A Meta-Analytic Review of Verbal Fluency Deficits in Huntington's Disease

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Abstract

A meta-analysis of 30 studies with 1511 participants was conducted to estimate and compare the magnitude of deficits upon tests of phonemic and semantic fluency for patients with Huntington's Disease (HD) relative to healthy controls. As has been found for patients with focal frontal cortical lesions (but not for patients with focal temporal cortical lesions), symptomatic HD patients were comparably impaired on tests of phonemic and semantic fluency (rs = .71 and .73, respectively). However, in contrast to patients with focal frontal lobe injuries, fluency deficits did not qualify as differential deficits relative to verbal intelligence or psychomotor speed. Therefore, for patients with HD, deficits on tests of phonemic and semantic fluency do not appear to reflect executive dysfunction, but a more generalised cognitive impairment.

Introduction

Whilst impairment in many cognitive domains has been documented in Huntington's disease (HD, see; Brandt, 1991) a very prominent view is that executive deficits characteristic of prefrontal dysfunction are a particularly striking feature of the disorder (Brandt, Bylsma, Aylward, Rothlind, & Gow, 1995; Caine, Hunt, Weingartner, & Ebert, 1978; Rosser & Hodges, 1994; Watkins et al., 2000). Consistent with this perspective, HD patients often perform poorly on tests designed to capture executive dysfunction, such as the Wisconsin Card Sorting Test (WCST; Rebok, Bylsma, Keyl, Brandt, & Folstein, 1995) tests of verbal fluency (Rosser & Hodges, 1994) and the Stroop interference test (Hanes, Andrewes, Pantelis, & Chiu, 1996). Moreover, clinical observation and patient and carer reports have been interpreted as revealing a behavioural picture similar to that seen following frontal lesions (Caine et al., 1978), whilst neuropathologically HD is associated with subcortico-frontal abnormalities (Cummings, 1993). Since executive processes are presumed to rely heavily upon the intact functions of frontal structures (see, e.g.; Shallice, 1988; Stuss & Benson, 1986) the presence of frontal abnormalities would therefore suggest that deficits in this aspect of cognition should be especially marked.

However, it has been argued that although there is a great deal of anecdotal evidence that HD represents a dysexecutive syndrome, actual empirical support for this perspective is surprisingly sparse (Lawrence et al., 1998). Since fronto-executive hypotheses have been offered to account for the cognitive and behavioural disturbances seen in a vast array of neurological and psychiatric disorders, in addition to HD, rigorous standards of proof must be applied when evaluating these hypotheses. Thus, since HD is characterised by multiple neurocognitive impairments, including deficits not associated with prefrontal dysfunction (Brandt, 1991), confirmation of a deficit on an executive task

would, in isolation, provide only limited support for an executive hypothesis. Instead, it must be shown that the executive deficit is in excess of the averaged performance deficit across a range of other cognitive tasks that are not considered to impose heavy executive demands (Laws, 1999; Miller, 1984).

Verbal fluency deficits in HD

To address whether HD is particularly characterised by executive dysfunction, performance on tests of verbal fluency has been studied extensively. For phonemic fluency participants are asked to generate as many words as possible beginning with a specified letter (e.g. F), while for semantic fluency search is constrained by a specified category (e.g. animals). Rosser and Hodges (1994) argue that identical executive processes are involved in the initiation and monitoring of both of these tasks, and in a recent meta-analytic review Henry and Crawford (in press-c) found quantitative support for this perspective. Whilst it is important to avoid conflating anatomy and cognition, as noted earlier, there is a great deal of evidence that executive processes are particularly dependent upon frontal cortical structures. Thus, since Henry and Crawford (in press-c) found that focal frontal lobe injuries were associated with large but equivalent phonemic and semantic fluency deficits ($\underline{r}$s = .52 and .54 respectively), this suggests that the two types of task impose equivalent demands upon executive control processes. However, Henry and Crawford (in press-c) found that, relative to patients with focal frontal lesions, semantic fluency was more impaired following focal temporal damage ($\underline{r}$ = .61), and this deficit was substantially larger than the corresponding phonemic fluency deficit ($\underline{r}$ = .44). Since there is a great deal of evidence that temporal structures are the neural substrates particularly responsible for semantic memory (see; Fink & Randolph, 1998), this was presumed to reflect the greater reliance of semantic fluency upon the integrity of semantic memory.

The finding that performance on tests of phonemic and semantic fluency is often equivalently impaired in HD (see; Monsch et al., 1994; Suhr & Jones, 1998) has been argued to constitute strong evidence that the disorder is particularly characterised by executive dysfunction, such as deficits in initiation and retrieval (Rosser & Hodges, 1994). However, discrepancies have been reported. Indeed, in the only meta-analytic review to date that has quantified the magnitude of the neurocognitive deficits associated with HD (Zakzanis, 1998) it was found that the deficit for semantic fluency was larger than the deficit for phonemic fluency (expressed as Cohen's d, the effect sizes were -2.49 versus -2.13, respectively).

Moreover, it remains unclear whether for HD patients, as has been found for frontal patients, the deficit in verbal fluency qualifies as a differential deficit relative to current VIQ and psychomotor speed. Indeed, for other neurological and psychiatric groups such as focal non-frontal lesions, depression, schizophrenia and Parkinson's disease, it has been found using meta-analytic techniques that whilst a prominent verbal fluency deficit is present, these deficits do not qualify as differential deficits relative to psychomotor speed and/or verbal intelligence (Henry & Crawford, in press-a, in press-b, in press-c, in press-e). Only for patients that have sustained a traumatic brain injury (TBI) has a pattern of deficits across tests of fluency, VIQ and psychomotor speed been found that parallels the pattern associated with focal frontal lesions. That is, for patients with TBI there is also evidence of a differential fluency deficit (Henry & Crawford, in press-d).

In relation to HD, in Zakzanis's (1998) meta-analytic review, the data in this regard were not particularly clear. Whilst the deficits for phonemic and semantic fluency (ds = -2.13 and –2.49, respectively) were larger than deficits upon measures of psychomotor speed (the Trail Making Test Part A; d = 1.92) and verbal intelligence (WAIS-R VIQ; d = -1.52), the deficits for a measure of general intelligence (WAIS-R Full scale; d = -2.08),

and a different measure of psychomotor speed (Digit Symbol; d = -2.03) were only marginally smaller than the deficit upon phonemic fluency, and were larger than deficits upon other executive measures, such as the Tower of London, Stroop interference and WCST perseverative errors (ds = 1.90, -1.87 and 1.42, respectively).

Moreover, interpretation of Zakzanis's (1998) results is complicated by the methodology that was used, as there may have been substantive differences between the studies that quantified each of the mean effects. For instance, whilst five studies contributed to the mean effect for phonemic fluency, three contributed to the mean effect for Stroop interference; there may have been little or no overlap between the studies contributing to each of these statistics, and consequently little or no overlap in terms of the participants sampled. This methodology is problematic since it is likely that there are substantive differences between patients with HD, such as in the severity of the dementia. Thus, when assessing whether a deficit upon one measure is larger than a deficit upon another, it is important that the same participants contribute to both the measures of interest to 'control' for any potential differences between patients; this methodology will be used in the present analyses. It is also important to note that in the present analyses a substantially larger number of studies contribute to the mean effects for both phonemic and semantic fluency than in Zakzanis's (1998) meta-analysis.

Alzheimer's versus Hungtington's Dementias

Standard clinical dementia batteries are now capable of identifying distinct neurocognitive profiles that differentiate dementia of the Alzheimer's type (DAT) from HD. However, it has been suggested that tests of phonemic and semantic fluency may also be of use in distinguishing between these two types of dementia (Rosser & Hodges, 1994), and this may be of particular clinical interest given their brevity and widespread use. A

common assertion is that whilst ‘cortical’ dementias such as DAT are typified by a pattern of worse semantic relative to phonemic fluency performance, ‘sub-cortical’ dementias such as Huntington’s and Parkinson’s disease (PD) are characterised by a pattern of comparable impairment upon the two types of fluency (Hodges, Salmon, & Butters, 1990; Rosser & Hodges, 1994). However, not all studies have found evidence consistent with this perspective. In a comparison of mildly demented patients with DAT, HD and PD, for example, Suhr and Jones (1998) reported equivalent deficits on phonemic and semantic fluency in all three groups. In the present study we will compare the relative prominence of deficits upon tests of phonemic and semantic fluency for patients with HD with the results found for studies involving DAT.

Cognitive dysfunction in pre-clinical HD

It also remains unclear whether there is pre-clinical cognitive dysfunction in Huntington's disease. As Lawrence et al. (1998) point out, this issue is far from being resolved, with some studies reporting evidence of pre-clinical cognitive impairment (de Boo et al., 1997), and others failing to find any difference between mutation-positive and mutation-negative participants (Blackmore, Simpson, & Crawford, 1995). Identifying a possible prodromal phase in HD where subtle but detectable behavioural and cognitive difficulties can be detected is of extreme importance to the gene carrier, and may have therapeutic implications. In the present study we will explore the possibility that deficits in phonemic and semantic fluency are associated with pre-clinical HD by quantifying mean effects for each of these measures.

Aims of the current meta-analysis

The first aim was to derive effect size estimates for phonemic and semantic fluency for patients with HD relative to healthy controls. This will be the first meta-analysis to compare the magnitude of deficits on these measures whilst ensuring exactly the same studies contribute to each, and will therefore permit an extremely rigorous assessment of whether the verbal fluency deficit associated with HD predominantly reflects executive dysfunction, or problems with semantic memory (Henry & Crawford, in press-c).

However, as noted, the presence of a deficit on a test of phonemic or semantic fluency does not by itself provide evidence of executive or semantic memory dysfunction, respectively; it may instead, reflect a general verbal impairment, or psychomotor slowing. Thus, the second aim was to estimate effect sizes for other cognitive measures in order to provide comparison standards, and thus assess to what extent fluency deficits in HD qualify as differential deficits. Premorbid intelligence as estimated by the National Adult Reading Test (NART; Nelson, 1982) and the reading sub-test of the Wide Range Achievement Test (WRAT; Jastak & Wilkinson, 1984) was included to address the possibility that if a fluency deficit is present, it reflects the fact that patients with HD have not been successfully matched to their controls for premorbid ability. It is also important to address the possibility that fluency deficits simply reflect a current generalised verbal dysfunction (see; Miller, 1984). Therefore the magnitude of the deficits on verbal fluency will be compared to the deficits on the Verbal and Full Scale IQs of the Wechsler Adult Intelligence Scales (Wechsler, 1955; 1981) to determine if the former qualifies as a differential deficit.

It will also be investigated whether deficits on tests of phonemic fluency are in excess of deficits on the WAIS Digit Symbol test (Wechsler, 1955; 1981), a widely used measure of psychomotor speed. This will address the possibility that deficits on tests of

verbal fluency reflect the presence of bradyphrenia (i.e. a generalised reduction in cognitive speed) rather than executive dysfunction. Performance on tests of phonemic and semantic fluency will also be compared with the Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983) as confrontation naming is considered to be very sensitive to the integrity of semantic memory (Hart, 1988) yet imposes only minimal demands upon effortful retrieval and cognitive speed.

For executive functioning, performance on categories completed and perseverative errors on the WCST (WCST CC and WCST PE respectively; Heaton, 1981) and the interference condition of the Stroop (Golden, 1978) will be recorded. A comparison of phonemic and semantic fluency with these other putative measures of executive function will be extremely informative both with respect to their convergent validity, as well as their relative sensitivity to the presence of HD.

The third aim is to compare the relative prominence of phonemic and semantic fluency deficits in HD with the corresponding statistics for patients with DAT by comparing data from the present analyses with data taken from an independent meta-analysis (Henry et al., in press). Finally, the fourth aim is to quantify the mean effects for phonemic and semantic fluency for pre-symptomatic and symptomatic HD gene-carriers.

Method

Sample of studies

A computer-based search involving the Web of Science, Psych Lit CD-ROM, and Science Direct databases was undertaken, using the following terms as search parameters; 'letter fluency', 'FAS', 'semantic fluency', 'category fluency', 'controlled oral word association', 'COWA(T)', 'word fluency' 'verbal fluency', 'oral fluency', 'phonemic fluency', 'executive test' and 'frontal test'. A manual search of most issues published after 1969 of the

following journals was also undertaken: Neuropsychology, Brain, Neuropsychologia, The Journal of the International Neuropsychological Society, The Clinical Neuropsychologist, Neuropsychiatry Neuropsychology and Behavioural Neurology, Journal of Neuropsychiatry and Clinical Neurosciences, the Journal of Clinical and Experimental Neuropsychology. It is recommended that a manual search be conducted in addition to a computer-based search (Cooper, 1985; Green & Hall, 1984). As Green and Hall (1984) point out, despite its apparent cost in time, this is often a very effective manner of searching, and may yield additional studies not found via other methods of search. This is particularly true in the present study, as tests of verbal fluency are so routinely administered, often in conjunction with a large number of other neuropsychological tests, they may not be referred to in the title, abstract or keywords. This means that a purely computer-based search will not identify many articles that are eligible for inclusion. The search was completed in December 2002.

The inclusion criteria were firstly that the patient group had to consist entirely of adults with diagnoses of HD; all pre-symptomatic patients had to have undergone genetic testing, and test positive for the Huntington's disease mutation. For the vast majority of studies that included symptomatic patients diagnosis was made by a neurologist on the basis of a positive family history, the presence of choreiform movements, and/or genetic testing. In addition, the study had to include a healthy control group free from neurological or psychiatric disease, and a measure of phonemic and/or semantic fluency. Effect size estimates for premorbid IQ, current VIQ, current FSIQ, Digit Symbol, BNT, WCST CC, WCST PE and Stroop were derived from studies that also reported verbal fluency results. For inclusion, the study must also have presented precise statistics convertible to effect size r; thus, studies in which fluency data was derived from graphical information or imprecise p-values were excluded (Butters, Sax, Montgomery, & Tarlow,

1978; Hodges et al., 1990; Randolph, Braun, Goldberg, & Chase, 1993). It should be noted that it was possible to include Snowden, Craufurd, Thompson and Neary's (2002) article in these analyses even though it did not provide precise statistics convertible to effect size r because Dr Snowden very kindly provided us with the extra information we required. Finally, studies also had to have been published in English in a journal.

Statistical analysis

Meta-analysis is a rigorous, quantitative alternative to the traditional review process, as it involves statistical integration of results. The basis of this methodology is the effect size, a standardised statistic that quantifies the magnitude of an effect. In the present study the effect size r was used, which corresponds to the degree of correlation between group membership (i.e. presence or absence of HD), and performance on the cognitive measure of interest. For each construct, effects were pooled to derive an estimate of the mean, with each effect weighted for sample size to correct for sampling error. To do so, the random effects meta-analytic model (Shadish & Haddock, 1994) was selected in preference to the more commonly used fixed effects model as it yields more generalisable parameter estimates. This is because, in the fixed effects model, the mean is presumed to reflect a common underlying effect parameter that gives rise to the sample observations. However, in the random effects model the mean represents a hyperparameter, as it allows for substantive differences beyond sampling error that differentiate the effects contributing to each respective mean (Raudenbush, 1994). Statistically, the crucial difference between these methodologies is in the calculation of standard errors and confidence intervals, which for the random effects model are typically larger. The National Research Council (1992) argues that the fixed effects model should be the exception rather than the rule, as it may lead to inappropriately strong conclusions.

To estimate the degree of heterogeneity of the effects contributing to each mean, the homogeneity statistic Q and the random effects variance (σ_θ^2) were estimated, as well as the SD of random effects, and the 95% confidence intervals (CI) within which random effects can be expected to fall. Q quantifies within-group heterogeneity (i.e. the degree to which the effects contributing to each respective mean can be regarded as homogenous). If the Q statistic associated with a mean effect is significant, this suggests that there are substantive differences between the effects contributing to that particular mean. In contrast, a non-significant estimate of Q suggests that once sampling error has been removed, no substantive differences between the effects contributing to the respective mean in question remain (i.e. the null hypothesis of homogeneity of effects cannot be rejected).

It was also important to test whether the difference in the magnitude of mean effects between phonemic versus semantic fluency, was statistically significant. However, there is no agreed upon method for statistically comparing mean effects using the random effects meta-analytic model. A particular difficulty is whether the degrees of freedom (df) in such analyses should be based on N (the number of participants) or K (the number of groups of participants). In the present work, t-tests were computed using the more conservative K as the df. It should be noted that only for the phonemic-semantic comparison were inferential statistics applied as for the other comparisons of interest, K ranged from between two and nine, and thus had low statistical power.

Since dementia severity will moderate the magnitude of deficits across individual studies, for each comparison, only studies that assessed both types of fluency were included. For example, although in total 27 independent groups of HD patients were assessed on phonemic fluency, and 17 on semantic fluency, since only 13 were assessed on both phonemic and semantic fluency, when comparing phonemic and semantic fluency, only data from these 13 groups were permitted to contribute to the analyses. This

effectively 'controls' for the effect of illness severity (i.e. it is exactly the same participants being compared upon each of the measures of interest). Mean effects were also calculated for each of the non-fluency variables identified (premorbid IQ, VIQ, FSIQ, Digit Symbol, BNT, WCST CC, WCST PE and Stroop) and compared with the corresponding effects for phonemic and semantic fluency. Again, to ensure that severity was controlled for, only studies that assessed both the fluency and non-fluency variable of interest were included in each comparison.

Finally, the null hypothesis that the mean effect size is zero was tested with the statistic Z; if the value of Z exceeds 1.96, this indicates that the mean effect differs significantly from zero at the .05 level. To interpret how important a particular effect was in practical terms, Cohen's (1977) guidelines were adopted. These suggest that a correlation of .1 should be regarded as representing a small effect, .3 as medium, and .5 as large. In addition, squares of the effect size multiplied by 100 were also presented as these latter quantities represent the percentage of the variance accounted for (PVAF) on a measure of interest by group membership (i.e. the presence of HD versus being a member of the healthy adult population).

Results

Participant characteristics

Thirty research articles published between 1986 and 2002 contributed to the present study. In total data from 727 HD patients and 784 controls were included in these research articles. Supplementary information, including a complete list of the papers included in this meta-analysis, can be found by following the link at http://www.abdn.ac.uk/~psy299/dept/. Patients and controls were closely matched for age (M = 43.6, SD = 7.28 versus M = 43.7, SD = 8.72 respectively) and gender (45.4% versus 44.9% male, respectively). Although on average patients received only half a year of education less than controls (M = 12.7, SD =

1.69 versus M = 13.2, SD = 1.71, respectively), this difference attained significance (t = 2.20, df = 21, p = .039).

Effect sizes for patients with HD relative to healthy elderly

[TABLE 1 ABOUT HERE]

Table 1 presents estimates of the weighted mean effects for phonemic and semantic fluency, their variability, and practical importance for symptomatic HD patients. Estimates of the weighted medians are also presented, as these statistics are more robust to the presence of outliers than mean values. For the mean and median effects, a positive sign indicates that patients have performed worse than controls. In the upper half of the table, mean effects are presented which have been calculated from any studies that included phonemic or semantic fluency (all studies). It can be seen that both these mean effects are significantly different from zero ($p < .01$), and in terms of practical importance as indexed by the PVAF, large in magnitude. However, for semantic fluency the mean effect ($r = .73$) is larger than for phonemic fluency ($r = .67$). For both mean effects estimates of Q are highly significant ($ps < .01$), reflecting the heterogeneous nature of the disorder. To avoid any potential confusion, it should be noted that these effect sizes differ from those presented in the abstract and elsewhere as the latter effect sizes are based on studies that included both phonemic and semantic fluency, whereas the former effects were based on any studies that included phonemic and/or semantic fluency.

It can be seen in Table 1 that when only groups of participants that assess both phonemic and semantic fluency measures are included in the analyses ($K = 13$), the deficit for semantic fluency is only marginally larger than the deficit for phonemic fluency ($rs = .73$ versus .71, respectively); this difference did not prove significant ($t = 0.31$, $df = 12$, $p = .76$).

Phonemic and semantic fluency deficits relative to other cognitive deficits

Table 2 presents estimates of the mean effects, their variability, and practical importance for premorbid IQ, current VIQ, FSIQ, Digit Symbol, BNT, WCST CC, WCST PE, and Stroop interference; these mean effects were calculated using only those studies that included the particular measure of interest in addition to phonemic or semantic fluency. Thus, it can be seen that for each measure, the mean effects for phonemic fluency have been re-calculated to ensure comparisons are fair (these effect sizes appear in the last column of Table 2). As noted previously, this methodology ensures that exactly the same participants are contributing to the mean effects for the two variables being compared. This was particularly important since it was found that the PVAF by phonemic and semantic fluency were both significantly and substantially negatively correlated with dementia severity as indexed by the Dementia Rating Scale (DRS; Mattis, 1988) indicating that as dementia severity increases, deficits upon the tests of fluency increase in magnitude; for phonemic fluency the correlation with the DRS was, $r = -.70$, $K = 10$, $p = .023$, for semantic fluency the corresponding correlation was, $r = -.85$, $K = 8$, $p = .007$.

[TABLE 2 ABOUT HERE]

Thus, it can be seen in Table 2 that for each non-fluency measure, for instance premorbid intelligence, two mean effects have been calculated; one for studies that also assess phonemic fluency ($r = .19$; $K = 3$), and one for studies that also assess semantic fluency ($r = -.02$, $K = 2$). Each fluency mean effect was also re-calculated for these comparisons. All mean effects with the exception of those for premorbid intelligence were significant, and six of the fifteen mean effects were associated with significant heterogeneity as indexed by Q ($p < .05$).

The effect sizes for both phonemic and semantic fluency are substantially in excess of the effect sizes for premorbid verbal intelligence (rs = .51 versus .19 for phonemic

fluency versus premorbid IQ; rs = .57 versus -.02 for semantic fluency versus premorbid IQ). However, there is no evidence that phonemic fluency is disproportionately impaired relative to either current VIQ or FSIQ (rs = .65 versus .63 for phonemic fluency versus VIQ; rs = .68 versus .68 for phonemic fluency versus FSIQ). Moreover, with respect to the measure of psychomotor speed (Digit Symbol), both the phonemic and semantic fluency deficits are of a smaller magnitude.

Finally, it can also been seen that phonemic fluency deficits are of a larger magnitude relative to the BNT, WCST CC and WCST PE, but the Stroop interference is slightly more sensitive to the presence of HD. Semantic fluency is more impaired than both the BNT, and the Stroop interference test.

Phonemic and Semantic Fluency Deficits for Patients with HD Relative to DAT

Presented in Table 3 are the mean effects for phonemic and semantic fluency for patients with symptomatic HD and DAT (DAT data taken from; Henry et al., in press). It can be seen that whilst for patients with DAT, the semantic fluency deficit is of an identical magnitude to the corresponding deficit for symptomatic patients with HD (r = .73), the phonemic fluency deficit is substantially smaller for DAT patients (rs = .57 versus .71 respectively).

[TABLE 3 ABOUT HERE]

Phonemic and semantic fluency deficits for pre-symptomatic HD patients

In Table 3 mean effects for phonemic and semantic fluency are also presented for pre-symptomatic patients with HD. It can be seen that there is evidence of a slight deficit for measures of phonemic and semantic fluency even in the pre-clinical stage of the disorder, but these are small in magnitude (rs = .12 versus .17 respectively). However, in

terms of the PVAF, the semantic fluency deficit is over twice as large as the phonemic fluency deficit for patients in the pre-clinical stage of the disease.

It is of interest that for symptomatic HD patients, the difference in terms of the PVAF between phonemic and semantic fluency is substantially (although not significantly) positively correlated with dementia severity as indexed by the DRS (r = .62, K = 7, p = .140). This suggests that the higher the score on the DRS (i.e. the less demented the patient is), the larger the difference between phonemic and semantic fluency.

Assessing the possibility of publication bias

A number of validity threats have been identified that may lead to imprecise conclusions in both non-quantitative and meta-analytic reviews. Particularly problematic is 'the file drawer problem' which refers to the fact that significant results are more likely to be published than non-significant results (Easterbrook, Berlin, Gopalan, & Mathews, 1991). To assess whether this bias posed a threat to the results of the present study, funnel plot diagrams were constructed for each of the fluency and non-fluency measures of interest. In these diagrams, sample size is plotted against the corresponding study-level effect; if statistically non-significant results have been discriminated against, there should be a relative absence of studies with small sample sizes that report weak effects. For none of the variables was there evidence of this bias operating.

Discussion

Verbal Fluency Deficits in HD

A prominent view in the literature is that HD should be regarded as a disorder particularly characterised by fronto-executive dysfunction (Caine et al., 1978; Watkins et al., 2000) and the pattern of comparable impairment upon tests of phonemic and semantic

fluency that is often reported has been regarded as evidence consistent with this possibility (Rosser & Hodges, 1994). However, when mean effects were calculated for phonemic and semantic fluency including all studies that assessed either of these measures, it was found that the semantic fluency deficit was the notably larger of the two (rs = .73 versus .67, respectively), as was found in an earlier meta-analytic review by Zakzanis (1998).

However, as noted earlier, it is important that the patients contributing to the mean effect for semantic fluency do not differ from the patients contributing to the mean for phonemic fluency, if comparisons between these two measures are to be fair. This rules out, for instance, the possibility that the group of patients contributing to the mean for the former are more severely demented than those contributing to the mean for the latter. When mean effects were re-calculated in the present study using a more rigorous methodology based only on studies that had assessed both phonemic and semantic fluency, it was found that there was virtually no difference in the relative sensitivity of the two measures to the presence of HD (rs = .71 and .73 for phonemic and semantic fluency, respectively).

Evidence for a Differential Executive Deficit in HD?

As discussed previously, a pattern of comparable impairment upon tests of phonemic and semantic fluency for patients with HD may reflect executive dysfunction if verbal fluency deficits qualify as differential deficits relative to verbal intelligence and psychomotor speed. In the present study, this pattern of results was not found. Although the fluency deficits did not simply reflect a failure to match patients and controls upon premorbid verbal IQ, they were virtually identical in magnitude to those observed for current VIQ and FSIQ. Both phonemic and semantic fluency were also substantially less impaired than Digit Symbol, a measure of psychomotor speed. It is of interest that in a

meta-analytic review of verbal fluency deficits in PD it was also found that, relative to Digit Symbol, neither phonemic nor semantic fluency were disproportionately impaired (Henry & Crawford, in press-e). As in that study, conclusions must be cautious given that very few studies contributed to the analyses involving Digit Symbol, but these results are at least consistent with the possibility that for patients with sub-cortical dementias such as HD and PD bradyphrenia or cognitive slowing may partially underlie fluency deficits.

There is a great deal of evidence that VIQ is a strong predictor of fluency performance and that fluency tasks impose substantial demands upon both language abilities and psychomotor speed (see; Salthouse, Atkinson, & Berish, 2003). Thus for some patient groups, fluency deficits may not primarily reflect executive dysfunction, but instead verbal or motor speed problems. Since fluency tests (like all cognitive measures) are multifactorial, deficits across different patient groups may not reflect the same underlying cognitive impairment (see; Miller, 1984). Thus, we would argue that it is the relative magnitude of deficits that is important. Where deficits on tests of fluency exceed deficits on verbal ability and psychomotor speed (as we have found to be the case for both patients with focal frontal cortical lesions as well as patients with traumatic brain injury (Henry & Crawford, in press-c, in press-d), this would be consistent with the possibility that the cognitive impairment underlying the fluency deficit may be executive dysfunction.

Given that HD is characterised by multiple neurocognitive impairments, deficits of verbal intelligence and motor speed would be expected. The evidence presented here for patients with HD shows that the fluency deficits are not differentially larger in magnitude than deficits in verbal intelligence or speed, suggesting that fluency deficits in HD may stem not primarily from executive dysfunction, but slowed cognitive processing speed and/or a deficit in verbal ability. Thus, although patients with focal frontal injuries and HD may be similar in that they exhibit equivalent deficits across measures of phonemic and

semantic fluency, the impairment underlying these fluency deficits appears to differ across these patient groups. We would suggest that only for the former group do fluency deficits primarily reflect executive dysfunction.

However, it should be noted that VIQ as measured by the WAIS may also impose some limited demands upon executive processes. It is often argued that the WAIS is relatively insensitive to the effects of prefrontal dysfunction (Dempster, 1992; Lezak, 1995; Stuss & Benson, 1986). However, others have argued that the insensitivity of the WAIS to prefrontal dysfunction may have been exaggerated (Parker & Crawford, 1992; Shallice, 1988). Nevertheless, the present rationale does not require that the WAIS be entirely insensitive; simply that it is less sensitive than validated executive tasks.

It could also be argued that a differential deficit in executive functioning does exist in HD but that the fluency tests were not sensitive enough to expose this; i.e. other executive measures may reveal such a deficit. Two facts argue against this alternative interpretation; a very substantial differential deficit on fluency relative to IQ is observed following focal frontal lesions (Henry & Crawford, in press-c) and TBI (Henry & Crawford, in press-d), and furthermore, in the present study phonemic fluency was much more sensitive to the presence of HD than the WCST, a widely used alternative measure of executive functioning.

Deficits as a Function of Semantic Fluency Category Type

It has been suggested that the retrieval demands of semantic fluency tasks may vary according to the semantic category involved, and in particular, a distinction has been made between broad semantic categories such as supermarket items and more constrained semantic categories such as fruits and vegetables (Randolph et al., 1993), with the latter thought to impose lower demands upon effortful retrieval processes. Thus, the

neurocognitive demands of some semantic fluency tasks may be more or less similar to phonemic fluency tasks, depending on the categories involved. Whilst it would be of considerable interest to quantify the effect sizes for each of the different types of categories, this in practice is not possible from the information provided in the primary studies. For the vast majority of studies that measure semantic fluency, the 'animal fluency' category is employed, either on its own, or as part of a larger group of categories. None of the studies that assessed more than one type of semantic fluency reported scores for each of the categories individually. Exploring whether the type of phonemic fluency that is used moderates the magnitude of the deficit is also not possible given that the vast majority of studies employ the variant 'FAS'. However, the possibility that the variant of phonemic or semantic fluency used moderates the magnitude of the deficit in HD should be investigated in future primary research.

Sources of heterogeneity in HD

For many of the variables assessed in the present study, the homogeneity statistic Q was significant. Since corrections had been implemented for sampling error, (the most serious source of artefactual variance; Hunter, Schmidt, & Jackson, 1982), this suggests that substantive differences between studies remain. For the majority of these mean effects, the significant heterogeneity observed cannot be attributed to the presence of a few extreme values as only two outliers were identified in the present study. Since exclusion of these outliers did not alter the basic pattern of results observed, they were retained.

Nevertheless, it is clear that there is considerable heterogeneity in the effects contributing to many of the mean effects. The magnitude of the heterogeneity observed for many of the mean effects reinforces the importance of adopting conservative meta-analytic methodology of the type used in the present study. As noted earlier, if two measures are to

be compared fairly, it is important that the patients contributing to the mean effect for one do not differ from the patients contributing to the other. In the present meta-analysis, a very obvious source of heterogeneity across studies is likely to be dementia status, as the patients contributing to the present meta-analysis varied markedly in this regard. As noted, both phonemic and semantic fluency were very significantly, and substantially correlated with dementia severity as indexed by the DRS (rs = -.70 and -.85, respectively).

However, it is likely that in addition to dementia severity there are other important moderators of these effects; it has, for instance, been suggested that age of onset (Gomez-Tortosa et al., 1998) may moderate the magnitude of cognitive deficits observed. Unfortunately, it was not possible to explore the influence of other such potential moderators in the present study as very few studies presented the prerequisite data. However, the degree of heterogeneity identified in the present study very strongly points to the importance of exploring the influence of such variables in future primary research. Thus, whilst in general patients with HD should be comparably impaired on semantic and phonemic fluency, for certain sub-groups this may not be the case.

It is, of course, also possible that the large Q values observed at least partially reflects heterogeneity across the controls sampled. It may, for instance, reflect differences in matching controls to HD participants across demographic variables such as age, education or gender. A review of the control profiles, however, suggests that this is unlikely to be the case. In virtually all the studies HD patients and controls were matched across most, if not all of these demographic variables. On the few occasions where they were not, or this information was not provided, there was no evidence that the magnitude of the effect sizes for phonemic or semantic fluency varied systematically from studies that adopted more rigorous matching criteria.

Distinguishing DAT and HD

Whilst patients with HD and DAT performed equally poorly upon a measure of semantic fluency (for both groups, r = .73), the latter group was substantially less impaired upon phonemic fluency (rs = .57 versus .71, respectively). Thus, whilst patients with HD exhibit comparable impairment upon the two types of fluency, patients with DAT are substantially more impaired on semantic relative to phonemic fluency. Indeed, the difference in terms of the PVAF between phonemic and semantic fluency was estimated to be 20.8% for patients with DAT, but only 2.9% for patients with HD. It is of interest that a similar pattern of results was found when comparing the results of meta-analytic reviews involving patients with PD and DAT. (Henry & Crawford, in press-e). Thus, the results across both of these earlier, as well as the present, meta-analyses do suggest that differentiating between 'cortical' dementias such as DAT and 'subcortical' dementias such as PD and HD may be possible by assessing the relative prominence of deficits upon tests of phonemic and semantic fluency.

However, Brown and Marsden (1998) have argued that many of the claimed differences between cortical and subcortical dementias can be attributed to differences in dementia severity, and have questioned the idea that there are distinctive patterns of cognitive impairment for the two types of dementia. This is a difficult issue to resolve in the present meta-analysis, as the extent to which the HD patients contributing to the HD analyses are equated in dementia severity to the DAT patients contributing to the DAT analyses is unclear. Many of the studies do not report scores on a standardised measure of dementia, and where studies do report these statistics, often the same measures are not used. For example, in the HD analyses the DRS was the most commonly reported measure of dementia severity, whilst in the DAT analyses, the Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) was typically used for this purpose.

Nevertheless, it is quite striking that the semantic fluency deficit for patients with both HD and DAT is identical in magnitude (r = .73). This suggests that the larger deficit upon phonemic fluency for the HD relative to the DAT group is not simply because the former patient group are more severely demented. Moreover, it is interesting to note that in a sample of patients carefully matched for overall level of dementia, precisely this pattern of results was found (Rosser & Hodges, 1994).

However, it is of interest that for patients with DAT the difference in terms of the relative sensitivity of phonemic and semantic fluency to the presence of HD as indexed by the PVAF was not significantly or substantially correlated with dementia severity (r = .16, K = 45, p = .29), whilst for patients with HD, the difference in terms of the PVAF was substantially (although not significantly) correlated with dementia severity on the DRS (r = .62, K = 7, p = .14). Whilst speculative, particularly since the number of studies contributing to the latter statistic was small in number, it may be that the overlap between HD and DAT in terms of the relative prominence of deficits upon phonemic and semantic fluency is greater in the earlier stages of the disease. That is, for patients with HD, in the early stages of dementia there may be a tendency for semantic fluency to be more impaired than phonemic fluency, but as the dementia progresses these deficits become more comparable in magnitude. However, for patients with DAT semantic fluency is more impaired than phonemic fluency to a comparable degree at every stage of the disorder. Indeed, it is of interest that in their comparison of patients with DAT, HD and PD, Suhr and Jones (1998) found that for all three groups parallel semantic/letter fluency deficits were found for patients who were only mildly demented. The results of the present meta-analysis suggest that using the relative prominence of phonemic and semantic fluency deficits to distinguish between HD and DAT may be more difficult in the earlier stages, but should clearly differentiate the disorders as the dementia grows more advanced.

Cognitive Impairment in Pre-clinical HD

As noted previously, earlier empirical studies have failed to agree on whether pre-symptomatic HD is associated with cognitive dysfunction (Blackmore et al., 1995; Lawrence et al., 1998). The present results are consistent with Blackmore et al.'s (1995) argument that minimal deficits may be apparent in pre-clinical HD but existing measures of assessment are not sensitive enough to identify them. Whilst there is evidence of a verbal fluency deficit in pre-clinical HD, the magnitude of this deficit is so small that many studies may simply lack the power to detect a statistically significant effect.

However, consistent with the possibility that semantic fluency may be more impaired than phonemic fluency in the earlier stages of the HD, patients in the pre-clinical stages of the disorder were found to be substantially more impaired on the former measure. Whilst the absolute magnitude of the deficits upon both these measures were small (rs = .12 and .17 for phonemic and semantic fluency, respectively), in terms of the PVAF the latter measure was over twice as large (1.3% versus 2.9%). Thus, pre-clinical HD does appear to be associated with cognitive dysfunction, but this may differ qualitatively as well as quantitatively from patients in the advanced stages of HD, as the latter group typically present with comparable deficits upon both types of fluency.

Limitations of the Present Study

The results of the present study contradict the prevailing view in the literature, and suggest that HD is not characterised by disproportionate executive dysfunction. However, it is important to emphasise that the estimates of Q for many of the mean effects indicate that there is considerable heterogeneity across the studies contributing to the present meta-analysis. Moreover, many of the mean effects have been calculated from a small number of studies; as Rosenthal and Dimatteo (2002) note, mean effects derived from a small number

of studies must be regarded as relatively unreliable. Thus whilst the present results provide evidence consistent with the possibility that fluency deficits in HD do not qualify as differential deficits relative to deficits on other cognitive measures such as VIQ, further research is needed to cross-validate and test the generalisability of these findings.

Summary and conclusions

As has been found for frontal patients and patients who have sustained a TBI, HD patients were comparably impaired on tests of phonemic and semantic fluency. However, in contrast to these other patient groups, for patients with HD fluency deficits did not qualify as differential deficits relative to measures that do not heavily load executive functions, e.g. verbal intelligence and psychomotor speed. Thus, in contrast to the prevailing view in the literature, there is no evidence that HD is particularly characterised by executive dysfunction, at least as indexed by tests of phonemic and semantic fluency. Relative to patients with DAT, patients with HD were comparably impaired on a measure of semantic fluency, but the former group were substantially less impaired upon phonemic fluency, indicating that these two etiologically distinct types of dementia may be differentiated from one another by the relative prominence of deficits upon these two measures. For patients in the pre-clinical stage of HD, although only small in magnitude, deficits were found upon tests of phonemic and semantic fluency.

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Table 1.

Verbal Fluency Performance for Symptomatic Patients with HD Relative to Healthy Controls

						95% CIs; mean							95% CIs; mean effects	
	M	Mdn	K	N	SE	Lower	Upper	Z	PVAF	Q	σ_θ^2	SD	Lower	Upper
All studies														
Phonemic fluency	**.67**	.66	27	1188	.031	.61	.73	21.8*	45.0	101.8*	.017	.13	.42	.92
Semantic fluency	**.73**	.67	16	634	.030	.67	.79	24.5*	53.5	36.0*	.007	.08	.57	.89
Only studies that include phonemic and semantic fluency														
Phonemic fluency	**.71**	.73	13	443	.043	.62	.79	16.5*	50.0	48.0*	.015	.12	.47	.95
Semantic fluency	**.73**	.74	13	443	.027	.68	.79	26.8*	53.9	19.5	.003	.06	.62	.85

*p < .01.

Table 2.

Performance on Tests of Verbal Fluency and other Cognitive Measures for Symptomatic HD Patients versus Healthy Controls

	M	Mdn	K	SE	95% CIs of mean Lower	95% CIs of mean Upper	Z	PVAF	Q	σ_θ^2	SD	95% CIs of mean effects Lower	95% CIs of mean effects Upper	
Studies that include PF														**PF M**
Premorbid IQ	**.19**	.09	3	.149	-.10	.48	1.3	3.6	7.5*	.048	.22	-.24	.62	**.51**
VIQ	**.63**	.56	8	.063	.50	.75	10.0*	39.3	30.1*	.022	.15	.33	.92	**.65**
FSIQ	**.68**	.68	4	.066	.55	.81	10.3*	46.9	9.1*	.010	.10	.49	.88	**.68**
Digit Symbol	**.84**	.69	5	.051	.74	.94	16.5*	70.6	7.9	.006	.08	.69	.99	**.75**
BNT	**.61**	.62	4	.067	.48	.74	9.1*	37.2	4.4	.006	.08	.46	.76	**.75**
WCST CC	**.35**	.46	5	.103	.15	.55	3.4*	12.3	15.7*	.038	.19	-.03	.73	**.53**
WCST PE	**.45**	.29	6	.105	.25	.66	4.3*	20.3	25.4*	.050	.22	.01	.89	**.58**
Stroop interference	**.61**	.58	9	.052	.51	.72	11.8*	37.7	16.7*	.011	.11	.41	.82	**.57**
Studies that include SF														**SF M**
Premorbid IQ	**-.02**	.09	2	.143	-.30	.26	-0.2	0.1	2.6	.026	.16	-.34	.29	**.57**
Digit Symbol	**.89**	.87	3	.049	.80	.99	18.4*	80.0	2.4	.002	.04	.82	.97	**.63**
BNT	**.61**	.62	5	.050	.52	.71	12.4*	37.6	4.5	.001	.04	.54	.69	**.83**
Stroop interference	**.52**	.41	5	.072	.38	.66	7.2*	27.2	5.6	.008	.09	.35	.69	**.61**

*p <.05

Note; the mean effects for phonemic and semantic fluency were recalculated for each comparison of interest. For example, only nine studies included both phonemic fluency and Stroop interference. In addition to calculating the mean effect for Stroop interference from these nine studies (r = .61), the mean effect for phonemic fluency was also recalculated based only on these nine studies (i.e. r = .57). Thus, in each comparison exactly the same participants have been tested upon each of the measures of interest, effectively 'controlling' for any substantive differences between studies, such as the stage of the disease.

Table 3.

Mean Fluency Effect Sizes for Symptomatic and Pre-symptomatic HD Patients, and Patients with DAT (DAT Data Taken from; Henry, Crawford, and Phillips, in press).

	M	Mdn	K	N	SE	95% CIs of mean		Z	PVAF	Q	σ^2_θ	SD	95% CIs of mean effects	
						Lower	Upper						Lower	Upper
Symptomatic HD														
Phonemic fluency	**.71**	.73	13	443	.043	.62	.79	16.5*	50.0	48.0*	.015	.12	.47	.95
Semantic fluency	**.73**	.74	13	443	.027	.68	.79	26.8*	53.9	19.5	.003	.06	.62	.85
Pre-symptomatic HD														
Phonemic fluency	**.12**	.12	4	208	.069	-.02	.25	1.7	1.3	0.9	–	–	–	–
Semantic fluency	**.17**	.14	4	208	.067	.04	.30	2.5*	2.9	1.6	–	–	–	–
DAT														
Phonemic Fluency	**.57**	.52	70	2674	.024	.52	.62	23.8*	32.6	600.3*	.033	.180	.22	.92
Semantic Fluency	**.73**	.68	70	2674	.017	.69	.76	42.7*	52.7	630.6*	.016	.128	.47	.98

*p <.05

— indicates that the random effects variance component is estimated to be zero.