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Capacity to Make Medical Treatment Decisions in Multiple Sclerosis: A Potentially Remediable Deficit

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Abstract

Ability to make decisions about medical treatment is compromised in significant numbers of people with neurological and psychiatric illness, and this incapacity frequently corresponds with compromised neuropsychological function. Although cognitive deficits occur often in people with multiple sclerosis (MS), no research has studied decisional capacity in that disease. The present investigation examined ability to understand treatment disclosures, which is a core component of decisional capacity, in 36 people with MS and 16 normal controls. MS patients with diminished neuropsychological function showed poor understanding of treatment disclosures compared to the control group, and diminished new-learning and executive function correlated with poorer understanding. Nonetheless, with sufficient cueing, the MS patients with diminished neuropsychological function were able to display understanding that was equivalent to the control group. Implications of these results for clinical practice and medical research involving people with MS are discussed.

Keywords

multiple sclerosis; neuropsychological function; informed consent; decision-making

Ability to make independent and autonomous decisions regarding medical treatment is a complex activity of daily living. Prior to making treatment decisions, patients are typically provided information concerning the risks and benefits of possible medical interventions. Ostensibly, they then carefully weigh these issues, and make a rational decision. According to one prominent model (Appelbaum and Grisso, 1998), patients face the choice of accepting or rejecting various medical options by considering four major domains. To make

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a competent decision, the individual must be able to 1) express a treatment choice; 2) appreciate the personal consequences of their choice; 3) make a rational decision concerning treatment; and 4) understand the treatment and its risks and benefits (Appelbaum & Grisso, 1995; Appelbaum, Lidz, & Meisel, 1987; Appelbaum & Roth, 1982). These capacities were derived from thorough reviews of the medical and legal literature. Although they vary somewhat with other proposed standards (cf. Marson, 2001; Marson, Ingram, Cody, & Harrell, 1995; Marson, Schmitt, Ingram, & Harrell, 1994), they are widely applied and are consistent with existing medical ethics and legal precepts. According to this influential approach, ability to make a decision regarding medical treatment may be compromised by neuropsychological dysfunction. Because disease-related cognitive abnormality is sometimes latent or subtle, medical providers may unwittingly violate the rights or autonomy of their patients, especially those with neurological or psychiatric illness.

Indeed, several studies have examined the impact of neuropsychological impairment upon capacity to make treatment decisions. Furthermore, numerous investigations have studied the capacity to give informed consent in clinical research trials. This follows because the ability to make decisions about medical research participation appears to parallel the capacity to make decisions about medical treatment – both may involve the same core capacities of understanding, appreciation, reasoning, and expression of choice. Together, research concerning capacity to make decisions about medical treatment and medical research reveals that each of these four capacities may be diminished by cognitive impairment, thereby rendering an individual unable to demonstrate appropriate decision-making capacity (Appelbaum & Grisso, 1988; Appelbaum & Grisso, 1995; Appelbaum & Roth, 1982; Appelbaum et al., 1987; Grisso; 1986; Grisso & Appelbaum, 1998; Marson, 2001; Marson et al., 1995; Marson et al., 1994; Roth, Meisel, & Lidz, 1977). Specifically, studies involving people with schizophrenia (Candilis et al, 2006; Carpenter et al., 2000; Combs et al., 2005; Grisso, Appelbaum, Mulvey, & Fletcher, 1995; Moser et al., 2002; Moser et al., 2006; Palmer et al., 2005), HIV (Moser et al., 2002), mania (Howe et al., 2005), Alzheimer's disease (Gurrera, Moye, Karel, Azar, & Armesto, 2006; Kim, Caine, Currier, Leibovici, & Ryan, 2001; Marson, Chatterjee, Ingram, & Harrell, 1996; Marson & Harrell, 1999; Palmer et al., 2005), diabetes (Candilis et al, 2008), and Parkinson's disease (Dymek, Atchison, Harrell, & Marson, 2001; Griffith, Dymek, Atchison, Harrell, & Marson, 2005) reveal that patients are often incapable of providing informed consent to treatment or medical research participation. Several recent reviews imply that ability to understand treatments and clinical research is among the decisional components most commonly diminished in people with these disorders (Dunn, Nowrangi, Palmer, Jeste, & Saks, 2006; Moye, Gurrera, Karel, Edelstein, & O'Connell, 2006; Palmer & Savla, 2007).

In addition to investigations using neuropsychologically-impaired groups, some studies have utilized correlational analyses, and examined the relationship between overall cognitive measures (e.g., Mini Mental Status Examination, Dementia Rating Scale (DRS) Total Score, or Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Total Score) and performance on measures of decisional capacity. Similar to studies involving group contrasts, overall cognitive dysfunction appears to correspond with poor decisional capacity (e.g., Appelbaum & Grisso, 1997; Bambara et al., 2007; Carpenter et al., 2000; Dunn et al., 2002; 2007; Palmer et al., 2005). Although these findings imply that neuropsychological dysfunction corresponds with decisional incapacity, they fail to delineate what aspects of neurocognition correspond with specific components of medical decision-making. Accordingly, a number of studies have begun to elaborate such relationships. Employing a variety of neuropsychological predictors and medical decision-making tools with several clinical populations, executive function, new-learning, and working memory emerge as salient correlates of understanding, reasoning, and appreciation of informed consent disclosures (Dunn, Candilis, & Roberts, 2006;Dymek et al., 2001;

Gurrera et al., 2006; Kovnick, Appelbaum, Hoge, and Leadbetter, 2003; Moser et al., 2002; Okonkwo et al., 2008; Palmer, Dunn, Appelbaum, & Jeste, 2004; Palmer & Jeste, 2006).

Across each of these investigations, it is clear that neuropsychological dysfunction corresponds with diminished ability to make competent medical decisions. Notably, capacity to understand medical ailments and treatment choices appears to be especially vulnerable to overall cognitive impairment and more specifically to problems in memory, working memory, and executive function (cf. Dunn, Candilis, & Roberts, 2006; Palmer & Savla, 2007 for compelling reviews). This implies that individuals with such deficits may be prone to misunderstand details of a treatment regimen, or they may have difficulty comprehending its risks and benefits.

Of course, the presence of neurological or psychiatric disorder does not automatically guarantee incompetent decisions. Notably, in the aforementioned studies, only some patients were incapable of providing informed consent. For instance, approximately half of people with Alzheimer's disease can exhibit capable decision-making, discriminate between studies of varying risk and benefit, and demonstrate similar comprehension of risk and benefit as do healthy elderly control subjects (e.g., Kim et al., 2001; Kim, Cox, & Caine, 2002). Hospitalized patients with schizophrenia or schizoaffective disorder score as well on standardized measures of informed consent capacity as do 69–89% of healthy control subjects (Candilis et al., 2008). Often those who exhibit decisional impairment cannot be identified by common demographic variables or even diagnosis (Carpenter et al., 2000). Furthermore, neuropsychological impairment does not equal decisional-incapacity. Although performance on neuropsychological tests typically accounts for an average of 40% to 60% of variance on measures of medical decision-making, considerable variation in decisional-capacity remains unaccounted for (e.g., Gurrera et al., 2006). Thus, it is important to recognize that much individual variation in decision-making capacity remains despite disease status or the presence of neuropsychological impairment.

In this context, investigations of competent decisions among neurologically-ill patients have been mainly limited to elderly individuals with cortical (Alzheimer's) and subcortical (Parkinson's) diseases. Considerably less is known in this regard concerning younger patients with neurodegenerative diseases, such as those with multiple sclerosis (MS). MS is a common neurological condition affecting thousands of Americans. It results in a wide range of sensory, motor, psychiatric, and neurobehavioral symptoms. Cognitive deficits occur in as many as 60% of patients with MS, and executive function, new-learning, and working memory are commonly diminished (Bobholz & Rao, 2003; Martin, Hohlfeld, & McFarland, 1996). For instance, with respect to these domains, performance deficits have been observed on a number of measures, including the Wisconsin Card Sorting Test, California Verbal Learning Test, or Paced Auditory Serial Addition Test, respectively (e.g., Rao, Leo, Bernardin, & Unverzagt, 1991a). Such impairment corresponds with considerable morbidity, with considerable evidence revealing that and neurocognitive dysfunction predicts diminished activities of daily living and increased disability (Benedict et al., 2005; Kessler, Cohen, Lauer, & Kausch, 1992; Rao, Leo, Ellington, et al., 1991).

Numerous beneficial pharmacological treatments for MS have been developed and tested within the past decade (e.g., Geisler et al., 1996; Pliskin et al., 1996). However, each has potential adverse consequences, and was tested in human trials. Participants in these clinical trials, where consequently exposed to significant risk. For patients receiving treatment and participants in clinical trials to make competent medical decisions, they must understand potential benefits and risks of interventions (Appelbaum & Grisso, 1995). Yet, because neuropsychological impairment is common in MS (Beatty et al., 1996; DeLuca, Barbieri-Berger, & Johnson, 1994; Gafman, Rao, Bernardin, & Leo, 1991; Geisler et al., 1996;

Kessler et al., 1992; Kujala, Portin, & Ruutiainen, 1996; Pliskin et al., 1996; Rao, Leo, Bernardin, et al., 1991; Rao, Leo, Ellington, et al., 1991; Tsolaki et al., 1994), patients may have difficulty understanding the details of medical intervention. As a result, providers may administer potentially risky treatments to their patients without obtaining adequate informed consent. Furthermore, investigators developing future interventions may unknowingly recruit participants whose ability to comprehend information or make complex decisions may be compromised (Kessler et al., 1992; Rao et al., 1991a). In doing so, clinicians and researchers may inadvertently fail to treat the participants in an appropriate manner. To our knowledge, no investigation has determined whether people with MS are at particular risk of providing inadequate informed consent to medical interventions.

In the present investigation, we attempted to explore this issue. In particular, we focused on understanding elements of an informed consent disclosure. Although this is only one of the four capacities presumed to underlie informed consent capacity, understanding is among the most extensively described and most commonly studied (Dunn et al., 2006). Towards this end, we used the Understanding Treatment Disclosures (UTD) instrument developed as part of the MacArthur Treatment Competence Study. It is one of the first measures implemented to assess informed consent capacity and has demonstrated reliability and validity in patients with psychiatric and neurological disorders (Appelbaum & Grisso, 1995; Grisso & Appelbaum, 1995; Grisso et al., 1995). It is considered a reliable and valid method of measuring understanding of medical disclosures (Dunn, Nowrangi, et al., 2006; Moye et al., 2006). Indeed, abundant research shows that the UTD and its direct descendant, the MacArthur Competence Assessment Tool (MacCAT), possess convergent and criterion validity. Regarding convergent validity, they correlate with other published measures of understanding disease status and treatment choices (cf. Gurrera et al., 2006; Moye et al., 2006). With respect to criterion validity, several studies have shown that the UTD and MacCAT understanding scales correlate with clinician judgments of decisional competency in clinical populations. Clinician judgment is typically considered the “gold-standard” criterion, and is relied upon by the courts in making determinations of decisional-competence (cf., Appelbaum & Grisso, 1995). In this vein, Pruchno et al. (1995) found that the UTD emerged as a major predictor of clinician judgments regarding decisional capacity of demented elderly patients. Likewise, Kim and colleagues (Kim et al., 2001; 2006) repeatedly found that the understanding scale from the MacCAT predicted clinician judgments of decisional competency for patients with either Alzheimer’s disease or schizophrenia. Notably, across these studies, clinicians did not rely upon responses from the UTD or MacCAT in arriving at their determination of decisional competence, implying that the understanding scales from the UTD and MacCAT are potent predictors of an independent clinical judgment. Indeed, they were employed as the sole criterion to determine whether schizophrenic patients were capable of deciding whether to participate in the multi-center Clinical Antipsychotic Trials of Intervention Effectiveness (Stroup et al., 2003). In accordance with reviews of the literature (e.g., Dunn et al., 2007; Moye et al., 2006), this suggests that the MacArthur instruments are generally accepted by the scientific community as valid measures of medical understanding.

The UTD provides the basis for the largest scoreable domain of decision-making capacity identified by Appelbaum and Grisso (understanding relevant information, including risks/benefits and alternatives), while allowing the part-by-part disclosures favored by the MacArthur studies and other investigations. Based on research involving other patient populations (e.g., Appelbaum & Grisso, 1995; Combs et al., 2005; Howe et al., 2005; Kim et al., 2001; Dymek et al., 2001), we hypothesized that neuropsychologically-compromised patients with MS would display poorer understanding of treatment options than either an unimpaired group of MS patients or a control group.

A second objective of the current study was to determine whether understanding of treatments may be enhanced. Among several patient populations, informed consent procedures have been modified to facilitate understanding of treatment issues (Dunn, 2006). For example, simplified explanations, repetition, and recognition cueing have increased patient understanding of treatment regimens in patients with schizophrenia (Appelbaum & Grisso, 1995; Carpenter et al., 2000; Combs et al., 2005; Dunn & Jeste, 2001; Grisso & Appelbaum, 1995; Grisso et al., 1995; Jensen, Madsen, Andersen, & Rose, 1993; Wirshing, Wirshing, Marder, Liberman, & Mintz, 1998). A number of investigations indicate that recognition cueing enhances ability to remember in people with MS (e.g., Gaudino, Chiaravalloti, DeLuca, & Diamond, 2001; Grisso & Appelbaum, 1995). By providing recognition cueing, people with MS – including those with significant neuropsychological impairment – may likewise realize an enhanced understanding of potential medical treatments.

A third objective of the current study was to evaluate what aspects of neuropsychological function contribute to patient understanding of treatment disclosures. Research involving patients with dementia or schizophrenia indicates that ability to understand treatment information corresponds with executive function, attention, and new-learning. In the present investigation, we sought to determine whether these aspects of neurocognition correspond with understanding of treatment disclosures (e.g., Gurrera et al., 2006; Palmer & Jeste, 2006). By identifying what neuropsychological domains correlate with poor understanding may inform and refine efforts to remediate decisional incapacity in people with MS.

Method

Participants

To recruit participants, notices were published in the newsletter of the local National Multiple Sclerosis Society chapter and in newspapers. The principal investigator also met with MS support groups. Ultimately, data were collected from 36 individuals with MS. A diagnosis of MS was confirmed by a board certified neurologist through chart review (including MRI and other laboratory studies) and physical examination, and these diagnoses were according to the Poser et al. (1983) criteria. The control group included 16 adult community participants without MS. These individuals were friends or spouses of the patients with MS. Patients were excluded if they had a psychiatric disorder which preceded onset of MS, current or past substance abuse or dependence, history of learning or developmental disorders, or any neurological disease or injury besides MS. Current psychiatric illness was not a criterion for exclusion. None of the patients was experiencing an acute exacerbation of MS symptoms at the time of study participation. The control group was screened for each of these characteristics. Participants were volunteers, and received no compensation for their participation.

Materials

All were administered a battery of neuropsychological tests which addressed three primary areas presumed necessary in providing informed consent (e.g., Grisso & Appelbaum, 1998; Marson, 2001; Marson et al., 1996), namely new-learning, executive function, and attention. Indeed, each of the measures (or highly similar variants) employed in this study have been utilized in prior investigations of informed consent capacity (Appelbaum & Grisso, 1997; Dunn et al., 2007; Palmer et al., 2007), thereby increasing the consistency of the current data with the existing literature. These areas of function have been shown to contribute to poor decisional capacity in prior studies. Additionally, these aspects of neurocognition are prone to being compromised in people with MS (Bobholz & Rao, 2003; Martin et al., 1996).

Owing to time constraints, we opted to utilize relatively brief measures of these areas of function.

California Verbal Learning Test-II (CVLT-II)—All participants were administered the CVLT-II (Delis et al., 2000), which is a standardized clinical measure of new-learning. This was administered to obtain an objective benchmark of ability to learn new information for each participant.

Wisconsin Card Sorting Test-64 (WCST: Kongs, Thompson, Iverson, & Heaton, 2000)—The WCST is a measure of executive function which involves abstract reasoning and concept formation. It is especially sensitive, albeit not specific, to frontal lobe dysfunction.

Digit Span—The Digit Span subtest from the Wechsler Adult Intelligence Scale-III (Wechsler, 1997) was used to measure attention span. This measure is often used to assess auditory attention and concentration.

Neuropsychological Dysfunction—The sum of impaired scores was used to classify patients as demonstrating at least mild neurobehavioral compromise. Each neuropsychological measure contained multiple indices. To reduce redundancy in our analyses, we focused on a single index from each measure including the Total Trial 1–5 Recall T-score on the CVLT-II, perseverative errors from the WCST, and Backward Span from the Digit Span Subtest as this subtest is a more appropriate measure of attention. These indices are typically considered among the most sensitive indicators of cerebral dysfunction for each test. Participants with MS were identified as having compromised cognitive function if scores on any one of these three indices fell at the fifth percentile or lower on each test's respective normative mean (Delis et al., 2000; Kongs et al., 2000; Wechsler, 1997). This value was chosen because it is a common benchmark of impaired performance in clinical studies of neuropsychological function (cf., Benton et al., 1994). Impairment on any one of these tests would comprise impairment on one third of the considered indices, and this also is a common benchmark used in classifying patients as having diminished function in clinical studies (e.g., Reitan & Wolfson, 1993). Patients who had one or more scores falling in the clinically-impaired range were classified as having at least mildly-compromised neurocognitive function.

Informed Consent Measure—To assess understanding of an informed consent disclosure, participants were administered the Understanding Treatment Disclosures Scale (UTD: Appelbaum & Grisso, 1995). The UTD exclusively assesses understanding of a fictional informed consent disclosure – one of the four capacities of consent delineated by Appelbaum and Grisso's model (Grisso & Appelbaum, 1998). In this perspective, understanding reflects a person's ability to comprehend the meaning and intent of information provided during the informed consent process. The UTD is similar to informed consent capacity measures used in previous research (Carpenter et al., 2000; Kim et al., 2001). During administration, participants receive an informed consent vignette describing pharmaceutical treatment of depression. The protocol contains five paragraphs of two-to-five sentences each. Material presented in this vignette includes the five basic elements required of an informed consent protocol (Appelbaum et al., 1987). Specifically, the protocol describes 1) depression and its symptoms, 2) a proposed treatment, 3) symptoms which the treatment is expected to relieve and the likelihood this will occur, 4) potential risks and the likelihood they will occur, and 5) a description of alternative treatments and their potential risks and benefits (Appelbaum & Grisso, 1995). Wording on the UTD is at a 7^{th} grade reading level (Grisso et al., 1995).

Understanding is assessed in three ways on the UTD. During uninterrupted disclosure, an entire informed consent disclosure is read aloud to the participant, and the participant reads along with the examiner. Subsequently, questions are asked of the examinee concerning the disclosure. For instance, to query the participant's understanding of the disorder, the examiner reads the following question: "I mentioned some unpleasant things, called symptoms, that people with depression experience. In your own words, what did I say are some of those things--what I called "symptoms?" Similar questions are asked concerning the nature and purpose of treatment, potential benefits of treatment, potential risks and discomforts of treatment, and alternative treatments. Criteria are provided to permit the examiner to score the accuracy of participant responses. Responses are scored, and the maximum possible value for uninterrupted disclosure is 10 points.

During element disclosure, the person is again read aloud a description of the treatment, but only in small successive steps. For example, the examinee is read aloud the portion of the informed consent disclosure concerning the nature of depression. The examinee is then asked to tell their understanding of what was presented. If they fail to demonstrate an accurate understanding of the material, the examinee is then asked more specific questions such as, "What are some of the symptoms of depression I just mentioned?" Similar to the uninterrupted disclosure, the maximum possible score is 10 points for the elemental disclosure.

Subsequent to completing each element disclosure, recognition cues are provided. For instance, the person would be asked to indicate whether the following statement was contained in the protocol description: "People who are depressed may enjoy new experiences (FALSE)." The maximum possible score attainable on the recognition items is 10 points. The UTD takes approximately 20 minutes to administer, and demonstrates satisfactory reliability. In addition, intra-class correlations range from .87 to .96 and Kappa coefficients are high (Appelbaum & Grisso, 1995).

Disability Status—To assess severity of disability, the Ambulation Index was used (Hauser et al., 1983). This measure, which is essentially the 25-foot timed walk from the MS Functional Composite (Fischer et al., 2001), has been used to assess physical disability resulting from MS. It is graded according to a seven-point likert scale, with higher scores indicating greater severity of disability (e.g., 0=Asymptomatic to 7=restricted to a wheelchair). Like the MS Functional Composite, it is commonly used to approximate severity of disability associated with MS (Beatty et al., 2003).

Procedure

The protocol was reviewed and approved by the Institutional Review Board at the University of Tulsa. After obtaining informed consent, the CVLT-II was given. During the interval between immediate and delayed recall, the WCST and Digit Span tests were administered. According to the CVLT-II manual, the delay interval between immediate and delayed recall should last no more than 25 minutes. During instances wherein the WCST took approximately 20 minutes to complete, Digit Span was administered after the CVLT-II delayed recall and recognition trials were completed. Afterward, the UTD was completed. Upon completing these tests, the Ambulation Index was administered.

Data Analytic Plan

We hypothesized that neuropsychologically compromised people with MS would have worse understanding of a medical disclosure. To address this hypothesis, we compared UTD scores of a control group to groups of MS patients with and without diminished neuropsychological test scores. Additionally, we anticipated that recognition cueing would

improve UTD performance compared to uninterrupted disclosure. To evaluate this hypothesis, UTD performance on the uninterrupted disclosure, elemental disclosure, and recognition indices were compared within subjects. Because poor neuropsychological function may attenuate ability of MS patients to benefit from recognition cueing, the UTD scores of the three participant groups were compared across the three indices using a mixed factor analysis of variance. For the sake of parsimony and to reduce the likelihood of Type I error, these two hypotheses were addressed using a single mixed factor analysis of variance. Three participant groups (control, MS-unimpaired, and MS-cognitively compromised) serve as the between groups factor, and performance across the three UTD indices (uninterrupted disclosure, elemental disclosure, recognition) served as the repeated factor. To further reduce the likelihood of Type I error, Bonferroni group contrasts were used to probe significant main effects.

To determine what aspects of neuropsychological function correspond with ability to understand treatment disclosures, a series of multiple regression analyses were used. Representative scores from the Wisconsin Card Sorting Test, California Verbal Learning Test-2, and Digit Span tests served as independent variables, and scores on the three UTD indices were the dependent variables. Because we are attempting to explain variance on the UTD, independent variables were simultaneously entered. To demonstrate unique variance accounted for by each independent variable, semi-partial correlations are reported (Stevens, 1996).

Results

Demographics

Among the people with MS, 7 obtained impaired scores on the WCST, 1 on the CVLT-II, and 6 on the Digit Span subtest. Of these, 1 was impaired on both the WCST and CVLT-II, and another was impaired on the WCST and Digit Span subtest. Consequently, based on their number of impaired scores, participants were classified as follows: 16 members of the control group (CTRL), 24 unimpaired patients with MS (MS-UN; no cognitive measure below the 5^{th} percentile), 12 cognitively-compromised patients with MS (MS-CC; at least one cognitive measure below the 5^{th} percentile).

To evaluate whether the three participant groups differed in demographic composition, a series of oneway ANOVAs were conducted. These analyses revealed that participant groups did not differ according to education ($F(2, 49)=2.04$, $p=.14$, $Eta^2=.07$). However, the groups differed significantly in age ($F(2, 49)=4.95$, $p=.01$, $Eta^2=.17$); this difference in age will be addressed as a covariate in the subsequent analyses. Bonferroni contrasts showed that the control group was significantly younger than the unimpaired patient group. Although the contrast between the MS-CC and control groups failed to achieve significance, its effect size (Cohen's $d=-.77$) was proximal to the significant contrast between the unimpaired and control group (Cohen's $d=-1.0$). There were no differences between the 2 MS groups. Data concerning demographic characteristics and scores on all tests appear in Table 1.

A non-parametric test was conducted to evaluate whether groups differed according to gender composition, and the results indicated the groups did not differ in this regard ($X^2(2)=2.00$, $p=.37$). Likewise, the groups were similar in ethnic composition ($X^2(4)=5.65$, $p=.23$). Participants were asked whether they were diagnosed with depression and receiving psychotherapy or taking anti-depressant medication. Although this may not be an especially sensitive indicator of depressive symptoms, it may serve as a specific indicator of clinical depression. There were no differences in rates of treatment between the two patient groups ($X^2(1)=0.29$, $p=.59$). To further determine whether depression corresponds with performance, scores on the neuropsychological tests and indices from the UTD were

correlated with treatment for depression. In no instance did a correlation approach significance. MS disease course was also evaluated using a non-parametric test, and there were no difference between the two patient groups ($X^2(2)=1.05$, $p=.31$). Owing to time constraints, the Ambulation Index was administered to 22 of the 36 patients with MS. A non-parametric test was computed to determine whether number of people who completed the Ambulation Index differed between patient groups, and there was no significant difference ($X^2(1)=1.03$, $p=.31$). A non-parametric test was computed to determine whether average Ambulation Index scores differed between groups, and they did not ($X^2(6)=4.63$, $p=.59$). Table 1 summarizes the descriptive statistics of the participant groups

Understanding Treatment Disclosures

Analyses of Group Performance Across UTD Indices—Data were analyzed to evaluate whether groups differed in their ability to understand the treatment disclosure (i.e., informed consent information). Consequently, scores on the each of the three UTD indices were compared across the three participant groups. As a follow-up analysis, we evaluated whether understanding of the treatment disclosure was enhanced by recognition cueing and the question probes employed during the element disclosure. Thus, scores on the three UTD indices were compared within subjects. Owing to the significant age difference between groups, we controlled for this effect through covariance in the analyses. To address these issues, data were analyzed in a 3 group (CTRL, MS-UN, and MS-CC) X 3 index (uninterrupted disclosure, element disclosure, recognition cueing) mixed factor ANCOVA. Group was the between groups factor, index was repeated within subjects, and age was the covariate.

In no instance did age account for significant variance on the UTD, and effect size estimates for age were small (Eta^2 =.06). The effect of group was significant ($F(2, 48)=8.02$, $p=.001$, $Eta^2=.25$). In following-up this main effect, scores on the UTD were collapsed across the three indices, and Bonferroni post-hoc contrasts showed that the control group and the unimpaired MS had better understanding than the cognitively-compromised MS group, but the control group and unimpaired MS group performed equivalently across the three indices. No other contrast was significant. The main effect of index was not significant ($F(2, 96)=0.40$, $p=.67$, $Eta^2=.008$). The interaction of group and index was significant ($F(4, 96)=7.91$, $p<001$, $Eta^2=.25$). Consequently, the simple effects of index for each group were analyzed.

The simple main effect of index was significant for the control group ($F(2, 30)=25.16$, $p<.001$, $Eta^2=.63$), the unimpaired MS group ($F(2, 46)=23.48$, $p<.001$, $Eta^2=.51$), and the cognitively-compromised MS group ($F(2, 22)=26.86$, $p<.001$, $Eta^2=.71$). For the control and unimpaired MS groups, Bonferroni contrasts revealed that understanding scores during uninterrupted disclosure were significantly lower than element disclosure or recognition cueing. Their scores on the element disclosure and recognition cueing portion of the UTD were equivalent. For the cognitively-compromised MS group, Bonferroni contrasts showed that element disclosure and recognition cueing resulted in higher understanding scores than with uninterrupted disclosure. Additionally, recognition cueing led to better understanding than element disclosure.

As a further follow-up of the interaction of group and index, the simple main effect of group on each index score was examined. These analyses were done to compare the understanding of the groups on each index. The groups had significantly different scores on the uninterrupted disclosure ($F(2, 49)=12.07$, $p<.001$, $Eta^2=.30$) and element disclosure scales ($F(2, 49)=6.92$, $p=.002$, $Eta^2=.22$). For uninterrupted disclosure, post-hoc Bonferroni contrasts between groups showed that the control group and the unimpaired MS group had better understanding than the cognitively-compromised MS group, and these two groups

performed equivalently to one another. For element disclosure, the control group had better understanding than the cognitively-compromised MS group. The unimpaired MS group was indiscriminate from the control group and the cognitively-compromised MS group during element disclosure. In contrast to the uninterrupted disclosure and element disclosure indices, no significant differences emerged on the recognition cueing index ($F(2, 49)=2.40$, $p=.10$, $Eta^2=.09$). Mean scores of the three groups on the UTD indices appear in Table 2.

Factors Predicting UTD Scores—To determine whether neuropsychological factors account for understanding of treatment disclosures, UTD scores were regressed upon the three neuropsychological indices. Data from all participants in the three groups were included. Tolerances of the CVLT-II Total Trial 1–5 Recall T-score, WCST Perseverative Errors, and Digit Span scaled score ranged from .73 to .95, implying that little multicollinearity existed.

The regression analyses are summarized in Table 3. The results reveal that CVLT-II Total Trial 1–5 Recall T-score ($t(48)=2.05$, $p<.05$) and WCST Perseverative Errors ($t(48)=-1.95$, $p=.05$) emerged as significant unique predictors of uninterrupted disclosure. Semi-partial correlations with uninterrupted disclosure were moderate. As recall increased, scores on the uninterrupted disclosure index improved, and as perseverative errors increased uninterrupted disclosure decreased. For element disclosure and recognition cueing, no neuropsychological test emerged as a significant predictor. Nonetheless, CVLT-II Total Trial 1–5 Recall was a marginally significant predictor of element disclosure ($p=.08$), and the semi-partial correlation coefficient was .22, implying that better recall corresponded with better understanding.

Discussion

These findings reveal that unimpaired patients with MS understand treatment disclosures as well as people without MS. In no instance did the unimpaired-MS patients perform more poorly than the control group on the UTD. Consequently, such individuals seem as capable as non-patients to make competent decisions regarding treatment or medical research.

In contrast, the cognitively-compromised MS group understood less information than the control group during uninterrupted disclosure, and effect size estimates for this contrast were considerable. Notably, understanding of the cognitively-compromised MS group was only 6.0 out of a possible total of 10 points during uninterrupted disclosure on the UTD. This score was nearly 3.0 standard deviations below the control group mean. Thus, they accurately understood only 60% of the treatment disclosure, suggesting that cognitively-compromised MS patients may have difficulty understanding as much as 40% of the information from an informed consent protocol. This hardly seems sufficient for patients to make an informed decision to consent to treatment or research and reflects the clinical importance of cognitive impairment in the understanding process. Nonetheless, it seems likely that most patients will be afforded the same kind of opportunities as those provided in this initial study – regardless of their capacity. Namely, patients and research participants will be provided with a written consent form that will be verbally explained. Unfortunately, the current findings imply that explaining treatment options in the usual fashion to patients with diminished neuropsychological function is insufficient. Indeed, cognitively-compromised MS patients may be incapable of understanding important elements of disclosure concerning treatment or research, thereby influencing their capacity to provide consent.

Nonetheless, because of probing during the element disclosure, the cognitively-compromised MS group was able to understand 80% of the information contained in the

fictional informed consent protocol. This reflected significantly improved understanding from uninterrupted disclosure. Yet, their performance remained significantly lower than the control group. However, with recognition cueing, the cognitively-compromised MS group understood 93% of information provided during the fictional treatment disclosure. This also reflected a significant increase from their score obtained during the uninterrupted disclosure. Moreover, with cueing the cognitively-compromised MS group displayed a level of understanding that was equivalent to the control group, and effect size estimates for this contrast were very small. As such, MS patients with diminished neuropsychological function benefited significantly from repetition and cueing, and their ability to provide consent was enhanced to “normal” levels. Thus, recognition cueing may permit clinicians and clinical investigators to obtain a robust informed consent from patients with MS.

Although the group differences reveal that diminished neuropsychological function places MS patients at risk of poor medical decision-making, these differences fail to indicate which domains of cognitive function are specific risks. Towards this end, the regression analyses revealed that new-learning and executive function predicted understanding of the fictional treatment vignette, and these variables accounted for as much as 28% of the unique variance in performance on the uninterrupted disclosure index from the UTD. Thus, individuals who perform poorly on the California Verbal Learning Test-II and the Wisconsin Card Sorting Test-64 will be least likely to understand details of an informed consent procedure. These data are consistent with prior studies of other clinical populations which revealed similar relationships (cf. Dunn, 2006). Nonetheless, it should be acknowledged that since only 28% of the variance was accounted for by these two measures, other aspects of cognitive function also probably contribute to understanding of treatment disclosures. Indeed, similar to Marson and Harrell (1999), it seems likely that ability to form abstract concepts, understand text and speech, sustain attention, and remember details of informed consent disclosures are necessary to understand medical information. Future research might endeavor to identify whether these, or other, domains are potent predictors of poor understanding.

These data parallel those obtained from patients with schizophrenia, major depressive disorder, mania, Alzheimer’s disease, Parkinson’s disease, and HIV (Appelbaum & Grisso, 1988; Appelbaum & Grisso, 1995; Appelbaum et al., 1999; Appelbaum et al., 1987; Appelbaum & Roth, 1982; Carpenter et al., 2000; Dymek et al., 2001; Griffith et al., 2005; Grisso, 1986; Grisso & Appelbaum, 1998; Grisso et al., 1995; Guerra et al., 2006; Howe et al., 2005; Kim et al., 2001; Marson, 2001; Marson et al., 1996; Marson & Harrell, 1999; Marson et al., 1994; Moser et al., 2006; Moser et al., 2002; Roth et al., 1977). Specifically, each of the aforementioned studies compared patients with disease-related neuropsychological impairment to a normal control group. Across each of these disorders, the patients tended to display poor understanding of medical treatment or medical research disclosures. In the current study, the patients with MS who displayed compromised neuropsychological performance manifested poor understanding of a medical treatment disclosure.

Additionally, similar to previous research (Dunn et al., 2002; Dymek et al., 2001; Gurrera et al., 2006; Kovnick et al., 2003; Moser et al., 2002; Moye et al., 2006; Okonkwo et al., 2008; Palmer et al., 2004; Palmer & Jeste, 2006), specific neuropsychological components had salient relationships with understanding. For instance, among patients with schizophrenia, Palmer et al. (2004) found that executive function, new-learning, and working memory predicted capacity to understand information pertaining to medical decision-making. In the current study, executive function and new-learning corresponded with ability to understand medical treatment choices, and working-memory nearly achieved significance. Although not significant, Digit Span nearly achieved a significant relationship with UTD scores, and its semi-partial correlation was similar to that of the WCST and CVLT. Although these

neuropsychological domains are unlikely exclusive predictors of decisional capacity, this pattern of findings implies that they are important for accurate understanding of medical disclosures.

Furthermore, as with earlier studies involving patients with schizophrenia (Appelbaum & Grisso, 1995; Carpenter et al., 2000; Dunn et al., 2006; Grisso et al., 1995; Grisso & Appelbaum, 1995; Jensen et al., 1993; Wirshing et al., 1998), understanding of informed consent disclosure was capable of enhancement. Thus, these data accord well with a growing body of literature concerning enhanced consent procedures. Although they imply that some patients with central nervous system disease are at risk of poor decision-making regarding treatment or research, their incapacity may be remediated.

Yet, these data are incomplete. Specifically, uncertainties regarding the generalizability of these data must be acknowledged. In particular, average scores on the neuropsychological tests were not severely deficient in the impaired MS group. For example, the cognitively-compromised MS group achieved a mean T-score of 49 on the California Verbal Learning Test-II Total Trial 1–5 Recall index. Although, as revealed in Table 1, some scores were severely impaired, mean performance for this group is essentially normal. Thus, our cognitively-compromised group included only a few participants with impaired memory, whereas most had essentially normal recall. As a result, these data may not generalize to people with MS who have severe neurobehavioral deficits. It seems likely that patients with more severe cognitive deficits will demonstrate more severe difficulties understanding treatment disclosures. It is also uncertain whether they will manifest improved understanding of treatment disclosures with recognition cueing, as did the mildly compromised MS patients in the current study.

Related to this issue, the neuropsychological battery administered in the current study may be somewhat insensitive to neuropsychological impairment in people with MS. For instance, backward span of the Digit Span subtest is of uncertain sensitivity in people with MS. Additionally, our battery addressed only some aspects of executive function, working memory, and new-learning. Other domains of function may also predict decisional-capacity. Perhaps with a more extensive battery including more sensitive measures, an increasingly precise understanding of which cognitive domains predict decisional incapacity may be obtained. We are currently addressing this issue in our laboratory.

It should also be acknowledged that our assessment of depression was less than optimal in this study. Specifically, we identified people as depressed if they had been diagnosed by their physician or were receiving treatment for major depression at the time of study participation. Thus, our assessment of depression was largely qualitative, and could have been strengthened by using a quantitative self-report measure of depressive symptoms. With such an instrument, varying degrees of distress may have been captured, thereby permitting us to assess whether subtle depressive features contribute to decisional incapacity. A number of studies have demonstrated that depression, as indexed by quantitative measures of distress, corresponds with poor performance on measures of executive function in people with MS (Arnett et al., 2001). Inasmuch as depression corresponds with poor reasoning, it may likewise correlate with worsening decisional incapacity. This should be examined in future research, especially because depressive distress is so common in people with MS (Voss et al., 2002). These considerations notwithstanding, they should be tempered by the findings of Appelbaum et al. (1999). In a sample of moderately depressed patients, none displayed impaired understanding of an informed consent vignette. Among severely depressed subjects as well, Cohen et al. (2004) found relatively high levels of research decision-making capacity. This implies that depression may not correspond with poor understanding of medical treatment choices. Furthermore, presence of diagnosed depression

in the current study failed to correlate with performance on the UTD or the neuropsychological battery. Nonetheless, it may be worthwhile to evaluate whether quantitative measures of depression correspond with decisional incapacity to clarify this situation.

Related to limited generalizability, the ambulation index was not administered to all patients with MS. Approximately half of the unimpaired MS group was administered the index because of time constraints. Consequently, a thorough depiction of mobility status for the unimpaired group is unavailable. In contrast all but two of the cognitively compromised MS patients were administered the ambulation index. Among these participants, modest disability was present on average. Additionally, patients were diagnosed according to the Poser et al. (1983) criteria rather than the revised McDonald criteria (Polman, Reingold, Edan, et al., 2005). This may further limit generalizability of the findings.

These data address understanding, which is but one of four domains of informed consent. These data reveal that the UTD is sensitive to detecting poor understanding of medical treatment disclosures in people with MS, and these data recommend its use in evaluating decisional capacity in that population. Nonetheless, as delineated by Grisso & Appelbaum (1998), capacity to express a treatment choice, and ability to appreciate, understand, and reason through treatment information are also required. Because the four requirements seem to be unique and have small intercorrelations (Appelbaum & Grisso, 1995), all four areas of decisional capacity must be examined in future research. Consequently, our data do not permit us to make general statements regarding decisional competence of people with MS. Furthermore, our method of measuring understanding may be non-specific. In particular, although it appears to measure understanding and comprehension of medical treatment, the UTD may also reflect memory performance. For example, it includes a recognition cueing component, and CVLT-2 Total Trial 1–5 Recall emerged as a salient predictor of UTD performance. It may be that the cognitively-compromised MS patients were displaying diminished memory for a medical disclosure rather than poor understanding on the UTD. Collectively, these limitations should temper any rash conclusions that MS patients with subtle neuropsychological deficits are unable to make independent and autonomous decisions regarding medical treatment or research participation. These considerations notwithstanding, this is the first study to our knowledge that examines medical decision-making in persons with MS and simultaneously offers strategies to enhance consent procedures. To protect the rights and well-being of MS patients, these findings provide a compelling impetus to address the issue with greater energy and attention.

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Table 1

Descriptive Statistics

	CTRL	MS-UN	MS-CC
Age	37.56 (9.99)	47.95 (10.85)	45.08 (9.53)
Education	16.00 (2.45)	14.45 (2.39)	15.17 (2.41)
Impaired Scores	0.00 (0.00)	0.00 (0.00)	1.17 (0.39)
Digit Span Backward Span	5.75 (1.39) Min=4/Max=8	5.00 (1.25) Min=4/Max=8	4.42 (1.62) Min=3/Max=7
WCST Perseverative Errors	6.06 (2.40) Min=4/Max=11	7.17 (3.47) Min=4/Max=17	18.83 (12.07) Min=4/Max=42
CVLT Total Trial 1–5 Recall T-Score	61.12 (9.76) Min=44/Max=80	53.75 (8.92) Min=38/Max=76	49.17 (10.57) Min=29/Max=68
Sex	10 Female/6 Male	19 Female /5 Male	10 Female/2 Male
Ethnicity	1 AsAm/15 Cauc	24 Cauc	1AfAm/11 Cauc
Disease Course		10 R-R 5 P-P or S-P 9 Uncertain	4 R-R 4 P-P or S-P 4 Uncertain
Receiving Depression Treatment	0 %	25 %	41 %
Ambulation Index		2.92 (2.32) n=12	3.33 (2.00) n=10

Note: Standard deviations appear in parentheses. CTRL=Control Group. MS-UN=MS Unimpaired. MS-CC=MS Cognitively Compromised. AsAm=Asian American. AfAm=African American. Cauc=Caucasian. R-R: Relapsing remitting. P-P: Primary progressive. S-P: Secondary Progressive.

Table 2

Mean UTD Scores by Group

	CTRL[A]	MS-UN[B]	MS-CC[C]	Bonferroni Contrasts Between Groups
	n **= 16**	***n*** **= 24**	***n*** **= 12**	
UTD Indices	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	
Uninterrupted disclosure[1]	8.63 (.89) Min=7 Max=10	7.79 (1.50) Min=4 Max=10	5.58 (2.53) Min=1 Max=8	A & B > C
Element disclosure[2]	9.94 (.25) Min=9 Max=10	8.96 (1.12) Min=5 Max=10	8.25 (1.95) Min=3 Max=10	A > C
Recognition cueing[3]	9.88 (.34) Min=9 Max=10	9.38 (.97) Min=7 Max=10	9.33 (.78) Min=8 Max=10	NS
Bonferroni Contrasts Across Scales for Each Group	1 < 2 & 3	1 < 2 & 3	1 < 2 < 3	

Note: CTRL=Control Group. MS-UN=MS Unimpaired. MS-CC=MS Cognitively Compromised. The significance level was $p<.05$ for all Bonferroni contrasts. For contrasts:

A=Control Group;

B=Unimpaired MS Group;

C=Impaired MS Group;

1=Uninterrupted Disclosure;

2=Element Disclosure;

*3*Recognition Cueing.

Table 3

Summary of Regression Analyses

UTD Indices	CVLT-II Total Trial 1–5 Recall T-Score	Digit Span Backward Span	WCST Perseverative Errors
Uninterrupted Disclosure	.24*	.22	−.23*
Element Disclosure	.22	.21	−.20
Recognition Cueing	.14	.14	−.09

Note. Values reported are semi-partial correlations.

* $p \leq .05$.