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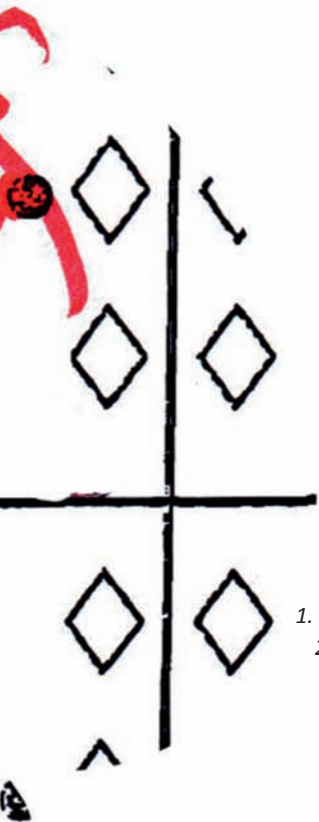**Issue Date**: 2012-11-14

Chapter 2

A review of cognition in Huntington's Disease

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Abstract

With the prospect of potential treatments for Huntington's disease (HD), non-invasive markers of disease progression are needed. Cognitive impairment has long been recognised as one of the core symptoms of HD. The first aim of this review is to provide insight into the onset and nature of cognitive loss in the progressing stages of HD. The second aim is to provide an overview of the cognitive functions that have been examined in an attempt to identify those areas that have the most potential to yield a cognitive biomarker. Literature, consisting of 110 studies, since the implementation of genetic testing until the beginning of 2011 has been included in this review. The clinical features of premanifest HD include deficits in psychomotor speed, negative emotion recognition and to some extent in executive functioning. The clinical profile of manifest HD includes impairment in memory, psychomotor speed, negative emotion recognition and executive functioning. Furthermore, potential candidate biomarkers should be most expected from such domains as working memory, psychomotor speed, recognition of negative emotions, attentional and visuospatial executive functions.

Introduction

Disturbance in cognitive functioning eventually ending in dementia is a core symptom in Huntington's Disease (HD), and was referred to in the first report by George Huntington when he discussed 'insanity' and 'impairment of the mind'[1]. An expanded cytosine adenine guanine (CAG) repeat on the short arm of chromosome four eventually causes neuronal loss in the brain. As a consequence of these brain changes disturbances in motor functioning, behaviour and cognitive functioning are the most frequently reported clinical symptoms. Despite HD classically being regarded as a disease of motor impairment, cognitive decline as an early symptom has increasingly been recognised. A recent report of the symptom type with which HD manifested, found that 8.4% of a group of 615 patients in Europe were rated by a clinician as having first disease symptoms of a cognitive nature. An additional 13.2% had a mixed onset of motor and/or cognitive and/or psychiatric symptoms[2]. In a group of 1238 patients, over a period of two to ten years after receiving the diagnosis, companions reported intellectual decline and memory loss[3]. Self-reporting of cognitive abilities has proven to be problematic in HD, as patients have been shown to demonstrate impaired awareness, which was found to relate to problems with executive functioning, memory and global cognitive functioning[4]. For this reason the need for objective assessments, e.g. formal neuropsychological testing, has become apparent. Although it has become clear through numerous reports of formal examination that cognitive decline occurs and worsens in the course of HD[5-9], the progression of decline over the stages of HD is not well-established.

With the growing prospect of potential treatment for HD, the need for accurate, sensitive and non-invasive biomarkers of disease progression has become clear. Since the discovery of the HD CAG repeat expansion in 1993, genetic testing has become widely available for both patients and family members[10]. Since then, at-risk individuals could undergo genetic screening. If found to carry the gene and with no overt symptoms, these individuals are referred to as premanifest gene carriers of HD. However, this test result gives little indication of how and when the disease will start, or in which disease stage patients are in. The ideal biomarker for HD would objectively pinpoint the start of the disease and/or current disease phase of a gene carrier. Any improvement (or stabilisation) as a result of an intervention would then accurately be reflected by this measure. Such a measure could thereby serve as an outcome measure in future clinical trials. To date, no single (cognitive) measure is generally accepted as a sufficiently sensitive measure to serve in such trials. Currently, the most frequently used outcome measures are such measures as the Total Functional Capacity Score (range 1-13) or the Mini-Mental state examination (range 0-30), however, these are often insensitive to small changes in function. The search for an adequate biomarker has given rise to many observational studies of all domains of the disease, including invasive, non-invasive, wet and dry biomarkers[11-14]. Cognitive research has attempted to identify candidate cognitive biomarkers for a long time and

much research has been performed to assess feasibility. However, again no single measure is currently accepted as a sufficiently sensitive marker of current or changing cognitive functioning.

This review has two aims, firstly, to provide insight into the onset and nature of specific and global cognitive loss in the successive stages of HD, secondly, to provide an overview of results from the functional (sub)domains that have been examined in an attempt to identify a cognitive biomarker.

Cognitive Domains and stages of Huntington's disease

From the start of research into cognitive functioning in HD in 1974 there have been many attempts to categorise the deficits seen into domains of cognitive functioning[15]. This has been done for two main reasons, first to try to grasp the nature of cognitive decline for diagnostic and treatment purposes, and secondly to identify cognitive biomarkers as a means for tracking disease progression. For the purpose of this review, the results of the reports that have been reviewed have been categorised in accordance with the above mentioned goals. Firstly, in accordance with the clinical diagnosis of cognitive decline and dementia, the five domains set out in the Diagnositic and Statistical manual of Mental disorders, fourth edition (DSM-IV)[16] were used as a starting point for classification. These are; amnesia, aphasia, apraxia, agnosia and executive dysfunctioning. As there is no evidence to suggest disorders in praxis in HD, rather only in motor functioning affecting psychomotor speed, we chose to collect all results under the classification *psychomotor speed*. The same is the case for agnosia, which in this review has been relabelled as *emotion recognition*, as this was found to be the most prominently examined function found to show deficiencies.

Although the division of functions exists, cognitive processes are complicated and complex and therefore it is often very difficult to pinpoint just one specific function that is responsible for the correct performance of a task. As a result the DSM-IV discusses a number of functions related to, or collected under, one of the main umbrella terms of the five domains. This sub-specification will also be discussed throughout this review. Specifically under the domain *memory*, we will address declarative, non-declarative, verbal, visual, working and general memory. Under *emotion recognition* the emotions happiness, surprise, sadness, fear, disgust, anger and general negative emotions will specifically be addressed. Under executive functions both general and the specific functions of attention, categorisation, verbal and visual-spatial executive functioning will be considered. Additionally, in terms of the search for a biomarker, an additional specific domain has proven to be of interest and will be used as a means to categorise experimental findings, namely global cognitive functioning.

Methods

All literature relating to cognition in HD between the discovery and application of direct genetic testing in the mid nineteen nineties and January 2011, was included. Literature searches were performed in four databases. The searches were performed with the following terms in Pubmed, ("huntington disease" (Majr) OR huntington (ti) OR huntington's (ti) OR huntingtons (ti) OR huntington* (ti) OR huntingtin* (ti)) AND (cognition OR cognitive OR "Cognition Disorders" (Mesh:noexp) OR psychology OR neuropsych* OR Neuropsychological Tests), Embase, (*Huntington Chorea/ OR huntington$.ti OR *Huntingtin/ OR huntingtin$.ti) AND (exp Cognition/ OR exp Cognitive Defect/ OR exp Psychology/ OR exp Psychological Aspect/ OR exp Neuropsychology/ OR Neuropsychological Test/ OR exp Learning disorder/ OR (cognition OR cognitive OR psychology OR neuropsych* OR Neuropsychological Test* OR learning).mp), Web of Science, ti= (huntington* OR huntingtin*) AND ts= (cognition OR cognitive OR psychol* OR neuropsych*) and PsycINFO, (exp *huntingtons disease/ OR huntington*.ti OR huntingtin*.ti) AND (exp Cognition/ OR exp cognitions/ or exp cognitive ability/ or exp cognitive assessment/ or exp cognitive impairment/ or exp cognitive processing speed/ OR exp memory/ or exp memory decay/ or exp memory disorders/ or exp memory trace/ or exp memory training/ OR exp Psychology/ OR exp Neuropsychology/ OR exp Neuropsychological Assessment/ OR exp learning/ or exp learning ability/ or exp learning disabilities/ or exp learning disorders/ OR (cognition OR cognitive OR memory OR psychology OR neuropsych* OR Neuropsychological Test* OR learning).

Of the approximately 1000 papers that were found with this search strategy the majority (± 75%) purely referred to cognition in HD without having objectively examined cognitive abilities or having an aim related to cognition and were therefore removed. The remaining ± 25% was examined and only included if they fulfilled the following criteria: were written in the English language, had examined human gene carriers or patients with directly confirmed presence of the HD gene and, for cross-sectional reports, had directly compared the cognitive performance of the HD participants to control subjects. Papers were excluded if: the study was performed prior to the implementation of the genetic test, data was collected as part of a clinical intervention trial, if it was not defined how HD was determined or tested, if patient data were compared to data from other patient groups or to norm data only[17]. This approach yielded 110 strictly selected papers, which is comparable to the report by Stout *et al.* (2011) of approximately 150 reports of "neurocognitive function" since the identification of the HD gene[18].

Each report was examined and the results categorised based on the domains of cognitive functioning as described above. For the majority of results it was evident how they should be categorised and sub-categorised as the authors had indicated how they had done so.

For other results where the described test had not been categorised by the authors, a categorisation was made based on the cognitive abilities required and/or how this had been categorised by other studies. The categorisation of the Verbal Fluency Test or the Controlled Oral Word Association Test (letters F-A-S) from the Unified Huntington's Disease Rating Scale (UHDRS), proved more complicated. In neuropsychological manuals it is often listed under language abilities[19], however in the majority of HD research it is regarded as a test of executive functioning[13,20,21]. To correspond to the majority of studies in the HD field, results from this specific test were categorised under executive functioning. For each domain the absence or presence of a significant difference to controls for the patient groups was noted. A study was classified as finding a difference between HD mutation carriers and controls when the authors had stated that this was the case, based on the statistical criteria they had described, and not on the basis of a significance cut-off point. This was done as many different statistical approaches have been taken, rendering direct comparability unfeasible.

Further subdivision in results per disease stage was achieved with the following. For HD patients a distinction was made between those with early or mild HD versus patients with moderate/severe or late stage HD, most often related to the disease stages defined by Shoulson and Fahn[22]. Where it was possible to ascertain the stage of severity of the disease from the text the presence or absence of a cognitive defect in this domain was noted only for that group. This same approach was taken to studies of premanifest HD. Numerous studies classified premanifest gene carriers based on the number of years to estimated disease onset[23] as either far from – or close to – disease onset. In practical terms this yielded a split on average around 10 years from estimated disease onset[11,13,24]. In cases whereby it was not clear in which phase or stage of the disease the participants fell, a notation of difference to controls was noted for both participant groups (ie. both premanifest groups, or both HD patient groups). From these notations it was possible to indicate the number of times that a difference to controls was or was not found, for each disease stages, for the cognitive domains. These data were used to construct graphical displays of the presence and staging of cognitive defects (figures 2-10).

Anmesia/Memory

In the domain memory, all functional tests related to the recall of previously learnt information or to the learning of new information were classified. This included sub-types of long-term memory such as declarative memory, with subdivision of semantic memory (factual information) and episodic memory (situation specific information related to a persons life). Also non-declarative memory was specified and related to all tasks testing skill related or automated procedural memory. Furthermore, in the subtype of short-term memory, working memory was included, referring to storage, retrieval and application of information that is required only briefly. In addition, two other sub-categories of short-
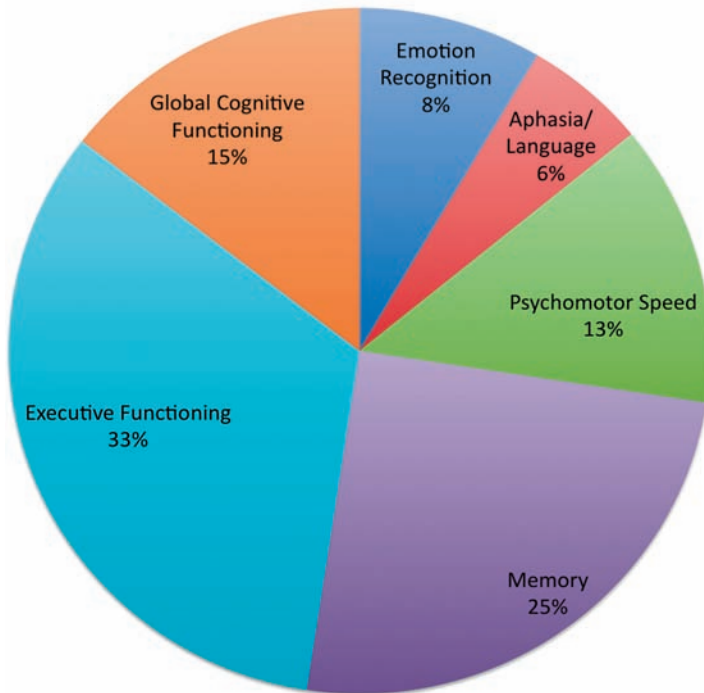
Figure 1. Proportion of research performed per separate domain of cognitive functioning.

term memory were recognised, namely verbal memory and visuo-spatial short-term memory[25]. In HD research a quarter of the research into cognition in HD has been related to memory (figure 1). The distribution of positive and negative findings in regards to memory research over the different stages of HD is shown in figure 2.

In manifest HD, cross-sectional findings in the various domains of memory provide a fairly homogenous profile of impaired memory functioning in both early and late stage HD[8,11,26-44]. Longitudinal studies found both evidence for the presence of the specific types of amnestic disorders in manifest HD[5,38,45-47], and against such deficiencies in the same or other subdomains of memory functioning[5,6,45,46,48]. The results from the smaller studies (n = 20-40) often (just) failed to reach significance for the majority of memory measures, and often found just a limited number of measures show significance. For example, a group of measures of memory approached statistical significance ($p<0.10$) over one- and two-year follow-up periods[48]. In other studies visual memory was found to decline over annual visits[45] and over 16 months[46]. This was also found by a moderately sized study which had reached significant levels ($p< 0.05$) for visuo-spatial memory. However, in this same group verbal learning, just failed to reach significance (p between 0.06 and 0.09) over 3 annual visits[5]. A larger study (117 early HD patients vs. 119 controls) did not find differences with a computerised visual working memory task over a one year period in patients with stage 1 HD, but did find this in patients in stage 2[6]. These findings do suggest that overall memory decline does occur in manifest HD and that for specific sub-domains there is a relative consensus in terms of decline in visual memory, and more uncertainty about verbal memory.
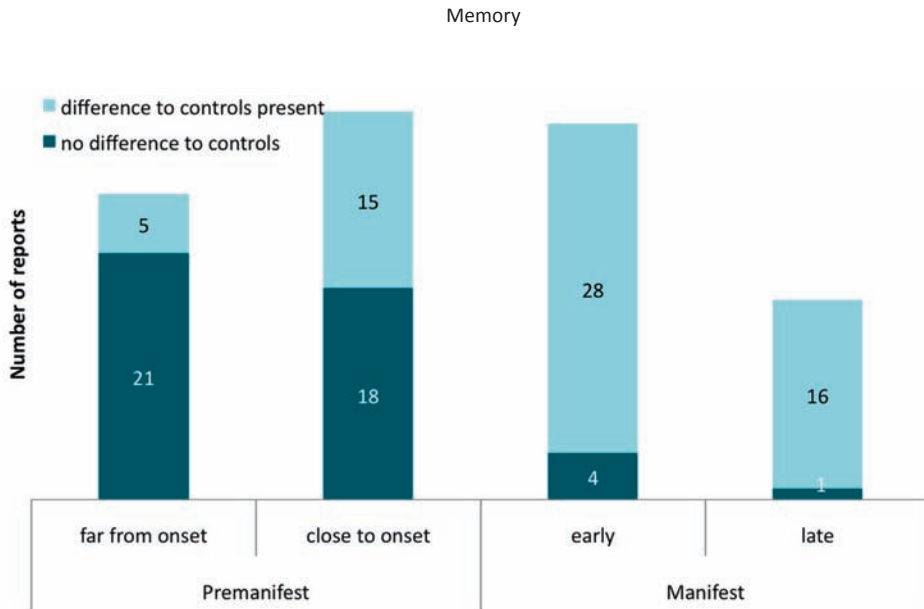
Memory

Figure 2. For the cognitive domain: Memory, the number of positive and negative findings over disease stages.

Memory functioning in premanifest gene carriers is not as clear cut as that of manifest subjects. Cross-sectionally, many different types of memory have been investigated and results show that in some studies evidence is found for a defect, albeit sometimes not in all, but in a limited number of subdomains[11,18,30,49-59], whereby for poorer working memory the most consistent findings were present (Figure 3). The larger studies (n>100) did show difference to controls with strong significance levels[11,18]. This was similar to smaller studies (n<30), who found differences in other sub-domains, such as prospective and visual memory[49] and explicit motor sequence learning[30]. Examination of the timing of onset of such deficits reveals that the majority of these findings apply to premanifest gene carriers close to onset, as is shown in figure 2. In contrast, there is also a substantial body of evidence to suggest that cross-sectional memory functioning in some domains, such as verbal memory, is equal to that of controls[21,32,38,42,60-68].

Longitudinal studies in premanifest gene carriers found that memory related tasks showed more decline over longer periods of time (120 and 30 months respectively) than in controls[9,47]. However, others, including shorter follow-up periods (12 to 24 months), found that there was no difference in task performance over time[6,64,69,70]. These results suggest that memory decline is a slow process in premanifest gene carriers.

The interpretation of studies of memory functioning is complicated by the many domains that have been investigated. All types of memory functioning are complex and thought to recruit numerous different brain regions. Therefore although one type of short term memory, say working memory is found to be poorer in HD, this does not mean that the sub-types of long-term memory are equally affected.
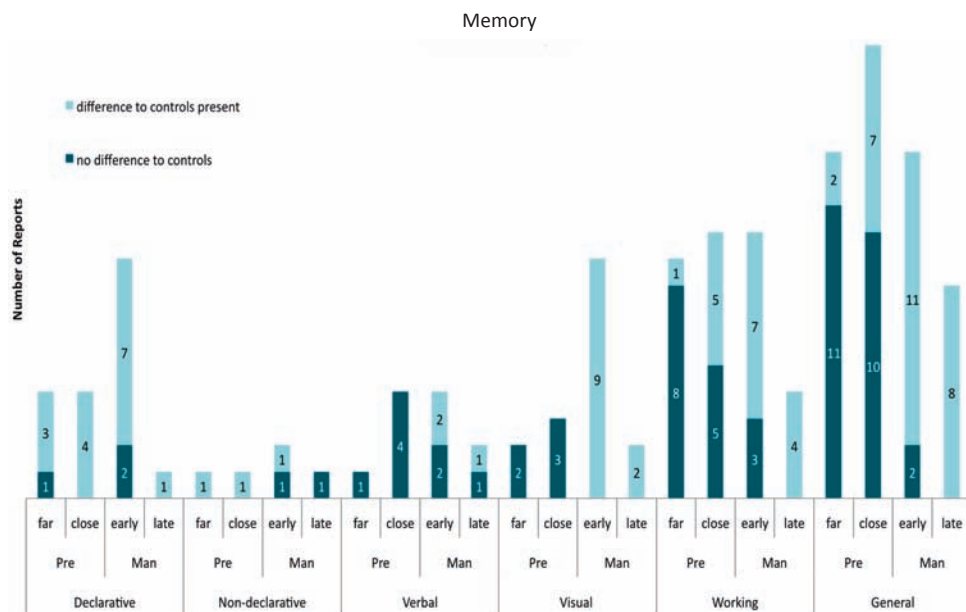

Figure 3. Memory research divided into sub-domains of memory functioning. The number in each section of a bar represents the number of positive versus negative findings.

For this reason it is preferable to examine the subtype of memory that is impaired, figure 3 shows the distribution of research findings over some domains of memory functioning (where subtype information was provided in the literature). From this graph it becomes clear that there is not one single pattern of memory impairment that is valid for all subdomains, rather that the impairment pattern is unique to each memory subtype. When taken together the findings from the cross-sectional studies strongly suggest that there are deficits present in (sub)domains of memory functioning that differentiate premanifest gene carriers from controls, however the limited evidence for further longitudinal decline may suggest that the rate of decline of memory functioning is not so pronounced. Of the subdomains of memory, the clearest findings related to problems with working memory, therefore this may be the most appropriate memory based candidate for biomarker selection.

Aphasia / Language

Aphasia relates to all language producing or understanding functions. An important issue arises when examining language abilities in HD as the motor impairment can also cause dysarthria, which could be mistakenly be regarded as a language problem. The presence of slurred or poorly comprehendible speech does not relate to the cognitive function required for speech production or understanding. Therefore when examining language abilities it has proven vital to distinguish between the content and the practical impairment. The language abilities that were collected under this domain were: spontaneous speech, ability to repeat words or phrases, comprehension, naming, reading and writing[19].

Of all cognitive domains the least amount of research has been performed into language functions in HD (Figure 1). In manifest HD, decline in language functions has been reported both cross-sectionally[38,71,-74], and over a number of years[38,45,47]. In premanifest gene carriers, except for one study[18], no differences in language function were found either cross-sectionally or over time (Figure 4)[38,47,61,66,73].
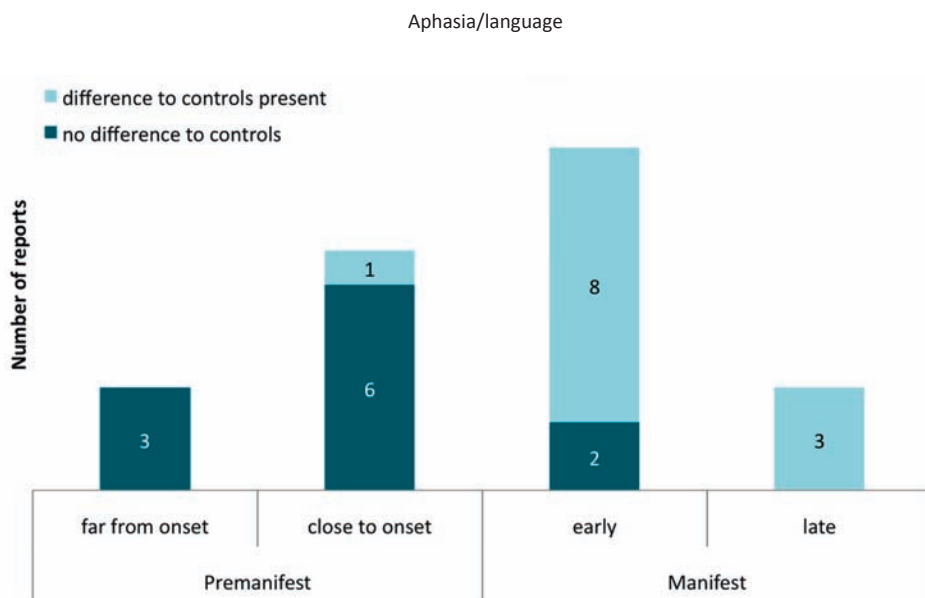
Aphasia/language

Figure 4. For the cognitive domain: Aphasia/language, the number of positive and negative findings over disease stages

Psychomotor speed

The speed of thinking and acting often referred to as psychomotor speed, has proven important in HD literature. Patients are known to have deficits in their motor abilities, one result of which is bradykinesia. However, the slowing of brain processes related to task performance is also an important measure of functioning and should ideally be separated from poor motor performance alone. Understandably, in clinical practice this can prove to be difficult. The speed and/or strength with which motor movements are performed, although not strictly responsible for the correct performance of a motor procedure, is also a domain often examined as part of neuropsychological testing. The deterioration of psychomotor speed often reflected by slowed performance of a task is a frequently reported phenomenon in HD.

In manifest HD all findings show the presence of a deficit in psychomotor speed[8,33,34,37,43,75-79], also longitudinally[5,6]. Given that the gene carriers are labelled as manifest based on the existence of motor deficits, the impact of motor impairment on cognitive functioning is to be expected. This was further investigated by Aron *et al.*, (2003) and differentiated between reaction time and movement time during a cognitive test. The separate analysis of these two constructs showed that the most purely motor based parameter, motor time, was not different between patients and controls, but that only the more cognitively related reaction time was different between the groups[75]. This suggests that despite their motor impairment, the HD patients are most slowed by their cognitive processes rather than their actual hand movements. That not all differences in cognitive performance can be explained by the negative influence of motor impairment was also demonstrated by Lawrence *et al.*, (1996) when they studied patients in the early stages of HD with impaired psychomotor speed. The influence of this slowing was examined in relation to the performance on other cognitive tasks in which psychomotor speed was incorporated. Even when psychomotor speed was accounted for, slowing did not explain the differences in visuo-spatial functioning[37].

The majority of cross-sectional findings in premanifest HD point towards slower psychomotor speed especially when the group premanifest gene carriers close to onset is examined (Figure 5)[18,49,50,52,55,60,65,77,78,80,81]. This was also confirmed longitudinally[6,9,69,82,83]. However, as seen in other cognitive domains not all reports found differences in psychomotor speed between premanifest gene carriers and controls, either cross-sectionally[21,60,61,64,66,84] or longitudinally[64,70]. Nonetheless, given that the largest body of evidence both from smaller and larger studies has repeatedly demonstrated this deficit, with sometimes highly significant results, psychomotor dysfunction does seem to be present prior to disease onset.
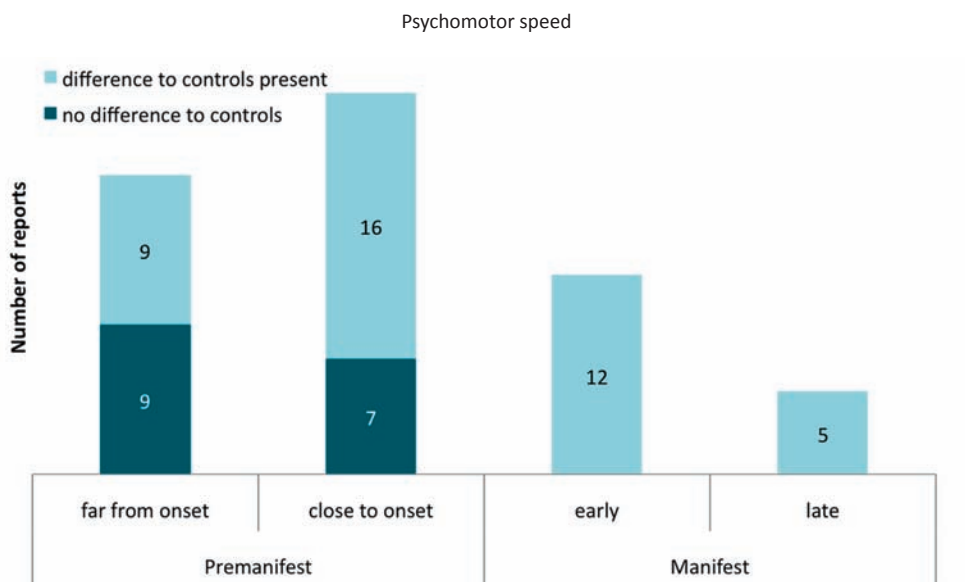
Psychomotor speed

Figure 5. For the cognitive domain: Psychomotor speed, the number of positive and negative findings over disease stages

Emotion Recognition

Research into problems with recognition in HD has been largely limited to the recognition of odor, faces and emotions (figure 6), with by far the most research performed on the latter. Recognition of emotion has been extensively researched in both premanifest gene carriers and patients with HD. This function could be categorised under memory, however, those with deficits of emotion recognition do remember what each emotion type means, only cannot recognise it upon presentation, therefore this is discussed as a separate domain.

In manifest HD the recognition of certain emotions was found to be different between patients and controls in almost all studies[11,67,73,85-91]. However, this does not apply for all emotions, with negative emotions most affected and no evidence for deficits in the recognition of positive emotions such as happiness and only one report of diminished surprise[89]. This extensive deficit of negative emotion recognition in manifest HD was also supported by evidence from longitudinal reports[6,91]. Figure 7 shows the distribution of findings in regards to specific emotion types and shows that there is the most evidence for problems with disgust, followed by fear. To gain more insight into these deficits Hayes *et al.* (2007), assessed patients with seven tests of emotion recognition and found consistent results with impairment in multiple types of disgust recognition[88]. In a subsequent study they examined patients in early to late HD and found that their impairment of anger,

fear and sadness recognition was correlated to a decline in general cognitive functioning, however the impaired recognition of disgust was not. Furthermore in the majority of patients disgust was the most poorly recognised emotion[89]. This suggests that disgust recognition is related to HD pathology and the recognition of other emotions maybe related to general cognitive ability.
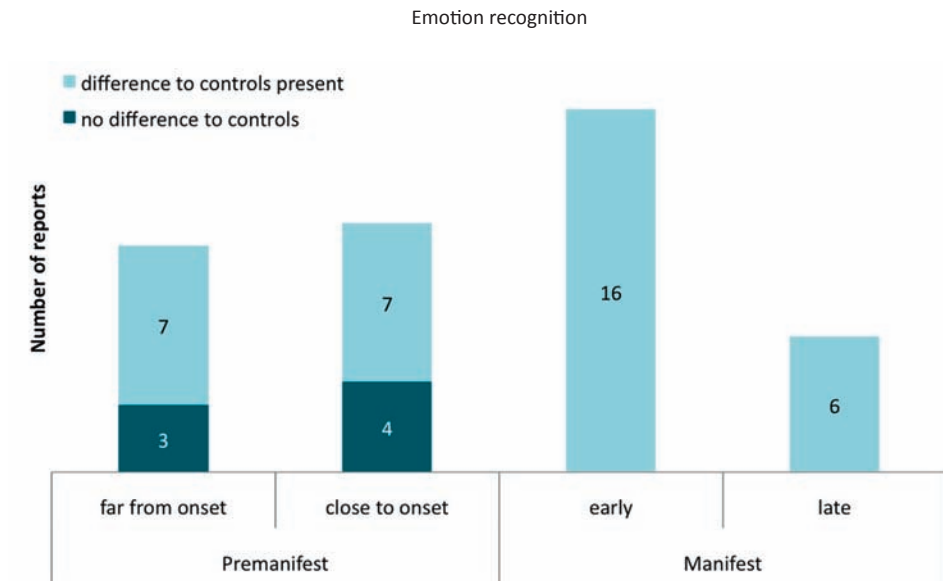

Figure 6. For the cognitive domain: Emotion recognition, the number of positive and negative findings over disease stages

In manifest HD there has been some evidence found for impaired odor recognition[11,92-94] and general recognition[76]. Odor recognition was not found to be different in premanifest HD to controls[93].

The first detectable emotion recognition deficits in premanifest HD appears to be poorer recognition of one or more of the negative emotions[67,85,91,95] also in gene carriers more than 12 years from disease onset[11,18]. Only one report found that premanifest gene carriers were worse at recognising a positive emotion, namely happiness[90]. A minority of studies report no differences in emotion recognition cross-sectionally[73,96]. However, even these studies demonstrated trends towards significance for emotions such as fear[73] in a group of 20 gene carriers, and to a lesser extent, in a small study of 13 gene carriers, disgust[96]. The only longitudinal study in a large sample size did not find decline over a one year follow-up[6].

Overall these findings do suggest that the recognition of negative emotions starts early on, and does not decline at a rapid rate initially but more so after disease onset. Although such longitudinal findings should be replicated, there does seem to be conclusive evidence that

recognition of negative emotions is impaired in both premanifest and manifest HD, which suggests potential as a biomarker.
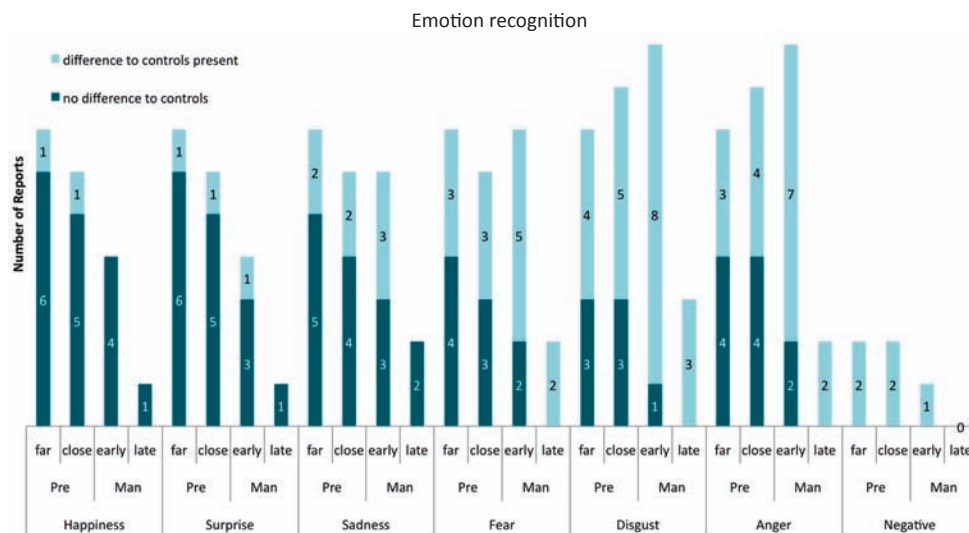

Figure 7. Emotion recognition – per emotion research divided into sub-domains of memory functioning. The number in each section of a bar represents the number of positive versus negative findings.

Executive (dys)functioning

The most commonly assessed area of cognitive functioning in HD research is that of executive functioning. All reports of higher order functions of attention, planning, categorising, sequencing and abstracting were collected under executive functioning. These are regarded as the most complex of behaviours and are needed to be able to adapt in flexible manner to many daily life situations, whereby conceptualisation of the task at hand, planning, action and evaluation of the performed task are required. Many different types of complex functioning shelter under the term executive function, these include, attention, task-switching, categorisation abilities and cognitive flexibility. As executive functioning requires so many integrated cognitive functions many factors can confound correct performance[19].

Early reports found problems in executive functioning, so much so that tests of this function were implemented in standardised assessment batteries, of which the Unified Huntington's Disease Rating Scale is the most frequently applied[97]. Motor, behavioural and cognitive functions are assessed with this tool. The three cognitive tests including in this rating scale are the Symbol Digit Modalities Test (SDMT), the verbal fluency or Controlled Oral Word Association (FAS,) and the Stroop Colour naming, Word reading and Interference cards (Stroop). Within HD research, findings regarding these three tests are often referred to as reflecting executive functioning.

Almost all cross-sectional reports demonstrate differences between manifest HD and controls[8,26,27,29,34,36-38,40-45,72,73,75,77-79,93,98-113], and in the few cases where this was not demonstrated this was always in early HD patients and not later stage HD (Figure 8)[58,114,115]. Impairment of executive functioning in manifest HD was also found longitudinally on numerous occasions[5,6,9,38,41,45,47,48,113,116].
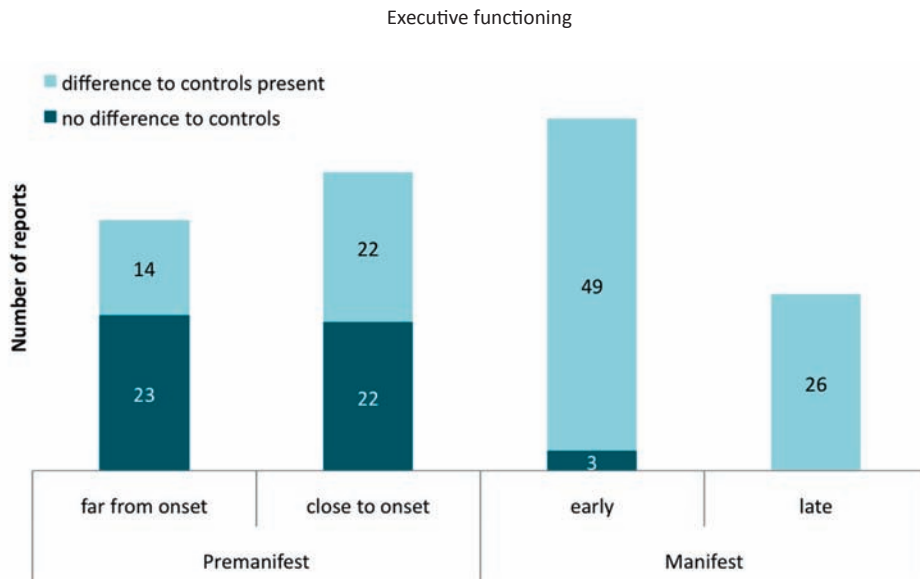
Executive functioning

Figure 8. For the cognitive domain: Executive functioning, number of positive and negative findings over disease stages.

The reports on executive functioning in premanifest gene carriers find almost equal support for and against the presence of a dysfunction. A number of studies regard their findings as evidence for the presence of subtle cognitive changes many years prior to the onset of motor symptoms[18,49,78] and some suggest that this domain would represent a good biomarker[50,77]. Those papers that find support for executive dysfunction in premanifest HD[38,52-54,65,73,81,96,101,117-121] include both studies with smaller and larger sample sizes (up to 700+ premanifest gene carriers). However just as many negative findings have been demonstrated[21,42,53,55,58,60-62,64,66,67,84,93,100,102,105,110-112,122] generally by studies with lower sample sizes.

Longitudinal research into executive functioning also provides a mixed view on whether or not this domain is effected in premanifest HD. Reports confirming the decline of executive functioning are present over 120 months in 43 premanifest gene carriers, over 12 months in 12 gene carriers and over 30 months in 38 gene carriers respectively[9,38,69] as are reports against the presence of a dysfunction over 24 months in 22 gene carriers and 36 months in 33 gene carriers[64,70].
From all these reports the conclusion can be drawn that executive functioning is impaired

in manifest HD. There is mixed evidence for executive dysfunction in premanifest HD, but that the majority of reports points towards a dysfunction, albeit with a slowly progressive decline. Lemiere *et al.*, (2002) suggested that some tests of executive functioning may be suitable for demonstrating differences between premanifest gene carriers and controls at one point, but not for showing evolution of disease progression over time[38]. It may be that premanifest gene carriers are worse at some times, stable over longer periods and that sudden drops in ability are related to staging within the disease. Furthermore, some but not all tests of executive functioning showed difference to controls, therefore it is important to identify which subtypes of executive functioning are affected. Noted however, that not all reports specified the subdomains of executive functioning examined. Figure 9 gives an overview of those reports that specified if their results pertained to sub-types of executive functioning, namely, attention, categorisation, verbal, visual or unspecified or to general executive functioning. The graph shows that there is little evidence for problems with categorisation, attention or verbal executive functioning in premanifest HD, and that there is evidence for early disturbances in visual and more general or mixed types of executive functioning. In premanifest HD, the impairment of visual-spatial executive function is seen as in manifest HD. Furthermore, in manifest HD the evidence for attention impairment is apparent, both in early and later stages.
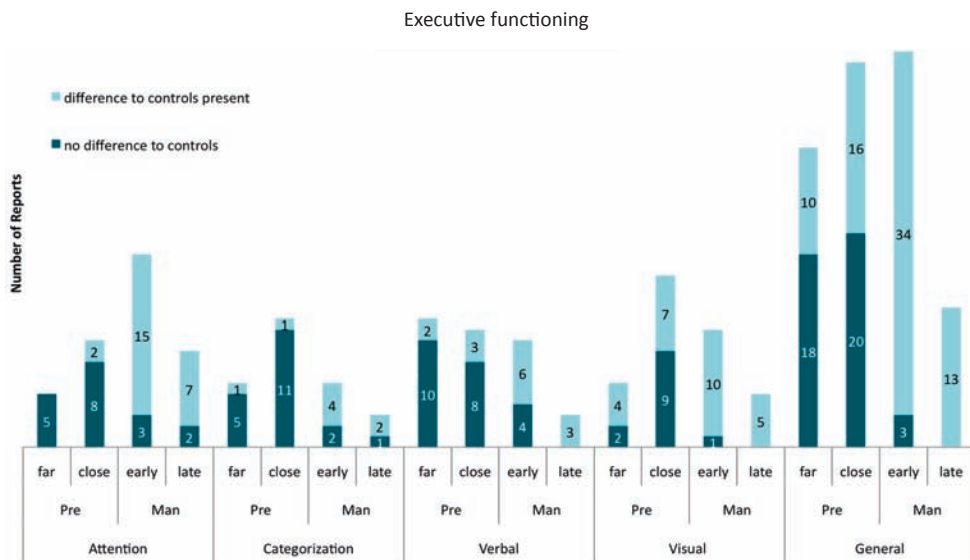

Figure 9. Executive functioning research divided into sub-domains. The number in each section of a bar represents the number of positive versus negative findings.

Global cognitive (dys)functioning

A number of different measures have been used to examine global cognitive functioning in both premanifest and manifest HD. The most commonly used have been the MMSE, various versions of the Wechsler Adult Intelligence Scale (WAIS), and the Mattis Dementia Rating Scale. More recently the National Adult Reading Test (NART) has been widely applied and, as an estimate of premorbid IQ, it is a very brief measure to administer as opposed to the many hours it can take to administer the WAIS or other IQ tests. These and other measures of multiple cognitive domains such as the Cambridge examination for mental disorders of the elderly (CAMCOG) have proven crucial in clinical settings for dementia screening purposes.

In patients with manifest HD the findings of impaired global functioning have been mixed (Figure 10). A number of studies clearly find differences between patients and controls[29,39,41,42,45,72,78,79,93]. However the stage at which this occurs is not yet entirely clear. It appears that there is less evidence for the early HD stage than there is evidence for the advanced HD group by both cross-sectional[114,115] as longitudinal design[38,41,45,47]. A study found poorer performance on the MMSE by HD patients. However, when the group was broken down into early and late HD, the early stage HD patients reached borderline significance and the result was mainly created by the late stage HD patients[115]. However, there is also evidence that these measures are not sensitive to change as reports of similar global cognitive functioning in manifest HD as controls are also available[93,107,110,116,123]. It must be noted however that of these reports, the majority are in early manifest HD. These reports of comparable functioning were also confirmed longitudinally by two studies[5,116].

As depicted in Figure 10, it does not seem as if measures of global cognitive functioning are sensitive to the subtle changes reported in premanifest HD but that, as the disease progresses in early and certainly later stages of HD, a broad deficit is measurable. As with the other domains different tests have been applied, and a clear sensitive measure is not apparent. Recently, a comparison study of the MMSE and the more recently developed Montreal Cognitive Assessment (MoCA) as screening tools for cognitive deficits in HD was performed. Both global cognitive functioning and subdomains of the two tests were examined in HD patients as compared to controls. Patients performed worse in every domain examined in at least one of the two tests, if not on both. The MoCa has the additional benefit to the MMSE in assessing the domains known to be affected, such as executive functioning. Overall on the basis of Reciever Operator Characteristic curves (ROC) the MoCA achieved higher sensitivity, and may be a better general screening measure due to its broader coverage of cognitive domains[72].
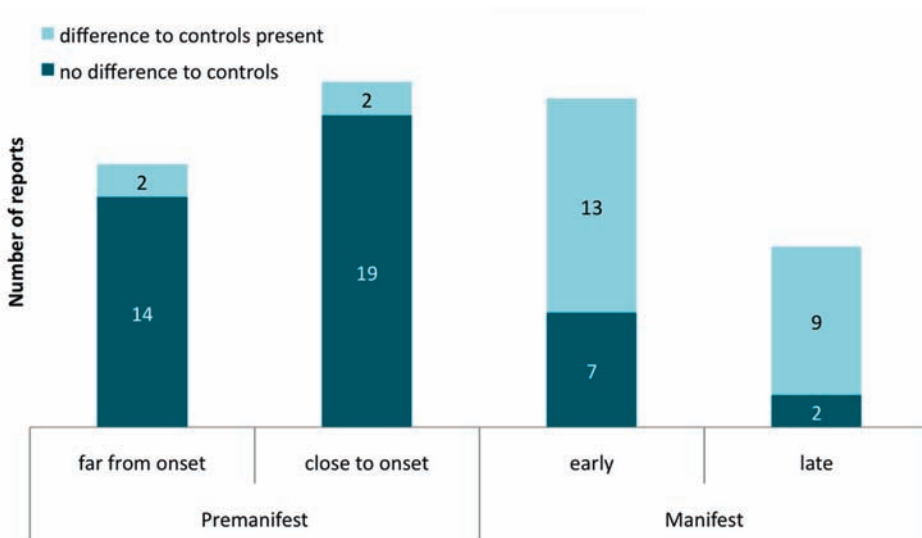
Global cognitive functioning

Figure 10. For the cognitive domain: Global cognitive functioning, the number of positive and negative findings over disease stages.

Findings in premanifest gene carriers were more homogeneous than those of the manifest groups. Overall the majority of studies did not find differences between premanifest HD and controls either cross-sectionally[42,50,58,60,61,66,93,95,110,123-126] or longitudinally[38,47,69,70,125].

A few reports do suggest changes in global functioning prior to disease onset, with such findings as premanifest gene carriers far from expected onset not being significantly worse than controls for global measures, but that premanifest gene carriers near to onset were worse[78]. The WAIS-R, for example, was used to assess the effect of proximity to disease onset on generalised measures of intelligence. Premanifest gene carriers close to onset (n=15) showed significantly lower total, performance and verbal IQ as opposed to healthy controls. Premanifest gene carriers far from onset only demonstrated lowered performance IQ. The authors regard these findings as support for a linear model of cognitive decline in premanifest HD, whereby not all functions decrease at the same time[49].

Discussion

This review aimed to provide information on the profile of cognitive functioning over the course of HD. Secondly we aimed to indicate which domains of functioning could provide the best candidate biomarkers for research purposes.

Amnesia/ memory

Memory deficits in premanifest HD are not clear cut, furthermore there is evidence that memory tests are susceptible to re-tests or learning effects[45]. More research is needed to confirm the presence of learning effects in memory tests, however if this is the case then such assessments are not suitable for tracking disease progression over time, both clinically or from a research point of view. Memory functions do seem impaired in manifest HD, and for this reason, memory functioning has been suggested as suitable state marker, namely a feature at some point during the course of the disease, rather than a trait marker, a feature present regardless of the course of the disease[33]. In terms of suitability of memory tasks for a biomarker of cognition in HD, the most promising candidate subdomain for delivering such as task seems to be working memory.

Aphasia /language

Language deficits in HD generally only occur after disease onset and are limited in their prevalence or severity. The literature on this subject has focused on many specific aspects of language functioning. This very specific approach indirectly demonstrates that global language deficits are not a main feature of the disease symptoms. For this reason language deficits do not seem to belong to the cognitive profile of HD. Furthermore, this domain does not seem to lend itself for application as a sensitive biomarker, especially not in premanifest gene carriers.

Psychomotor speed

Changes in psychomotor speed are suggested to be among the first changes in premanifest gene carriers, and this is regarded as support for the hypothesis that subtle cognitive changes occur 10 years or more prior to disease manifestation[6,49,50]. Furthermore cognitive slowing may be a good target for a cognitive biomarker. Evidence for this can be found in results from a large group of premanifest gene carriers that were compared to healthy controls on a battery of cognitive tests, which cross-sectionally revealed differences in tests of memory, executive function and psychomotor speed. The surprising element of these findings lays in the higher sensitivity of low demand cognitive tests, as opposed to more complex tests. These low demand tests all had a psychomotor timed element to them, which indicate suitability of such tests[52].

Emotion recognition

Diminished recognition of negative emotions can appear very early in the disease process, and may be pathologically linked to HD. Currently the most likely candidate for a cognitive biomarker is disgust recognition. However, due to the negative longitudinal findings over periods of three and twelve months, a longer longitudinal follow-up is desirable to understand the potential rate of change of this deficit and its suitability as a sensitive biomarker. The reports on this domain have examined in detail different emotions, so to further validate and understand this construct, gain could be achieved by combining

emotion recognition assessments and functional MRI scanning.

Executive (dys)functioning

Deficiencies in executive functions are part of the cognitive profile in HD, with some subtle changes detectable prior to motor onset of the disease. Executive functioning has also long been regarded as a good candidate biomarker for cognitive functioning in HD, however this statement may be too broad as not all reports of executive functioning showed difference to controls. The sudden rise in evidence for attention dysfunction in manifest HD as opposed to the lack of findings in premanifest HD may suggest that attention is an appropriately sensitive marker of disease state. Distinguishing between the subtypes of executive functioning may be vital in identifying the most appropriate biomarker. That this distinction may be important in premanifest HD was also noted by Lawrence *et al.*, (2000), who discussed that in depth analysis of visual and spatial functions may be relevant to understanding the early cognitive changes in HD[36]. Future research should focus on attention and visual sub-types of executive functioning as the other potential biomarker candidates.

Global cognitive (dys)functioning

The overall evidence for impairment in global functioning is not persuasive, with little to no evidence of impairment in premanifest HD, and with almost equal numbers of reports for and against the presence of a deficit in early manifest HD. For this reason it may be relevant to establish premorbid IQ levels from a clinical point of view at some point during diagnostic or treatment procedures, but not to measure IQ over several time points as the longitudinal evidence is insufficient. In our opinion such measures are not sensitive enough to be considered as a biomarker.

Limitations and considerations

Reviewing the cognitive literature was complicated by a number of issues, and some limitations have consequences for the conclusions drawn. The literature search was limited by the choice of search terms used. In compiling the figures we did not take into account size of the groups studied. However, in drawing our global conclusions, we did to some extent take into account the sample sizes and other methodological issues when appropriate. The study sizes discussed varied from numerous smaller studies with 10 or 15 participants and moderately sized studies of 30 to 100 participants to a limited number of studies with more than 500 subjects in a group. The increase in sample size positively affects the chance that significant differences between groups will be found. This is positive when trying to investigate subtle changes that may be overshadowed by inter-subject variability, however if a difference is demonstrated with a small study size this may indicate that the sensitivity of this deficit is very high. This same concept applies to the presence and length of follow-up studies. For successful biomarker evaluation longitudinal

assessment of the results is essential. However, how long should this follow-up ideally be? The longitudinal studies discussed in this review varied in length from three months to ten years. This issue could not entirely be taken into account when compiling the results or when drawing conclusions. This may have affected the conclusions drawn. However, there is no golden rule that can be followed as to under which circumstances we feel a deficit is proven. These differences in length of follow-up restrict the potential for attempting to understand in great detail the nature of cognitive changes in HD. However, this issue is not entirely restrictive as the presence of positive findings from studies of all sizes has allowed us to draw conclusions on important functional domains as well as general assumptions on when the deficits become apparent or seem to be most prominent.

A further problem was posed by the manner in which groups were defined. Although all studies based their disease assessment on the absence or presence of motor symptoms, there was large variation in how 'motor symptoms' were defined. Some reports did not specify how this was determined. Others defined premanifest HD in a varied manner either using a definition of low Total Motor scores on the UHDRS with predefined cut-off points to the use of diagnostic confidence ratings[97], also with different cut-off points. In this review we have approached the findings based on the manner in which the authors describe the groups. However this can potentially seriously impact the conclusions drawn in regards to the stage at which a deficit is present. This variability makes it complicated to interpret numerous findings, and therefore it would be advisable for the HD research community to construct guidelines for study design, so that future communications are directly comparable.

Reports of dysfunction in a particular cognitive domain may be clouded or over-reported due to the majority of papers only investigating sub-domains of a function, this was taken into account as much as possible but it remains challenging to draw global conclusions. Furthermore, in the later disease stages, other disease aspects can have great impact on test performance. Such results can be confounded by medication, severe movement disorder, behavioural issues and other functional limitations. Depression, apathy and anxiety, as some of the most frequently occurring (30-60%) behavioural issues, and these can directly effect motivation and test performance, as well as the treatment given for such conditions[127,128]. It was not possible to take all this into account when comparing results.

Highly sensitive measurement techniques have proven useful in the detection of early changes. Devices such as oculomotor eye trackers have been used to register responses in a memory task in premanifest HD and found that these outcomes measures were sensitive to subtle differences to controls[69] Furthermore, although performance on memory tasks was not different between premanifest gene carriers and controls, measurement by EEG

recording[63] and fMRI scanning[68] did show differences in brain reactions using memory tasks. For this reason it is advisable, where possible, to make use of such technological enhancements. The use of physiologically based measurement tools such as MRI in combination with cognitive assessments may prove most sensitive. This is especially so when investigating the subtle changes associated with premanifest HD, because the results are then supported by other objectively quantified measures with known correlations to brain changes in HD.

Despite its limitations, this review also has its strengths, which lie in the comprehensive nature of the study and the objective assessment of the articles. Furthermore this review tries to discuss both the division of disease stage according to premanifest and manifest, but also their subdivision, in an attempt to provide information on the staging of deficits. Prior to this review no single paper had addressed cognitive functioning in all disease stages. The strict selection criteria imposed on the papers included allow for conclusions to be drawn that can have relevance from both a clinical and scientific point of view.

Conclusions

Drawing conclusions for clinical purposes from research papers should be approached cautiously. The results and conclusions discussed above are based on group differences and can never be projected onto a personal basis without considering the individual at hand. Having said this, the overall profile of cognitive disorder in HD can be summarised as follows. In premanifest gene carriers there are typically no to little deficiencies in memory, language or global cognitive functions. Differences can be found in tasks assessing the functions of psychomotor speed, negative emotion recognition, and to some degree in executive functioning. In manifest HD adequate functioning appears to remain intact for the longest periods for language and global functional domains, however as a result of the progressing cognitive decline resulting in dementia, during end stage HD, these functions can also show marked deterioration. During the progression of the disease, impairments can be expected in memory (especially visuo-spatial), psychomotor speed, negative emotion recognition, and executive functioning. For this reason we suggest that these four functional (sub)domains should be recognised when clinically diagnosing substantial cognitive decline or dementia due to Huntington's Disease.

The most promising domains and sub-domains for providing a cognitive biomarker appear to be working memory, measures of psychomotor speed, recognition of negative emotions (in particular disgust), attention and executive functions, because measures of these functions seem to detect early changes that progress during the disease. Having said this, the importance of longitudinal investigation of such candidates must be reiterated. A biomarker will only prove useful when it is sensitive to change over time, preferably not only in manifest but also in premanifest HD.

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