

MS vs. HD: Can white matter and subcortical gray matter pathology be distinguished neuropsychologically?

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This study was conducted to examine the neuropsychological effects of white matter and subcortical gray matter pathology. Nineteen patients with multiple sclerosis (MS), 16 with Huntington's disease (HD), and 17 normal controls (NC) participated. Participants completed the California Verbal Learning Test (CVLT), Rotary Pursuit (RP) and Mirror Tracing (MT) tasks, and the Symbol Digit Modalities Test (SDMT). The principal findings pertain to a dissociation in procedural memory: on RP, the HD group demonstrated impaired sequence learning compared to the MS group, which performed similarly to the NC group, yet on MT, the MS and HD groups demonstrated normal perceptual-motor integration learning. On the CVLT, both patient groups performed better on recognition than on recall. On the SDMT, both patient groups performed worse than the NC group, with the HD group performing more poorly than the MS and NC groups. These results suggest that involvement of white and subcortical gray matter may produce different neuropsychological effects.

INTRODUCTION

Characterization of the neurobehavioral features of dementing disorders is an important research goal. The conceptual distinction between cortical and subcortical dementias (Cummings & Benson, 1984) has stimulated much investigation in behavioral neurology and neuropsychology over the past three decades. Although the idea initially generated considerable debate (Brown & Marsden, 1988; Whitehouse, 1986), this concept has led to a greater understanding of the role of subcortical structures in neurobehavioral function, and improved methods for distinguishing between different types of dementia (Cummings, 1990). The concept of subcortical dementia, however, has limitations. First, some overlap exists between neurobehavioral manifestations of the cortical and subcortical

dementias, rendering more difficult the clinical distinction between various disorders (Brown & Marsden, 1988; Whitehouse, 1986). Second, few cerebral disorders have exclusively cortical or subcortical neuropathology, and a secure classification of these disorders is complex (Brown & Marsden, 1988; Whitehouse, 1986). Third, although subcortical dementia is thought to be associated with a relatively consistent pattern of neuropsychological deficits (Cummings & Benson, 1992; Savage, 1997), these deficits may be somewhat inconsistent (Robbins et al., 1994; Suhr & Jones, 1998). Finally, the subcortical dementias comprise a large number of disorders that present with a diverse array of neurological and neurobehavioral features, and unique aspects of individual disorders may be obscured by the use of a general category.

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One clinical and empirical approach to address these concerns involves consideration of the specific neurobehavioral impact of cerebral white matter involvement. This strategy permits a more precise analysis of deficits that can be ascribed to various subcortical disorders as compared with each other and with those affecting the cerebral cortex. White matter comprises about one-half the volume of the adult brain, and consists of vast numbers of myelinated axons connecting a diverse array of cortical and subcortical gray matter structures (Filley, 2001). In the cerebrum, association and commissural white matter tracts travel within and between the hemispheres, linking widespread areas into distributed neural networks that subserve the higher functions of the brain (Filley, 2001). A wealth of clinical research and experience indicates that disorders of cerebral white matter, including the prototypical white matter disease multiple sclerosis (MS), can produce clinically significant neurobehavioral dysfunction that may reach the severity of dementia (Boerner and Kapfhammer, 1999; Cummings & Benson, 1992; Filley, 2001; Rao, 1986). In these disorders, damage to white matter may be confined to myelin alone, or also involve axons (Kuhlmann, Lingfeld, Bitsch, Schuchardt, & Brück, 2002), in which case neurobehavioral manifestations tend to be more severe and lasting (Filley, 2001). Although the neuropathology of MS and other white matter disorders may include the cortical or subcortical gray matter to some extent, mounting evidence indicates that damage to the white matter is sufficient by itself to produce neurobehavioral sequelae that range from subtle neuropsychological disturbances to frank dementia (Filley, 1998, 2001). Moreover, studies of various cerebral white matter disorders suggest that affected individuals may develop a specific dementia syndrome that can be distinguished from that of patients with cortical dementias or subcortical dementias that primarily affect gray matter (Filley, 1998, 2001). The profile resulting from white matter involvement includes impairments in sustained attention, memory retrieval, frontal lobe function, visuospatial skills, and psychiatric status, with relative preservation of language, procedural memory, and extrapyramidal function (Filley, 1998, 2001).

A plausible neuropathological argument can be made for considering the neurobehavioral impact of cerebral white matter disorders separately from disorders of the subcortical gray matter (Filley, 1998, 2001). MS, for example, is a demyelinating disease of cerebral white matter, and an appropriate model to demonstrate the impact of white matter damage on neurobehavioral function (Filley,

1998, 2001). In contrast, the classic subcortical dementias such as Huntington's disease (HD) are neurodegenerative diseases that feature selective involvement of subcortical gray matter (Cummings & Benson, 1992). In particular, HD is characterized by early and selective dendritic and neuronal loss in the striatum (caudate and putamen), first apparent in the medial part of the caudate (Vonsattel & DiFiglia, 1998). Even before these microscopic changes are apparent, functional imaging studies in HD patients demonstrate decreased glucose metabolism (Hayden et al., 1986) and dopamine receptor binding in the striatum (Andrews & Brooks, 1998), and hypometabolism in the caudate has been shown to correlate with cognitive impairment (Berent et al., 1988). Although metabolic and structural changes in the frontal cortex have also been documented, frontal changes may represent secondary cortical deafferentation within frontal-subcortical circuits that include the striatum (Andrews & Brooks, 1998), and the primary neuropathological event in HD appears to be striatal degeneration. Thus HD serves as an example of subcortical gray matter dysfunction in contrast to the subcortical white matter involvement that is characteristic of MS.

The purpose of this study was to determine whether white matter and subcortical gray matter pathology could be distinguished by comparing the neuropsychological performance of MS patients to that of HD patients. Although at least 10–20% of MS patients (Boerner and Kapfhammer, 1999; Rao, 1996) and nearly all of those with HD develop dementia during the disease course, both patient groups in this report were studied early in the disease and, therefore, were not demented. We adopted this strategy because studying patients at the stage of early cognitive impairment facilitates the delineation of neuropsychological differences that most clearly reflect the differential neuropathology of MS and HD. We chose to focus on memory dysfunction (both declarative and procedural) and sustained attention in these diseases, as the differentiation of deficits within these domains may be most useful in establishing reliable differences. The neuropsychological performance of MS and HD patients has been contrasted in two previous studies (Butters, Goldstein, Allen, & Shemansky, 1998; Caine, Bamford, Schiffer, Shoulson, & Levy, 1986), but neither one was expressly designed to test conceptually-driven hypotheses about how the effects of white matter pathology might differ from those of subcortical gray matter pathology, and the patient groups in these studies were not ideally matched.

The memory impairment associated with white matter pathology is thought to differ from that seen in cortical dementia by better performance on recognition than on recall, and from that of subcortical gray matter dementia because of preserved procedural memory, or skill learning (Filley, 1998, 2001). Much research has led to the development of an empirically based theory of motor control which proposes that motor skill learning is based upon different cognitive processes with distinct neural bases; in particular, sequencing involves the basal ganglia and supplementary motor area, whereas perceptual-motor integration involves the posterior parietal lobe and premotor cortex (Willingham, 1998). Patients with basal ganglia involvement would accordingly be expected to have specific difficulty with procedural memory tasks of sequence learning but not perceptual-motor integration learning, while patients with white matter pathology would be expected to perform normally on both types of procedural memory tasks due to the lack of involvement of brain regions that support the performance of these tasks. Sustained attention deficits are closely related to slow information processing speed, and are thought to result from reduced conduction velocity in white matter pathways (Filley, 1998); these deficits are also seen in disorders of the subcortical gray matter. Our hypotheses, therefore, were that the MS group, like the HD group, would display better performance on recognition than on recall in declarative memory, but only the HD group would manifest impaired procedural memory in terms of sequence learning, and that MS and HD groups would demonstrate comparable levels of impaired information processing speed.

METHOD

Participants

Nineteen patients with clinically-definite MS (Poser et al., 1983) and 16 with genetically confirmed symptomatic HD were recruited from the Department of Neurology at the University of Colorado Health Science Center and the Colorado Neurological Institute, with the assistance of the Colorado Chapter of the National Multiple Sclerosis Society. Seventeen normal controls (NC) recruited from the Denver area via advertisements on the university campus also participated in this study. The study was approved by the Colorado Multiple Institutional Review Board; all participants gave written informed consent. Clinical characteristics of the subjects are shown in Table 1.

TABLE 1
Characteristics of the Multiple Sclerosis (MS), Huntington's Disease (HD) and Normal Control (NC) Groups

Characteristic	Group					
	MS		HD		NC	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Age (years)	45.1	6.2	44.6	8.0	43.7	8.0
MMSE score	29.2	1.1	28.4	1.7	29.9	0.5
Education (years)	15.5	1.9	14.6	3.1	16.2	1.5
Gender (M/F)	(3/16)		(9/7)		(2/15)	

Note. MMSE = Mini-Mental State Examination. ANOVA demonstrates a significant difference among groups on MMSE score, $F(2, 49)$, $p < .01$, with post-hoc Tukey HSD tests revealing a significant difference ($p < .01$) between the HD and NC groups only.

All three groups were matched for age. An attempt was made to match groups for overall cognitive functioning with the use of the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975). Analysis of variance (ANOVA) demonstrated a significant difference among groups on MMSE score, $F(2, 49) = 6.31$, $p < .01$, with post-hoc Tukey HSD tests revealing a significant difference ($p < .01$) between the HD and NC groups; the two patient groups were not significantly different from each other. Participants were also required to have at least a high school education, and the three groups were matched for educational level. A significant difference in gender distribution was noted among the groups, $\chi^2(2, n = 52) = 10.18$, $p < .01$. All participants were of white, non-Hispanic ethnicity.

The MS patients all had the relapsing-remitting subtype of the disease (Poser et al., 1983), and they had been diagnosed for an average of 8.0 years ($SD = 5.2$). None were in a state of relapse at the time of study participation. The MS patients had either never taken immunomodulatory medications of any kind ($N = 14$) or taken them for less than one year ($N = 5$).

The clinical diagnosis of HD was based on (1) the presence of typical motor abnormalities and cognitive or personality changes, and (2) confirmation with molecular genetic analysis showing a CAG repeat length > 37 in the gene locus for HD. The HD group had been diagnosed for an average of 2.5 years ($SD = 1.5$).

Exclusionary criteria for all participants included neurological disorders other than MS or HD, traumatic brain injury with loss of consciousness, alcohol or other substance abuse, coronary artery disease, chronic obstructive pulmonary disease, uncontrolled hypertension, diabetes mellitus, renal disease, liver disease, endocrine disorders, visual or

motor impairment that might interfere with neuropsychological testing, severe depression, and use of medication that was judged to cause drowsiness or confusion. Some participants in all groups (9 MS, 11 HD, and 3 NC) were taking medications for disorders including depression, anxiety, insomnia, fatigue, spasticity, urinary frequency, neuropathy, hypertension, and hypercholesterolemia; only two HD patients were taking neuroleptic drugs.

Neuropsychological tests

Participants were administered a neuropsychological test battery designed to test multiple aspects of procedural and declarative memory, as well as information processing speed.

Rotary Pursuit (RP) (Lafayette Instrument, 1998)

This is a test of procedural learning and memory. The RP (photoelectric version) task involves the learning of repetitive motor sequences, which is especially dependent upon the striatum (Willingham, 1998). An initial set of up to 3 trials was used to determine, individually for each participant, how many rotations per minute yielded an initial on-target performance of about 5 seconds. This rotation rate was then used for the entire session, which consisted of 3 blocks, with each block comprised of 8 20-second trials. There was a 20-second delay interval between trials. The 3 blocks were separated by intervals of about 10 minutes.

Mirror Tracing (MT) (Lafayette Instrument, 1996)

This is a test of procedural learning and memory. It involves the learning of new mappings between visual cues and motor responses, which is particularly dependent upon brain regions outside the striatum (Willingham, 1998). A stopwatch records the time taken to trace the pattern and a counter records the number of times the stylus deviates from the pattern (e.g., errors). Testing consisted of 2 blocks with 5 trials per block. There were no intervals between trials, and the 2 blocks were separated by intervals of 10–15 minutes.

California Verbal Learning Test (CVLT) (Delis, Kramer, Kaplan, & Ober, 1987)

This is a well-known test of verbal memory. Standard scores (mean = 0, $SD = 1$), based on normative data stratified by age and gender, for long delay free recall (LDFR) and discriminability were used in this study. Use of the standard scores

inherently controls for the varying distributions of males and females in the groups. The contrast score between discriminability and LDFR was also used to examine recognition performance relative to recall performance.

Nine Hole Peg Test (Fischer, Rudick, Cutter, & Reingold, 1999)

This is a test of manual dexterity that consists of a board with nine holes arranged in three parallel rows of three each and an attached shallow cup holding nine small wooden pegs. The test involves moving the pegs one at a time from the cup to the holes in the board and then back to the cup. The examinee does this twice with each hand, as quickly as possible, and the average completion time is computed. In this study, the Nine Hole Peg Test was used as a measure of upper extremity movement disorder.

Symbol Digit Modalities Test (SDMT) (Smith, 1995)

This is a test of sustained attention that measures information processing speed. The SDMT involves the substitution of digits for symbols as quickly as possible within a 90 second time frame. The total number of correct items in 90 s was used as the measure of information processing speed, and the oral version was used to control for the effects of movement disorder.

RESULTS

RP

Results of this test are depicted in Figure 1. The MS, HD, and NC groups were tested at mean rotations per minute of 21.8 s ($SD = 7.1$), 21.0 s ($SD = 10.4$), and 29.8 s ($SD = 5.7$), respectively. The groups differed significantly from each other, $F(2, 46) = 6.4$, $p < .01$, with post hoc Tukey HSD tests revealing that the MS group was tested at a slower speed than the NC group, $p < .05$, and that the HD group was tested at a slower speed than the NC group, $p < .01$. All 3 groups were well matched on initial time-on-target performance, with the MS, HD, and NC groups scoring means of 5.0 s ($SD = 0.4$), 4.9 s ($SD = 0.3$), and 5.0 s ($SD = 0.6$), respectively; these differences were not significant. Significant correlations were observed between Nine Hole Peg Test score and mean time-on-target scores for all 3 blocks (across each block's 8 trials), with Pearson r s ranging from $-.34$ to $-.40$, $ps < .05$.

Time-on-target scores were analyzed in a repeated measures analysis of covariance (ANCOVA)

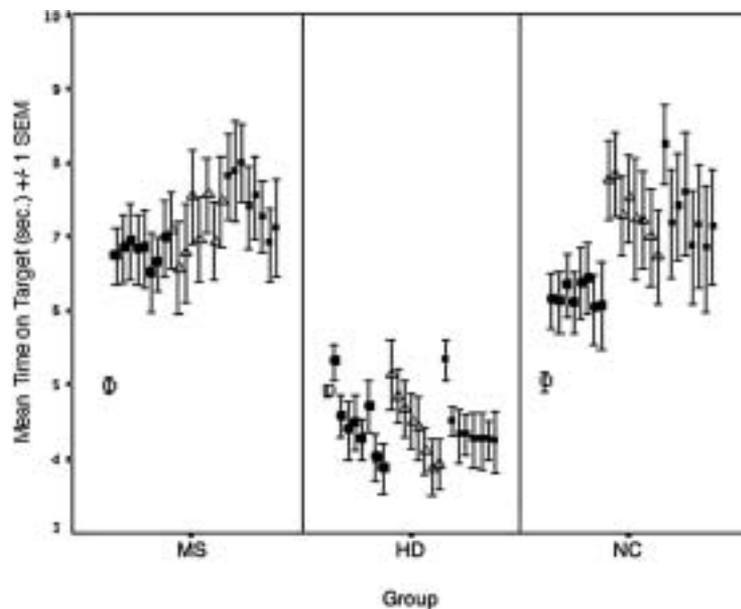


Figure 1. Rotary pursuit results for patients with multiple sclerosis (MS), Huntington's disease (HD), and normal controls (NC). Open circles represent initial time-on-target. Solid circles, open triangles and solid squares represent 8 trials for each of 3 blocks.

with variables of group (MS, HD, NC), block (Block 1, Block 2, Block 3), and trial (8 trials per block); trials were nested within blocks. Nine Hole Peg Test score was the covariate, to control for the effects of movement disorder. Although the results are the same whether or not Nine Hole Peg Test score was used as a covariate, we report the more conservative ANCOVA results to rule out the possibility that movement disorder could have contributed to group differences on RP across multiple trials, given that Nine Hole Peg Test scores correlate significantly with time-on-target scores for all 3 blocks. Results revealed significant differences among the three groups, $F(2, 42) = 9.8, p < .001$. Follow-up tests revealed that the HD group demonstrated less skill learning than the MS group as evidenced by a significant effect of group, $F(1, 27) = 26.3, p < .001$, and a significant interaction between group and trial, $F(2, 196) = 2.0, p < .05$. The interaction between group and block approached significance, $F(2, 56) = 2.4, p = .10$. As an evaluation of overall skill learning on RP, mean performance on block 3 was compared to initial starting performance for all three groups; mean performance was significantly better on block 3 for both the MS and NC groups ($p < .01$) but not for the HD group.

MT

On MT trial 1, completion time did not differ significantly among the 3 groups, with the MS, HD,

and NC groups scoring means of 70.1 s ($SD = 41.9$), 98.6 s ($SD = 59.7$), and 63.00 s ($SD = 42.7$), respectively. However, the 3 groups differed significantly on mean errors made on trial 1, $F(2, 49) = 6.2, p < .01$, MS = 27.7 ($SD = 23.9$), HD = 62.5 ($SD = 50.2$), NC = 24.8 ($SD = 22.1$), with post-hoc Tukey HSD tests revealing that HD group made significantly more errors than both the MS group, $p < .05$, and NC group, $p < .01$. The MS and NC groups did not differ significantly from each other. Significant correlations were observed between Nine Hole Peg Test score and mean completion time for both blocks (across each block's 5 trials), with Pearson r s ranging from .32 to .39, $ps < .05$, and between Nine Hole Peg Test score and mean errors for both blocks, with Pearson r 's ranging from .51 to .52, $ps < .01$.

Completion time scores (Figure 2, top) and error scores (Figure 2, bottom) were analyzed in separate repeated measures ANCOVAs with variables group (MS, HD, NC), block (Block 1, Block 2), and trial (5 trials per block; trials were nested within blocks). Nine Hole Peg Test score was the covariate, to control for the effects of movement disorder. There was a main effect of group on errors, $F(2, 46) = 6.0, p < .01$, but not completion time. Follow-up tests revealed that both the MS and HD groups demonstrated skill learning by tracing the star pattern progressively faster across blocks, $F(1, 31) = 39.9, p < .001$, and trials, $F(4, 124) = 14.0, p < .001$, and by making fewer errors across blocks, $F(1, 31) = 50.3, p < .001$, and trials, $F(4, 124) = 7.8, p < .001$. For

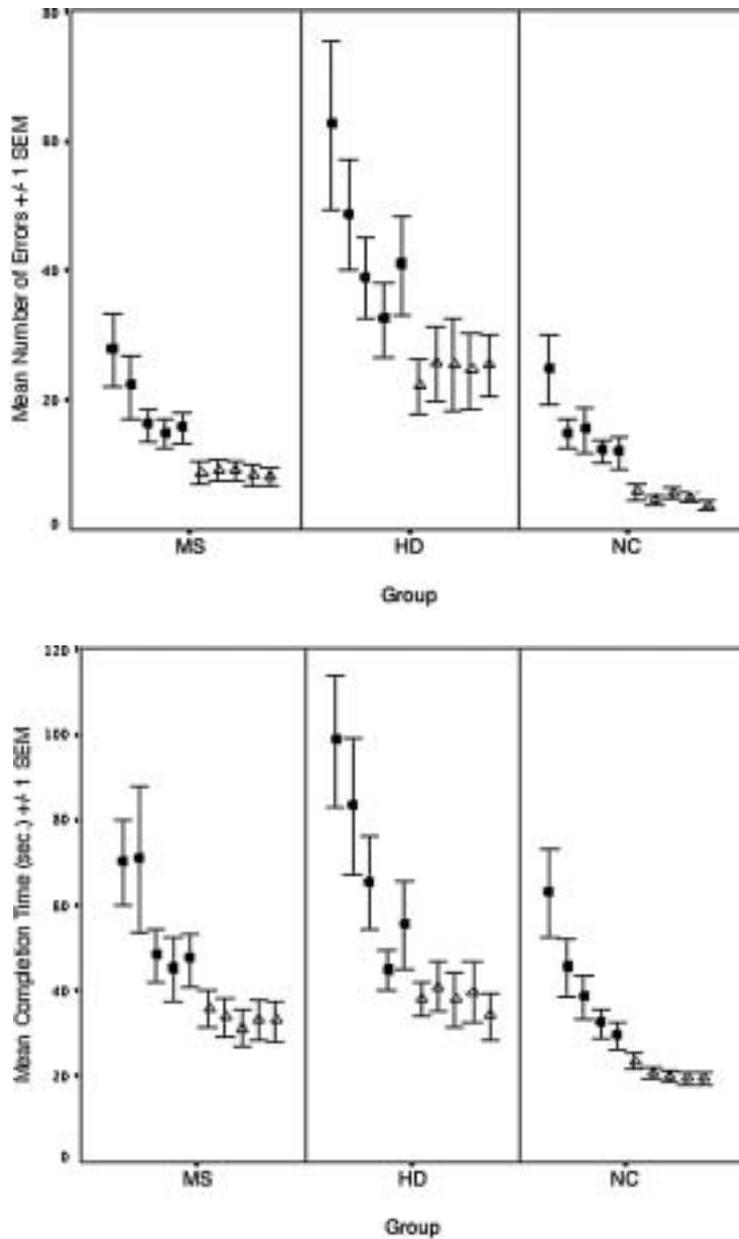


Figure 2. Mirror tracing results for patients with multiple sclerosis (MS), Huntington’s disease (HD), and normal controls (NC). Top demonstrates mean completion time; bottom demonstrates mean number of errors. Solid circles and open triangles represent 5 trials for each of 2 blocks.

both skill-learning measures, there were block x trial interactions, indicating that within-block improvement across trials decreased across blocks: for completion time, $F(4, 124) = 9.6, p < .001$; for errors, $F(4, 124) = 8.7, p < .001$. There was no effect of group on completion time, but a main effect of group on errors revealed that the HD group made more errors than the MS group, $F(1, 30) = 6.8, p < .05$. Overall, the MS and HD groups improved similarly on MT as reflected by the lack of group x trial interactions for either completion time or errors and the lack of a group x block interaction for comple-

tion time. There was a significant group x block interaction for errors, $F(1, 31) = 5.0, p < .05$, indicating that the HD group improved more rapidly than the MS group from Block 1 to Block 2.

CVLT

A Kruskal-Wallis test was used to compare the CVLT standard scores because they do not represent a true interval scale. Because the CVLT standard scores are widely familiar, however, mean values

TABLE 2

CVLT and SDMT Scores for the Multiple Sclerosis (MS), Huntington's Disease (HD) and Normal Control (NC) Groups

Neuropsychological Test	Group					
	MS		HD		NC	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
CVLT Long Delay Free Recall	-0.89	1.15	-1.69	1.54	0.12	0.86
CVLT Discriminability	0.00	0.58	-0.88	1.02	0.12	0.33
CVLT Contrast	+ .89	1.13	+ .81	0.89	.00	0.79
SDMT Total Correct	54.0	15.2	40.3	13.3	67.2	16.0

Note. CVLT = California Verbal Learning Test; SDMT = Symbol Digit Modalities Test.

rather than ranks are reported in Table 2. The Kruskal-Wallis test revealed significant differences among the groups for both LDFR, $\chi^2(2) = 13.9, p < .01$, and discriminability, $\chi^2(2) = 12.3, p < .01$. Post-hoc multiple comparison procedures appropriate for use after a significant Kruskal-Wallis test (Siegel & Castellan, 1988) demonstrated a significant difference between the HD and NC groups for both variables, $p < .05$, LDFR $d = 1.46$, discriminability $d = 1.33$; the differences between the MS and HD groups were not significant. In addition, the difference between the MS and NC groups was small, $d = 0.25$, and not significant for discriminability, but approached significance for LDFR ($p = .07$). Nevertheless, the effect size corresponding to LDFR was $d = 0.99$, representing a large magnitude difference between the MS and NC groups (Cohen, 1988). This effect size is as large or larger than in other well-controlled studies that found statistically significant differences between exclusively relapsing-remitting MS patients and controls in delayed recall performance on a list-learning task ($d = 0.76$, Beatty, Goodkin, Monson, & Beatty, 1989; $d = 0.45$, Ling & Selby, 1996; $d = 1.08$, Pozzilli, 1991), suggesting insufficient power in our nonparametric analyses to detect a meaningful difference.

A Kruskal-Wallis test on the contrast score between discriminability and LDFR for all three groups was also statistically significant, $\chi^2(2) = 8.5, p < .05$. Post hoc multiple comparison procedures revealed a significant large difference between the MS and NC groups, $p < .05, d = 0.91$, while the large difference between the HD and NC groups, $d = 0.96$, approached significance ($p = .06$); the difference between the two patient groups was small, $d = 0.08$, and not significant. The contrast scores for the MS and HD groups reflect notable improvement of at least 4/5 of a standard deviation

on recognition compared to free recall, and suggest that the nonparametric test of the HD versus NC effect did not have enough power to detect a meaningful difference. The NC group's contrast score of zero was not surprising given its initially average performance on LDFR based on the CVLT normative sample (Delis et al., 1987). To closely examine the difference between discriminability and LDFR in a different manner, we also compared performance on these two variables within each group by using a paired samples *t* test, which essentially tests whether the contrast score is significantly different from zero. A significant difference was found in the MS group, $t(15) = -3.72, p < .01$, and in the HD group, $t(15) = -4.33, p < .01$, indicating that both groups showed significant improvement on discriminability relative to LDFR. No significant difference was observed in the NC group.

We conducted post hoc analyses to determine whether the groups differed in their initial learning of the CVLT words. ANOVA revealed a significant difference among all groups on *T* scores corresponding to total learning across trials 1–5, $F(2, 49) = 3.99, p < .05$. Post hoc Tukey HSD tests revealed that the only significant pairwise difference on total learning across trials 1–5 was between the HD ($M = 35.6, SD = 16.0$) and NC ($M = 47.8, SD = 9.4$) groups, $p < .05; d = 0.97$; the difference on total learning between the MS ($M = 43.2, SD = 11.4$) and HD groups was not statistically significant, $p = n.s.; d = 0.56$.

SDMT

Mean number of correct items is reported in Table 2. ANOVA revealed a significant difference among groups, $F(2, 49) = 13.4, p < .01$. Post hoc Tukey HSD tests revealed a significant difference between the MS and HD groups, $p < .05, d = 0.96$, a significant difference between the MS and NC groups, $p < .05, d = 0.85$, and a significant difference between the HD and NC groups, $p < .01, d = 1.83$; the magnitude difference for all three comparisons was large. To determine whether the three groups also differed in their overall accuracy on the SDMT, we calculated the proportion of correct responses to number of attempts (MS: $M = 99.2, SD = 1.5$; HD: $M = 96.5, SD = 5.2$; NC: $M = 98.9, SD = 2.5$). ANOVA demonstrated a significant difference among groups, $F(2, 49) = 3.5, p < .05$. Post hoc Tukey HSD tests revealed that the NC group did not significantly differ from either of the two patient groups, though the MS group was significantly more accurate than the HD group, $p < .05, d = 0.84$.

DISCUSSION

As hypothesized, our results indicate that while both the HD and MS groups demonstrate intact procedural memory in terms of perceptual-motor integration learning, only the HD group demonstrates impaired procedural memory in terms of sequence learning, and both the MS and HD groups display better performance on recognition than on recall in declarative memory. The results were obtained with groups of well-diagnosed patients of similar age, education, and overall level of cognitive functioning. The finding of impaired sequence learning only in the HD group indicates that dysfunction of the subcortical gray matter can produce a different pattern of procedural memory impairment than dysfunction of the white matter, while the finding that both groups share better recognition than recall in declarative memory suggests that MS is similar to traditional subcortical dementias (Cummings, 1990; Cummings & Benson, 1984). That these neuropsychological similarities and differences were found among groups of patients with neurological disorders affecting primarily subcortical gray or white matter regions lends preliminary support to the notion that white matter and subcortical gray matter pathology can be distinguished neuropsychologically.

The findings with respect to perceptual-motor integration learning relate specifically to skill learning that involves the integration of perceptual and motor processes and not skill learning that is more purely perceptual, such as that assessed by mirror reading and incomplete figure tasks. Our results closely resemble previous research findings comparing HD patients and normal controls (Gabielli, Stebbins, Singh, Willingham, & Goetz, 1997). While our study has the advantages of genetic confirmation of HD, more than twice as many HD patients who completed both skill learning tasks, statistical control for the effect of movement disorder, and use of a patient group (MS) with primarily white matter involvement, both studies found that HD patients show impaired sequence learning as measured by the RP task and, conversely, good perceptual-motor integration learning as measured by the MT task. Moreover, the MS patients in our study showed good performance on both tasks, which was similar to that seen in the NC group. These findings are consistent with a recently proposed neuropsychological theory of motor skill learning (Willingham, 1998), which posits that different forms of procedural skill learning can be dissociated behaviorally because they have distinct neural bases. The selectivity of impairment on the RP task by HD patients

supports the notion that subcortical damage in HD, primarily in the striatum, accounts for the sequence learning deficit. On the other hand, the preservation of both sequence learning and perceptual-motor integration learning in MS patients is likely due to the sparing of the striatum in this primarily white matter disease. The critical point is that the distinct sequence learning and perceptual-motor integration learning findings argue against a singular subcortical dementia concept that posits generalized impairment in procedural learning and memory.

Both the MS and HD groups were impaired relative to controls on the SDMT, supporting the notion that deficits in sustained attention are associated with white matter pathology as well as disorders of subcortical gray matter. The HD patients, however, demonstrated greater impairment than those with MS, an unexpected finding in view of the cognitive slowing that is recognized to result from involvement of both white and subcortical gray matter (Cummings & Benson, 1984; Albert, Feldman, & Willis, 1974). In MS patients (Zakzanis, 2000) and in both symptomatic HD patients (Lemiere, Decruyenaere, Evers-Kiebooms, Vandenbussche, & Dom, 2002) and presymptomatic HD individuals (Brandt, Shpritz, Codori, Margolis, & Rosenblatt, 2002; Lemiere et al., 2002; Paulsen et al., 2001), deficits in information processing speed have been documented with the written version of the SDMT. Because we used the oral version of the SDMT, which minimizes the influence of movement disorder, the HD patients may have performed worse than the MS group due to visual scanning and tracking functions that are drawn on by the test (Spren & Strauss, 1998) and known to be impaired in many HD patients (Fahn, 1995), and in some MS patients as well (Frohman, Frohman, Zee, McColl, & Galetta, 2005). A more compelling reason for this difference, however, may be that at the current mild stage of their diseases, the MS patients manifest less notable deficits in sustained attention and information processing speed than those with HD. We speculate that whereas striatal neuronal loss can disrupt sustained attention and information processing speed early in HD, the considerable redundancy of white matter tracts permits the maintenance of these functions in early MS because only some of the critical tracts are disrupted by demyelination. Studies that have utilized more impaired MS patient samples have found greater decrements in speed of information processing with neuropsychological tests that are not confounded by the presence of movement disorder (Demaree, DeLuca, Gaudino, & Diamond, 1999; Diamond, DeLuca, Kim, & Kelley, 1997),

presumably because more extensive white matter damage has occurred.

This study suggests that dissociable memory deficits may be useful for differentiating white matter and subcortical gray matter disorders, and thus contribute to the neuropsychological assessment of dementia. These distinctions are most evident in the early stages of dementing diseases (Filley, 2001), and may even be detected before dementia has developed, as in our participants. In accord with our finding that HD, but not MS, patients exhibit a sequence learning deficit, different studies have found that patients with traditional subcortical dementias such as HD and Parkinson's disease (PD) are impaired on the RP (Heindel, Butters, & Salmon, 1988; Heindel, Salmon, Shults, Walicke, & Butters, 1989) and other sequencing tasks (Ferraro, Balota, & Connor, 1993; Knopman & Nissen, 1991). Conversely, other studies have shown that patients with cortical dementias such as Alzheimer's disease (AD) learn the RP (Eslinger & Damasio, 1986; Heindel et al., 1989) and other sequencing tasks (Ferraro et al., 1993; Knopman & Nissen, 1987) normally. Our finding of relatively normal perceptual-motor integration learning in HD and MS is consistent with studies showing that patients with HD and PD perform normally on various perceptual-motor integration tasks (Frith, Bloxham, & Carpenter, 1986; Willingham, Koroshetz, & Peterson, 1996). Patients with AD also perform normally on MT (Gabrielli, Corkin, Mickel, & Growdon, 1993) and other perceptual-motor integration tasks (Willingham, Peterson, Manning, & Brashear, 1997). Studies examining procedural memory specifically in MS have found that these patients perform normally on a wide range of procedural memory tasks (Beatty, Goodkin, Monson, & Beatty, 1990; Rao et al., 1993).

In terms of declarative memory, the MS and HD groups in our study both demonstrated better recognition than recall, a common pattern in both MS (Rao, 1986) and traditional subcortical dementia (Cummings & Benson, 1984; Lafosse et al., 1997), including HD that has not yet progressed to the advanced stages (Butters, Wolfe, Martone, Granholm & Cermak, 1985; Delis et al., 1991; Kramer et al., 1988; Moss, Albert, Butters, & Payne, 1986; however, see Brandt et al., 1992) and PD (Breen, 1993; Gabrieli, Singh, Stebbins, & Goetz, 1996; Massman, Delis, Butters, Levin, & Salmon, 1990); importantly, this pattern is not seen in cortical dementias such as AD (Delis et al., 1991; Kramer et al., 1988; Lafosse et al., 1997; Moss et al., 1986; Wilson, Bacon, Fox, & Kaszniak, 1983). The pattern of better recognition than recall on verbal memory tests in subcortical dementia has customarily been

interpreted as evidence for a retrieval deficit (Cummings & Benson, 1984). This pattern has also been interpreted as evidence for a retrieval deficit in MS (Grafman, Rao, & Litvan, 1990). Recent work, however, suggests that MS patients show deficiencies in the initial acquisition of information (DeLuca, Barbieri-Berger, & Johnson, 1994; DeLuca, Gaudino, Diamond, Christodoulou, & Engel, 1998; Demaree, Gaudino, DeLuca, & Ricker, 2000), casting doubt on impaired retrieval as the explanation for performance characterized by worse recall than recognition. The nature and severity of this deficient acquisition require further study and cannot be adequately addressed in the context of the present investigation beyond noting that the MS and NC groups did not significantly differ in their total learning on the CVLT. However, our research group is currently examining this issue more closely in another project.

While this study specifically considers MS and HD, our data may apply more broadly to disorders that primarily affect either the brain's white matter or subcortical gray matter. In particular, the role of the white matter in neurobehavioral function deserves attention. The concept of white matter dementia (WMD) was proposed in 1988 to highlight the cognitive changes that can be attributed to white matter dysfunction (Filley, Franklin, Heaton, & Rosenberg, 1988). While many patients with white matter disorders have neuropsychological impairment less severe than that implied by the term dementia, even this degree of cognitive dysfunction may be problematic clinically and, in some individuals, prove to be a harbinger of dementia at a later time (Filley, 2001). Our findings, together with the results of previous studies, suggest that a unique pattern of dissociable memory deficits can be used to characterize early white matter dysfunction and distinguish it from the syndromes produced by subcortical gray matter and cortical disorders. The generalizability of our findings to other white matter disorders needs careful scrutiny, given that white matter disorders differ in etiology, and the nature, pattern, and extent of white matter involvement (Filley, 2001).

Two previous studies have compared the neuropsychological performance of MS and HD patients (Butters et al., 1998; Caine et al., 1986). Both studies concluded that MS and HD patients exhibit generally similar patterns of neuropsychological impairment. However, one study (Caine et al., 1986) did not account for a possible difference in overall level of cognitive functioning by either matching patients for it or controlling for it statistically. The study of Butters and colleagues (1998) attempted to equate groups by controlling

for general level of performance variables that are partially comprised of the dependent variables themselves, which inappropriately reduces the between-group variance one is attempting to explain; it is difficult to interpret differences between groups when they are equated, even if only partially, on the dependent variables. Beyond addressing such methodological considerations, investigations may be more likely to detect meaningful neuropsychological differences between subcortical dementias that affect primarily white or subcortical gray matter if tests are selected on the basis of conceptually driven hypotheses such as those driven by the concept of WMD.

Some limitations should be considered in the interpretation of our data. First, it could be argued that procedural memory performance in both patient groups was affected by the presence of movement disorder. However, all groups were equated for initial level of performance on the RP task. Although initial performance level could not be equated on the MT task, the analyses of data from both procedural memory tasks statistically controlled for the effects of movement disorder by using performance on the Nine Hole Peg Test, a quantitative measure of upper extremity movement disorder, as a covariate. It is therefore unlikely that our procedural memory findings were confounded by the presence of movement disorder. Moreover, almost identical RP and MT results were obtained in a previous study of HD patients and normal controls (Gabrieli et al., 1997). Our results may also have been influenced by the unequal distribution of men and women in the two patient groups. Although there are no normative data about the relative performance of men and women on the RP and MT tasks, the previous study with nearly identical RP and MT results (Gabrieli et al., 1997) had a greater number of female than male HD patients, suggesting that gender is not an important determinant of performance on these tests. Furthermore, gender does not have a significant effect on oral SDMT performance (Smith, 1995) and the CVLT standard scores inherently take gender into account, arguing against a gender confound in our results. Also, although the two patient groups were equivalent on overall level of cognitive functioning as assessed by the MMSE, it should be noted that the MMSE has limited sensitivity to cognitive impairment in MS (Beatty, 1990) and HD (Randolph, Tierney, Mohr, & Chase, 1998).

Our hypotheses that the HD group, but not the MS group, would demonstrate impairment on the rotary pursuit task, while both groups would demonstrate generally intact performance on the

mirror tracing task, essentially posited a single dissociation in terms of procedural learning. Our data, therefore, provide limited support for the notion that sequencing and perceptual-motor integration have distinct neural bases. Inclusion of a group of patients with posterior parietal and/or premotor cortex lesions would have been necessary to predict a double dissociation on the two motor skill tasks with the HD group. Nevertheless, findings that posterior parietal or premotor cortex lesions produce perceptual-motor integration deficits in both monkeys and humans (Halsband & Freund, 1990; Halsband & Passingham, 1982; Petrides, 1985), along with previously mentioned motor skill findings in patients with HD, PD, MS, and AD, and the results of the present study, together provide converging support for the position that motor skill learning is based upon different cognitive processes with distinct neural bases (Willingham, 1998). Our more focused aim, however, was simply to demonstrate differential patterns of neuropsychological performance between groups that reflect the presence of either white or subcortical gray matter dysfunction.

Another limitation is the lack of neuroimaging data to determine the location and extent of white matter and subcortical gray matter involvement in our patient groups. Correlation of our neuropsychological data with measures of white matter lesion burden in MS would have been informative. The absence of neuroimaging data prevents us from addressing the question of neuropathological specificity in MS and HD. MS, for example, is known to involve both cortical and subcortical gray matter to some extent (Filley et al., 1998), and conversely, HD has some degree of associated cortical pathology (Whitehouse, 1986). We believe, however, that these two disorders can meaningfully be used to represent white and subcortical gray matter dysfunction, respectively. Neuroimaging evidence has supported the notion that the burden of cerebral white matter disease correlates with cognitive dysfunction in MS (Filley, 1998, 2001), and other evidence closely links caudate atrophy in HD with the degree of cognitive impairment (Bamford, Caine, Kido, Plassche, & Shoulson, 1989; Starkstein et al., 1992).

Recent work has demonstrated that treatment with immunomodulatory medications can significantly reduce cognitive decline in MS patients within two years of treatment onset (Fischer et al., 2000; Pliskin et al., 1996). This potential confound is unlikely to have affected test performance in our MS patients because most had never taken immunomodulatory medications, and those that had taken them had done so for less than a year. It is

also apparent that our MS and HD participants were not in fact demented, as demonstrated by their capacity to live independently in the community and achieve normal MMSE scores. The detection of cognitive deficits early in these diseases, however, is important; progression to dementia occurs in at least 10–20% of MS patients (Rao, 1996), with one study reporting a prevalence of 23% (Boerner & Kapfhammer, 1997), and virtually all HD patients become demented at some point. Moreover, the empirical study of cognitive loss is most illuminating early in the course of both MS and HD because the isolation of specific neurobehavioral deficits becomes more difficult as the cognitive impairments advance. Indeed, including only cognitively impaired MS and HD participants in the present study may have yielded a different pattern of results.

The implications of these data are both clinical and theoretical. In clinical terms, the neuropsychological distinctions between MS and HD may pertain to the assessment of early neurobehavioral changes in these disorders, as well as white and subcortical gray matter disorders generally. Our data suggest some possible utility of assessing procedural memory to improve patient management. For example, patients with white matter dysfunction may have greater capacity to engage in rehabilitation because of their relatively spared procedural memory. Theoretically, our results may help clarify the understanding of subcortical contributions to behavior, particularly the role of the white matter. Much work remains to be done, including studies such as ours examining other disorders of subcortical gray and white matter. Our data provide some evidence that the white matter serves a unique role in behavior that can yield important insights into brain function.

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