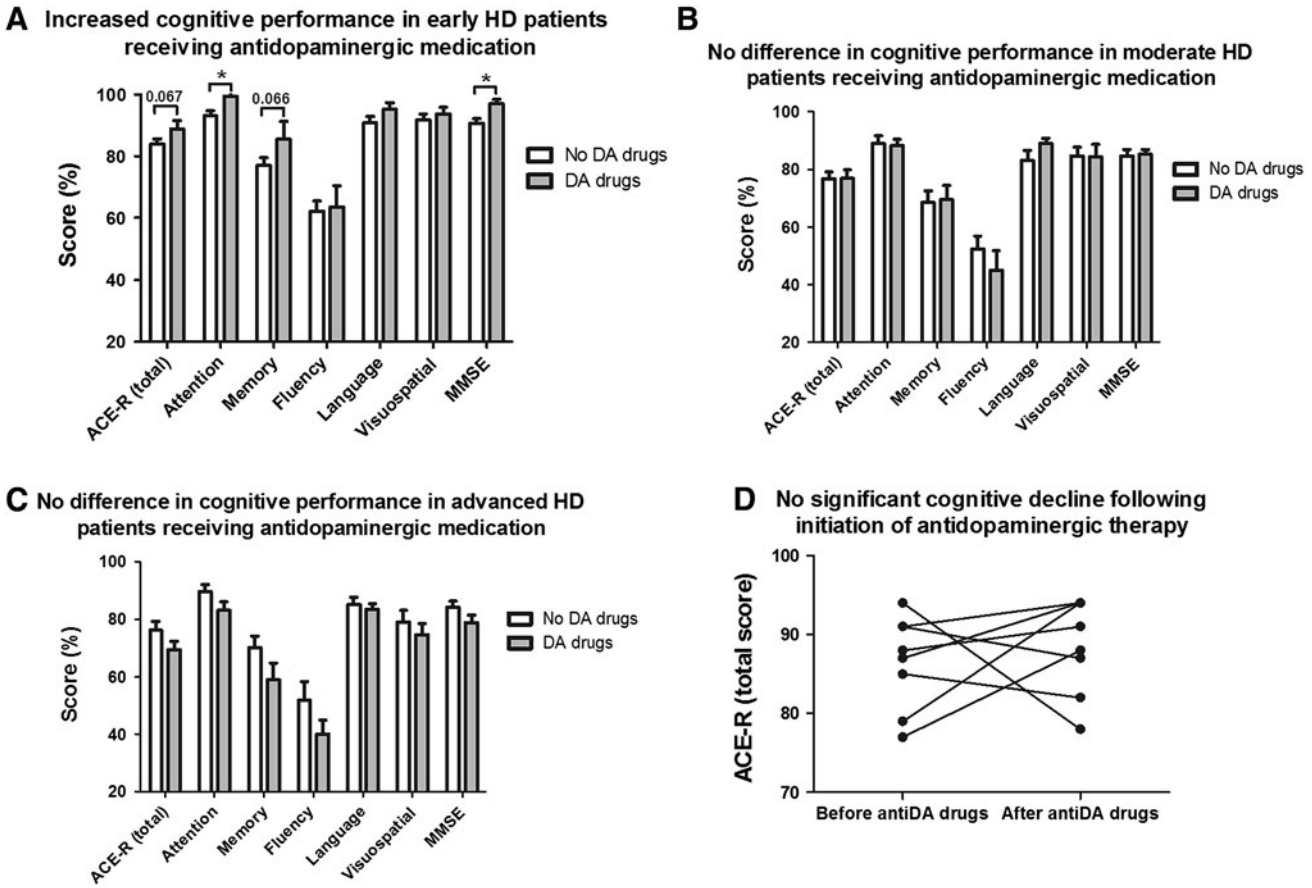

Fig. 3 The effect of antidopaminergic medication on cognition. **a** Early HD patients receiving antidopaminergic medication had significantly better scores on the MMSE and attention domains with a trend towards better overall ACE-R score. There were no significant differences in cognition of patients in **b** the moderate or **c** the advanced stages of the disease. **d** No significant cognitive decline in eight patients followed up after initiation of antidopaminergic medication

Investigating the effect of antidopaminergic medication in independent groups of patients is complicated by the fact that patients chosen to receive such medication may inherently have a different subtype of disease. To avoid this we further examined the effect of antidopaminergic drugs on cognition using a within-subjects design, by analysing cognition in participants who were not receiving such treatment when attending the clinic but were then prescribed it subsequently. Participants with concurrent changes to any other medication that may affect cognition, particularly antidepressants, were excluded from this analysis. A small number of participants ($n = 8$) fulfilled this criteria. There were no significant changes in MMSE, ACE-R or any subdomain scores 6–18 months following the initiation of antidopaminergic treatment (Fig. 3d).

Discussion

In this study, we have demonstrated that the ACE-R is an easy and practical test to monitor cognition at all stages of HD, regardless of therapy. In preHD participants there was a selective impairment in phonemic, but not semantic fluency. Global cognitive decline was observed in the early manifest stages of HD and this worsened further with disease progression. Whilst this cross-sectional study highlighted the progression of cognitive deficits in HD using the ACE-R, longitudinal changes in performance over 6–18 months showed no changes, despite a decrease in functional measures confirming that cognitive decline is slow and develops over a number of years. Finally, previous concerns that antidopaminergic medication may contribute to cognitive decline were unfounded in this study, with a suggestion that they could even improve some aspects of it in early disease.

Verbal fluency has been reported to be affected in manifest and premanifest HD [11, 25], and, therefore, is routinely included in many cognitive assessments in this disorder. However, there is no consensus on the extent of impairments in phonemic compared to semantic fluency. In this study, we show a selective decrease in the phonemic fluency in preHD when compared with controls, in line with previous evidence using this test in other diseases with subcortical pathology such as progressive supranuclear palsy [23]. Whilst a previous study agreed with this [31], others have found no significant differences between the two types of fluency [25] or larger effects on semantic fluency [11]. In addition, a meta-analysis aiming to evaluate the magnitude of impairment in the two tasks found that, although both types of fluency were impaired, the magnitude of the deficit for semantic fluency was greater than that for phonemic fluency [6]. A possible reason for this is that deficits in phonemic fluency, which have been proposed to be frontal-lobe dependent, are affected many years before disease onset and, hence, are present in most preHD participants. Semantic fluency is thought to be dependent on the temporal cortex [1, 5] with possible contributions from the hippocampus [4], structures which are affected much closer to disease onset and are, therefore, only present in a subgroup of preHD participants and in manifest cases. Evidence to support this comes from a previous study which found that, when comparing preHD close and preHD far, there was a significant decline in semantic, but not phonemic, fluency [31]. This means that, depending on how close to onset the recruited preHD population is, deficits in semantic fluency may or may not be detected. Considering that in this study the median time to diagnosis of the preHD population was higher compared to previous studies [31], semantic fluency deficits may not have been detected in our cohort for this reason.

Cognitive deficits in preHD have been reported to varying degrees and the discrepancy in findings may be explained by the criteria used to define preHD participants. In the literature, most studies use one of two measures, either the UHDRS TMS score or the diagnostic confidence scale (DCS). In this study we used a UHDRS TMS score of ≥ 5 which is similar to that of TRACK-HD [27, 28, 30]. However, other studies use the DCS, where a clinician assigns a diagnostic probability that a participant has manifest HD based on motor abnormalities. A diagnostic score of 4, indicating motor abnormalities that are unequivocal signs of HD (≥ 99 % probability), is used to define manifest participants. Since the UHDRS TMS is not taken into account, preHD participants included in these studies recruit, on average, participants with a wide range of UHDRS scores, ranging from 0 to 34 in some studies, and a higher mean UHDRS score (mean 5.53) [22]. Some of these participants included in such studies may have early manifest disease, where cognitive impairment is more prominent, and their inclusion may drive effects in the preHD population tested. It would therefore be worth standardising the criteria used to define preHD/HD participants so that future studies can be comparable and reproducible.

Extensive cognitive decline in manifest HD

In this study, participants with a TMS ≥ 5 were defined as having manifest HD and due to this strict cut off we were able to test the very earliest stages of the disease. We found that, relative to preHD, there was extensive cognitive decline with reduced MMSE and ACE-R scores with decreased performance in the memory, fluency and visuospatial subdomains. This global cognitive decline argues against previous suggestions that HD is mainly a dysexecutive syndrome [11–13] and in agreement with what has been reported pathologically and radiologically in other studies (e.g. TRACK-HD) [26, 28]. However, despite this

global cognitive decline, early stage HD patients are still functioning at high levels and so this may be an optimal stage to assess agents that are designed to prevent further cognitive decline.

It is important to acknowledge that the majority of the data presented in this study is cross-sectional and the longitudinal data obtained from this study showed no decrease in ACE-R scores over a period of 6–18 months despite worsening functional measures. This probably reflects the insidious cognitive decline that occurs in HD over a number of years and is relatively easy to demonstrate using cross-sectional comparisons, as the different groups used span a time period of 15–20 years. An additional reason behind the lack of longitudinal change may be the small number of patients who attended a follow up visit. This is in agreement with a previous study from our lab that showed minimal longitudinal cognitive change in a group of 18 HD patients who were assessed annually for a period of 5 years using a number of cognitive assessments [15]. Although other studies have been able to demonstrate statistically significant changes over the period of 1 year, the actual numerical changes were very small and such studies have typically used larger numbers of patients ($n = 87$) to see such an effect [24]. This will be especially problematic for small-scale trials aiming to evaluate therapies designed to attenuate cognitive decline rather than provide a robust improvement in cognition.

No cognitive decline following antidopaminergic treatment in HD

Prescription of antidopaminergic drugs to treat the chorea and behavioural problems of HD has led to some concerns about their effect on cognition [16–18]. Furthermore, a recent study reported worse performance in an emotional recognition task in early HD participants receiving neuroleptics compared to those who did not [9]. In this study we have shown that antidopaminergic treatment does not impact upon global cognitive performance and in fact, there was a trend towards better total ACE-R and significantly better MMSE scores in early HD patients receiving antidopaminergic medication in comparison to those who were not. However, we did not do this systematically so no firm conclusions can be made given the bias in those who were treated with such drugs As such, double-blind placebo-controlled studies of the effect of such drugs on cognition are needed in order to better investigate this.

Conclusions

This is the first study to test the utility of the ACE-R in a premanifest and manifest HD population. We have shown that this brief, inexpensive and practical way to measure global cognitive performance has great potential use in assessing this aspect of HD regardless of stage or treatment. Evidence from using the ACE-R argues against HD being primarily a dysexecutive syndrome as patients at the very earliest stages of the disease were impaired in a variety of subdomains including some that are not thought to be dependent on frontro-striatal circuits. With measures to predict accurately disease onset in preHD participants on an individual basis currently lacking, the early HD group may be an ideal group for disease modifying therapies because, despite the global cognitive impairment detected in this study, they are still able to function at high levels. Intervention at this stage may attenuate further cognitive decline that was observed in the moderate HD group. However, the ACE-R is unable to detect longitudinal cognitive change in a small number of participants over short periods of time (<18 months) and thus any such trials will face many practical challenges such as having to recruit a large number of participants with long follow up times.

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Conflicts of interest The authors have no competing interests with regards to this work.

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