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Review article

The influence of cognitive impairment on health-related quality of life in neurological disease

Mitchell AJ, Kemp S, Benito-León J, Reuber M. The influence of cognitive impairment on health-related quality of life in neurological disease.

Background: Cognitive impairment is the most consistent neurological complication of acquired and degenerative brain disorders. Historically, most focus was on dementia but now has been broadened to include the important construct of mild cognitive impairment.
Methods: Systematic search and review of articles linked quality of life (QoL) and cognitive complications of neurological disorders. We excluded QoL in dementia.
Results: Our search identified 249 publications. Most research examined patients with brain tumours, stroke, epilepsy, head injury, Huntington's disease, motor neuron disease, multiple sclerosis and Parkinson's disease. Results suggested that the majority of patients with epilepsy, motor neuron disease, multiple sclerosis, Parkinson's disease, stroke and head injury have subtle cognitive deficits early in their disease course. These cognitive complaints are often overlooked by clinicians. In many cases, the cognitive impairment is progressive but it can also be relapsing-remitting and in some cases reversible. Despite the importance of severe cognitive impairment in the form of dementia, there is now increasing recognition of a broad spectrum of impairment, including those with subclinical or mild cognitive impairment. Even mild cognitive difficulties can have functional and psychiatric consequences–especially when they are persistent and untreated. Specific cognitive deficits such an inattention, dysexecutive function and processing speed may affect a number of quality of life (QoL) domains. For example, cognitive impairment influences return to work, interpersonal relationships and leisure activities. In addition, fear of future cognitive decline may also impact upon QoL.
Conclusions: We recommend further development of simple tools to screen for cognitive impairments in each neurological condition. We also recommend that a thorough cognitive assessment should be a part of routine clinical practice in those caring for individuals with neurological disorders.

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Introduction

Cognitive impairment is the most consistent neurological complication of acquired and degenerative brain disorders. The majority of patients with epilepsy, multiple sclerosis, Parkinson's disease (PD), stroke and head injury have documented cognitive impairments, often early in their disease course (1). To some extent, this is reflected in self-reported losses (also called subjective memory complaints or meta-memory) but detailed neuropsychological testing is required in order to fully map the degree of impairment (2–5). Yet the degree to which the burden of disease is influenced by changes in cognitive dysfunction is poorly understood. There may be several reasons for this. Cognitive deficits are more appropriately conceived as a cumulative loss of neuronal function supported by specific systems in the brain rather than a single homogenous loss and the impact of heterogeneous losses is difficult to study (6). Pre-existing cognitive reserve will influence to what extent new insults impact upon the individual. In addition, cognitive deficits rarely occur

in isolation. Separating the effects of cognition from the effects of lack of insight, behavioural problems and other neurological impairments require thorough study design. A further factor is that cognitive deficits are rarely static. They are influenced by natural history of disease, treatment variables and even neuropsychological testing itself.

Many different brain insults are capable of causing a spectrum of deficits from subclinical neuropsychological change through mild cognitive impairment to severe dementia. Compared with classical neurological symptoms such as weakness and sensory loss and established psychiatric complications such as depression or anxiety, the impact of cognitive deficits on the patient and their primary carers has been relatively under investigated. There is accumulating evidence to suggest that patients with neurological disorders are particularly concerned about the preservation of cognitive function, perhaps because of the impact on quality of life (QoL) (7).

The concept of health-related quality of life (HRQoL) is one way to measure the burden of disease. For several decades, clinicians have relied on measurement of impairment (loss), disability (function), handicap (participation) to understand the impact of disease (8). However, considerable individual differences in perceived wellbeing, satisfaction and distress are not measured adequately by these constructs (9,10). HRQoL is a much broader concept than impairment or disability but can be difficult to define and measure. The World Health Organisation has revised its taxonomy of International Classification of Impairments, Disabilities and Handicaps (ICIDH) to incorporate QoL (11,12). Higher ratings of QoL are not just important phenomenologically but are also recognised as an important measure of satisfaction with care and adherence with treatment (13). Exploration of the predictors of HRQoL is helped by a clinically applicable definition. Here we use the definition of HRQoL suggested by Mitchell et al. (14). That is, the sum of all sources of satisfaction and wellbeing minus all health-related threats (including anticipated threats).

Studies in other areas of medicine reveal multiple predictors of QoL (Box 1). In neurological disorders, there are considerable threats to the self as a result of symptoms in fundamental areas of higher function such as speech and motivation in addition to the threats posed by cognitive decline. Meta-analyses suggest that HRQoL is weakly associated with impairment, moderately correlated with disability and highly correlated with handicap (15). Thus, the link between cognitive impairment and burden of disease is unlikely to be simple. HRQoL may be reduced by current cognitive losses as well as the threat of possible future losses. Cognitive domains such as memory, attention, communication, planning, insight and even personal identity could effect satisfaction and daily living in specific ways. Here, we examine possible links between cognitive impairments across neurological disease and impact on HRQoL. Where possible we highlight where specific cognitive domains have been studied in relation to specific areas of HRQoL.

Box 1. Predictors of Poor QoL

Strong predictors
- Cognitive impairment
- Depression/demoralisation
- Lack of autonomy
- Lack of support
- Chronic Pain
- Lack of participation (*handicap*)

Moderate
- Fatigue
- Anxiety
- Communication difficulties
- Bladder and sexual problems
- Rapidly progressive disease
- Low self-esteem and self-deprecation
- Comorbid conditions
- Functional loss (*disability*)

Weak
- Long duration of disease
- Subtypes of disease
- Forced unemployment
- Biological disease burden
- Older age
- Female
- Neurological symptoms and signs (*impairment*)

After Mitchell et al. (14).

Methods

Our aim was to systematically review the relationship between cognitive impairment and HRQoL in neurological conditions. We excluded Alzheimer's disease and other dementias that are not preceded by a neurological disorder because the link with HRQoL is likely to be distinct in these conditions and also care is usually provided in a different setting. References for this review were identified by searches of the following dates from inception to October 2009: Web of Knowledge, Scopus, Pubmed, Wiley-Blackwell full text, Sciencedirect full text, Lippincott Williams & Wilkins full text and Ovid full text. The terms 'quality of life', 'disability', 'handicap', 'participation', 'perception', 'self-efficacy', 'carer or care

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giver', 'health-related quality of life' and 'mild cognitive impairment' or 'cogniti$' or 'neuropsycholog* or memory or dysexecutive' were entered. Articles were also identified through hand searches.

Our search initially identified 4793 articles by abstract search and 1872 by limiting to title search. Of the 1872 articles, there were 421 meeting abstracts, 221 book reviews, 64 editorials, 43 letters and brief communications, and 48 review articles. Of the remaining 1075 primary articles, only 180 examined patients with neurological disease. These formed the basis of this review together with 69 other papers found by citation or hand searches.

QoL in neurological conditions causing cognitive impairment

Brain tumours

Cognitive abnormalities in those with central nervous system (CNS) tumours are common, usually as a direct result of the tumour invasion, but increasingly recognised to occur as a complication of treatment (16,17). Recent studies, suggest that although both chemotherapy and radiotherapy can cause cognitive deficits, focal radiotherapy in patients with glioma is rarely the main reason for cognitive impairment (16–18). Neuropsychological effects may occur beyond the local tumour site (19). Compared with healthy controls, patients with gliomas have significant reductions in information-processing speed, psychomotor function, attentional functioning, verbal and working memory, executive functioning and HRQoL (20). Cognitive function is also recognised as an independent prognostic factor in the survival of glioma patients (21,22). Not infrequently cognitive deficits are subclinical in those suffering CNS tumours, but tests for attention, memory and word fluency appear to be the most sensitive in detecting subtle dysfunctions. Of particular note, cognitive decline frequently occurs before magnetic resonance imaging (MRI) evidence of disease progression if assessed sensitively (23). Unfortunately, there has been little progress in practical methods to test cognitive abnormalities in this population (24).

There has been growing interest in the link between cognitive impairment and HRQoL in brain tumours. Subtle cognitive deficits can prevent brain tumour long-term survivors from returning to premorbid autonomy and occupations (25). In general, when operable, successful resection of the tumour leads to improvement in HRQoL (26). For those with ongoing complications, the burden of symptoms correlate with HRQoL (27). Neuropsychiatric symptoms and communication difficulties have been strongly associated with high perceived disease burden (28). Giovagnoli and colleagues compared 94 glioma patients with 24 patients with other chronic neurological diseases and 48 healthy subjects (29). The Functional Living Index-Cancer (FLIC) provided HRQoL self-evaluations. In glioma patients, higher FLIC total scores were related to better cognition, physical performances and mood. Compared with healthy subjects, all glioma patients were cognitively impaired and more anxious, and two groups with short duration of recurrence were also more depressed. Glioma and chronic disease patients showed similar FLIC scores and autonomy. Li et al (30). examined the relationship between cognition and QoL in 208 patients with brain metastases post-radiotherapy. Cognition was statistically significant correlated with the activities of daily living (ADL) and QoL measured by the Functional Assessment of Cancer Therapy (FACT). Interestingly, scores on all eight neuropsychological subtests deteriorated weeks or months before functional and QoL decline.

Several options are available to measure HRQoL in those with brain tumours from single item tests to complex semistructured questionnaires (31). Regarding therapeutic options, there have been a handful of trials of recording HRQoL and cognition (32). One group recently documented improvements in both cognition and HRQoL following an open label trial with an acetylcholinesterase inhibitor (33). A second group trialled combined cognitive-rehabilitation and reported high satisfaction with a problem-solving-therapy intervention for 19 patient/caregiver pairs (34).

Cerebrovascular accidents (stroke)

Stroke is well known to adversely influence current cognitive performance (35), HRQoL (36) and ultimately mortality (37). Stroke survivors with frequent complications report poorer HRQoL in the area of memory and thinking, and those with an ischaemic stroke and concordance reported poorer communication (38). Two large studies have recently reported rates of post-stroke cognitive impairment of approximately 40–55% (39,40). The relative risk of dementia after stroke is five-fold compared with that in aged-matched controls (41,42).

What then is the link with HRQoL? Certainly extent of the lesion and depression are associated with poor post-stroke HRQoL but other factors are also important (43,44). Kwa et al. (45) conducted one of first studies to specifically examine cognitive aspects in 129 patients with ischaemic stroke. Cognitive function was assessed with the Cambridge cognitive battery (CAMCOG) and HRQoL with a visual analogue scale (VAS). Regression analysis revealed

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that disturbed global functional health, larger volume of infarcts and severity of aphasia were significantly independent explanatory factors for poorer HRQoL. Thus, in a relatively high functioning group, there was no significant impact of cognitive impairment on the patients' HRQoL, beyond the effect on other domains. Jonkman et al. (46) found similar results first observing that QoL improved to a modest extent in the period 3–12 months after the stroke and that change in QoL was correlated with depression, neurological deficit, but not with cognitive disturbances. However, Hochstenbach et al. (47) used more comprehensive neuropsychological testing in 164 stroke patients and found HRQoL was associated with deficits on specific tests measuring spatiotemporal and/or sequential aspects of behaviour. Poor HRQoL was more likely if patients had a poor result on the Trail making Test B. In a follow-up study 2 years later, significant improvements across time were noted for all cognitive domains and interestingly the largest improvement was found in the attentional domain; the least, in the memory domain (48). A small subset of patients accounted for the significant cognitive improvement because most patients showed no improvement or declined. In a small group of 35 stroke patients after a stroke, Kauhanen et al. (49) found that infarct volume, aphasia, impaired motor function and impaired cognitive function were linked with poorer QoL, but again depression was the most significant. Halari et al. (50) looked at 95 participants with chronic aphasia (>1 year) from three different sites. Emotional distress, involvement in activities, extent of communication disability and number of comorbid conditions explained 52% of the variance in HRQoL. Nys et al. (51) examined 143 patients within the first 3 weeks post-stroke using the Montgomery Asberg Depression Rating Scale and Stroke-Specific Quality of Life Scale. Cognitive impairment (especially problems with visual perception and construction), increasing age and functional dependence predicted a reduced QoL.

Unlike many neurological conditions, here have been several serious attempts to validate instruments to measure stroke-related cognitive change but as yet no consensus about which test is optimal for clinical practice (52–55). Regarding interventions some early studies have reported positive effects of cognition and HRQoL with various rehabilitation packages (56).

Epilepsy

Cognitive deficits in patients with epilepsy can be static (for instance, when deficits are associated with hippocampal sclerosis), episodic (for example, when deficits are post-ictal) or progressive (memory deficits in recurrent status epilepticus) (57). Cognitive deficits associated with the adverse effects of medication are potentially reversible, whereas deficits caused by structural changes (including epilepsy surgery) are not.

Although there are numerous studies of QoL in epilepsy, the potential influence of cognitive impairment on QoL has received relatively little attention and with no allowance for epilepsy type or treatment received. Patients with partial epilepsy (even those able to maintain regular employment) are now recognised to be at risk for cognition impairment (58). Previously there was also an assumption that poor HRQoL must be attributed directly to seizure frequency or medication side-effects. In a landmark study, Perrine et al. (59) looked at 257 patients with various types of epilepsy from 25 epilepsy centres in the United States. Mood, psychomotor speed, verbal memory and language correlated significantly with selected scales of the QoL in Epilepsy-89 inventory and were predictive of overall QoL. Mood was the strongest predictor in regression analysis. In a study of 65 patients with temporal lobe epilepsy (TLE), regression analysis showed that overall QOLIE-89 score was predicted by the factor Mood and Questionnaire of Memory Efficiency score. The QOLIE-89 factor cognition was predicted by the Questionnaire of Memory Efficiency score and the memory, mental speed, perception and praxis factors of the neuropsychological test battery (60). Engelberts et al. (61) looked at 56 outpatients with partial epilepsy who were compared with 56 matched healthy controls. Mental aspects of HRQoL such as fatigue were lower, whereas physical functioning was unaffected. These patients also expressed reductions in mental functioning as indicated by low self-perceived cognitive functioning. Duration of epilepsy, seizure type, seizure frequency, localisation, years on carbamazepine and carbamazepine dosage were not related to cognitive functioning or HRQoL. In a further study by Engelberts et al. (62) looked at cognition (attention, memory and processing speed) in relatively stable outpatients with partial epilepsy treated with carbamazepine. A lower speed of information processing affecting everyday life functioning was found. Lower levels of self-perceived neuropsychological functioning were reported, whereas HRQoL was unimpaired relative to healthy controls. Piazzini et al. (63) examined a large group of 815 patients recruited from 24 secondary and tertiary Italian centres for the care of epilepsy using the Epi-QoL. The main predictors included gender, seizure frequency, prognostic categories, number of medications, comorbidity, presence of cognitive impairment, psychiatric

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disturbances and disability. Meneses et al. (64) studied only 71 patients with focal epilepsy of moderate severity but with comprehensive neuropsychological testing. Attentive matrices and semantic fluency predicted several aspects of HRQoL with the exception of social functioning.

Several groups have examined the effects of epilepsy surgery on cognitive performance and others on HRQoL but not in the same study. Those who achieve an improvement in seizure control usually report improved HRQoL (65,66). The effect is particularly marked where an individual regains independence and social function (67). What then is the effect on cognition? Resective procedures, especially in the dominant hemisphere, usually cause memory impairment (68,69). Both anterior temporal lobectomy and amygdalohippocampectomy have been shown to worsen verbal learning and memory (70). Preoperative ability status, age at the time of surgery and the extent of the resection of functioning tissues are the most important factors determining post-operative memory reserve (71,72). However, this detrimental effect has to be balanced against positive cognitive benefits of seizure control. In patients with improved seizure control, there was evidence of recovery of memory and non-memory functions (73).

Head injury (traumatic brain injury)

Cognitive deficits are one of the most important complications of head injury, being closely related to global severity (74,75). Some form of memory disturbance almost always accompanies moderate or severe head injuries, and not infrequently mild head injury as well (76). Yet, severe cognitive deficits occur in less than 5% of head injuries (77). Reduced attention, memory deficits (anterograde amnesia) and word-finding difficulties are also seen but are typically transient. Risk factors for cognitive deficits are penetrating injuries, head injuries in elderly patients and lesions to frontal or dominant temporal lobes (78). Recovery seems to occur more quickly in domains including memory, verbal abstraction and manual dexterity than in other domains (79).

Cognitive deficits after head injury have an important influence on long-term outcome (80). Return to work has been studied extensively in this regard. Early cognitive deficits affecting attention, memory and orientation have been used as predictors of functional recovery and return to work (81,82). However, relatively few studies have looked specifically at QoL as an outcome (83). Lannoo et al. (84) studied 158 patients with severe head injuries in comparison with group of 32 patients with traumatic injuries to parts of the body. Head injury patients had poorer scores on the sickness impact profile (SIP) scales for mobility, intellectual behaviour, communication, home management, eating and work. Tate and Broe (85) examined the long-term predictors of disability in 70 individuals with varying levels of disability after severe traumatic brain injury. Examination of specific domains of psychosocial functioning (occupational activities, interpersonal relationships and independent living skills) revealed different patterns of significant predictor variables. Occupational activity was best predicted by physical impairment and memory, whereas interpersonal relationships were predicted by time post-trauma, cognitive processing speed and behaviour. Independent living was predicted by physical impairment and behavioural regulation and memory deficits. Wood and Rutterford (86) looked at multidimensional predictors of long-term outcome in 131 participants more than 10 years after injury. In this study, impairment in working memory did not predict QoL.

Occupational status is one objective measure of global functioning that correlates with QoL ratings in a variety of medical disorders (87–89), including head injury (90). A number of independent groups have examined cognitive performance as a predictor of return to work (91–93). In general, the factors most consistently associated with employment outcome included pre-injury occupational status, functional status at discharge, global cognitive functioning, involvement in rehabilitation services and emotional/behavioural complications. Specific cognitive domains may have particular importance (93–95). Even in the case of mild traumatic brain injury, verbal memory, verbal fluency and a speed test of planning and strategy are predictive of work status 3–15 months later (96). In brain injury, there are well-designed randomised trials of neuropsychological rehabilitation showing that treatment can influence long-term outcomes including HRQoL (97–100).

Huntington's disease

Changes in executive function and memory function are often noticeable at least 2 years before the clinical development of the condition in at-risk carriers (101). Most, but not all, studies have found that the severity of cognitive impairment is determined by the number of CAG repeats. Deficits are progressive, and the point prevalence of dementia in definite Huntington's disease is somewhere between 30 and 50%, depending on the sample and instrument used.

QoL has been poorly studied in this condition, particularly in relation to cognitive change. Helder et al. (102) assessed 77 patients with a clinically confirmed diagnosis of Huntington's disease (HD) using the SIP. Total motor score, MMSE scores

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and the duration of HD were significantly correlated with patients' scores on the SIP, and predicted a significant amount of variance of the physical dimension of the SIP, but not of the psychosocial dimension. Ho et al. (103) studied 70 patients with HD using the Unified Huntington's Disease Rating Scale (UHDRS) motor, Beck Depression inventory and SF36. Poor HRQoL was associated with higher levels of depressive mood and lower functional capacity but interestingly motor symptoms and cognitive function were not particularly influential.

Regarding assessment, several small-scale studies have proposed certain generic instruments to detect cognitive change in HD (104,105). Relatively little has been published concerning the value of different HRQoL instruments in Huntington's disease (106,107) and there have been no therapeutic trials in this area.

Motor neuron disease

Significant neuropsychological impairment is present in at least one-third of all sufferers of classical MND (108). Until recently, MND was seen as a pure disorder of the motor system with a low incidence of cognitive impairment. Increasingly, it is recognised that patients with MND without dementia often manifest fronto-temporal type cognitive impairment. Indeed MND and fronto-temporal dementia can overlap in both familial and sporadic cases of MND (109). Selective cognitive impairment in the form of verbal fluency deficits, most likely indicating executive dysfunction, appears relatively early on in the course of the disease, and language functions may become vulnerable as the disease progresses. Dementia occurs in 5–10% of sufferers, with an increased risk of frontal lobe dementia in the late stages of disease (110). Authors have looked for biological markers of cognitive decline in MND. Provisional work suggests that on PET functional imaging greater impairment of medial temporal lobe activity occurs in MND with fronto-temporal dementia compared with those without dementia (111). Nevertheless, cognitive impairment is not an invariable feature of MND and can be difficult to detect (112).

The relationship between cognitive decline in MND and perceived QoL has rarely been studied. Of note, in some conditions, cognitive impairment appears to have a modest, but significant impact on patients' desire for hastened death (113). In a study of 31 patients with MND, QoL scores were found to correlate positively with the existence of confiding and emotional support and also correlated negatively with the presence of self-rated everyday cognitive difficulties but not with affective state (114). As with other neurological disorders, both fatigue and depression are associated with poorer QoL in subjects with MND (115,116). Instruments to measure QoL are available but their validation is unclear (117).

Multiple sclerosis

When examined carefully, specific cognitive deficits can be seen in over 50% of patients, often in the earliest phases of disease (118,119). However, up to half of such cases are overlooked when using a routine examination alone (120), and personal accounts may be also be revealing (121). Even in patients with short disease duration of less than 2 years, discrete impairment of cognitive function may be found in up to 60% on neuropsychological testing without impacting activities of daily living (122,123).

Most (124–127) but not all (128) studies document an association between cognitive deficits and lowered HRQoL. Cutajar et al. (126) evaluated patients with MS in a cross-sectional study. A relationship was found between both memory impairment and executive function and HRQoL. Gold et al. (127) compared 80 MS patients with cognitive dysfunction with 107 unimpaired patients, separated on the basis of the symbol digit modalities test (SDMT). Cognitively impaired patients showed significantly higher depression and anxiety as well as lower HRQoL. Shawaryn et al. (124) used the paced auditory serial addition test (PASAT) as a measure of cognitive impairment in 90 patients with MS. Information-processing speed predicted mental and emotional aspects of HRQoL on the Medical Outcomes Trust's Short Form-36 (SF-36) and both the EDSS and the PASAT predicted depression. Benedict et al. (129) found that cognitive decline predicted mental components of HRQoL (in unadjusted analysis) and ability to maintain employment. Most recently, Benito-Leon et al. (130) examined all degrees of cognitive impairment using neuropsychological testing as well as the Clock Drawing Test and MMSE screening instruments in 191 MS patients. After controlling for depression comprehensive (but not simple) ratings of cognition significantly contributed to poor HRQoL. In addition, all degrees of cognitive impairment, severity of fatigue and higher physical disability were independent predictors of low FAMS instrument total scores. Our search only identified one trial linking rehabilitation with improvements in HRQoL (131). Patti et al. (131) found improvements in HRQoL in those randomised to an intensive 6-week rehabilitation package.

Parkinson's disease

Cognitive impairment is increasingly recognised as an important feature of PD (132). A substantial

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proportion develop Lewy body dementia (133,134). Specific cognitive domains are affected even in early disease stages (135) and clinical criteria have been suggested (136). Common problem areas include executive performance, which is more severely affected than visuospatial function, which in turn is more severely affected than memory and language.

Schrag et al. (137) examined the factors that influence HRQoL using the specific Parkinson's disease Questionnaire (PDQ39). The factor most closely associated with disruptions in HRQoL was the presence of depression (explaining 54% of the variance). Disability, postural instability, a history of falls or of gait difficulties and cognitive impairment (as determined by MMSE) also contributed to poor HRQoL. In a small study, Croyle et al. (138) showed that neuropsychological deficits were linked with pool QoL. Also in a community study of 114 patients with idiopathic PD, Weintraub et al. (139) showed that increasing severity of depression and worsening cognition on the MMSE were associated with greater disability using the UPDRS ADL score, accounting for 37% of the variance in disability. Unfortunately, QoL *per se* was not examined. Klepac et al. (140) studied 124 consecutive PD patients without dementia based on DSM-IV criteria and Mini Mental State Examination. In multivariate analysis, after multiple adjustments better cognitive performance was independently associated with better HRQoL.

Treatments for cognitive decline are showing some promise in PD and may influence QoL (141). A rehabilitation program of 6 weeks, including both motor and cognitive training, was applied to 20 patients affected by PD in the early stages, presenting with mild cognitive deficits, but no dementia. At the end of the scheduled sessions, the patients showed a significant improvement in verbal fluency, logic memory and Raven's matrices tests, when compared with baseline (142).

Conclusions

A spectrum of cognitive impairments complicates the course of a substantial proportion of patients with all the neurological conditions discussed in this systematic review. In the case of epilepsy, Huntington's disease, motor neuron disease, multiple sclerosis and PD deficits accumulate early in the disease course, sometimes pre-clinically. Although much attention has focussed on dementia, there is increasing recognition of the importance of a broad spectrum of impairments, such as those rated as subclinical, minimal or mild (143).

Given that cognitive difficulties are a key part of neurodegenerative and acquired brain disorders, it is surprising that they often undetected and untreated (144). Even frank dementias often go unrecognised for many years (145). Yet cognitive symptoms predict future mortality in healthy and dementia populations (146,147) and have prognostic value in other medical disorders (148). Moreover, cognitive deficits are an important outcome variable in themselves. This systematic review shows that in many neurological conditions mild, moderate and severe cognitive change is perceived as a significant burden by both patients and carers. In other areas of medicine, perceived memory difficulties, poor concentration and impaired problem solving are important predictors of low HRQoL (149), as well as the ability to continue successful employment (150,151). However, losses in specific domains appear to affect global outcomes in different ways. For example, Artero et al. (152) examined predictors of decline in disability over a 3-year period in patients with mild cognitive impairment. Decline in visuospatial performance on cognitive tests was the most significant predictor of decline in ability to dress, bathe, use the telephone or retain mobility. Decline in attention also reduced the capability of independent toileting, and a decline in language was associated with poor telephone use. Memory impairment alone did not have a large effect. Similarly, after head injury return to work may be best predicted by memory problems, whereas interpersonal relationships are more closely tied with cognitive processing speed and behaviour (153). Cognitive difficulties can also adversely influence personal and social interactions. For example, the inability to predict the actions of others and remember previous interactions is likely to erode personal relationships and thereby threaten social support. In several areas (particularly brain injury), neuropsychological rehabilitation programmes have helped patient and caregiver satisfaction and improved HRQoL.

This systematic review is limited by the paucity of research in many neurological conditions. Relatively few studies have examined the progression of deficits or specific cognitive domains in relation to HRQoL. There is also considerable uncertainty about what degree of severity of cognitive change is necessary in order to produce a measurable effect on global wellbeing. Further research is required to examine vulnerability and reliance factors in HRQoL and in particular the role of social support and insight. Nevertheless, we suggest that a thorough cognitive examination should be part of routine clinical practice in those caring for neurological patients.

References

1. Heilman K, Valenstein E. Clinical Neuropsychology (Medicine) (Hardcover). New York: Oxford University Press, 2004.

https://doi.org/10.1111/j.1601-5215.2009.00439.x Published online by Cambridge University Press

2. Matotek K, Saling MM, Gates P, Sedal L. Subjective complaints, verbal fluency, and working memory in mild multiple sclerosis. Appl Neuropsychol 2001;**8**:204–210.
3. Marrie RA, Chelune GJ, Miller DM, Cohen JA. Subjective cognitive complaints relate to mild impairment of cognition in multiple sclerosis. Mult Scler 2005;**11**:69–75.
4. Hendriks MPH, Aldenkamp AP, Alpherts WCJ, Ellis J, Vermeulen J, van der Vlugt H. Relationships between epilepsy-related factors and memory impairment. Acta Neurol Scand 2004;**110**:291–300.
5. Gass CS, Apple C. Cognitive complaints in closed-head injury: relationship to memory test performance and emotional disturbance. J Clin Exp Neurophyschol 1997;**19**: 290–299.
6. Mitchell AJ. Neuropsychiatry and behavioural neurology explained. Edinburgh: W. B. Saunders, 2004.
7. Fisher RS, Vickrey BG, Gibson P et al. The impact of epilepsy from the patients' perspective Part I: descriptions and subjective perceptions. Epilepsy Res 2000;**41**:39–51.
8. Halbertsma J, Heerkens YF, Hirs WM, de Kleijn-de Vrankrijker MW, Dorine Van Ravensberg CD, Napel HT. Towards a new ICIDH [International Classification of Impairments, Disabilities and Handicaps]. Disabil Rehabil. 2000 Feb 15;**22**:144–156.
9. Geyh S, Kurt T, Brockow Tet al. Identifying the concepts contained in outcome measures of clinical trials on stroke using the international classification of functioning, disability and health as a reference. J Rehabil Med 2004; **36**(Suppl. 44):56–62.
10. Gottlieb A, Golander H, Bar-Tal Y, Gottlieb D. The influence of social support and perceived control on handicap and quality of life after stroke. Aging Clin Exp Res 2001;**13**:11–15.
11. World Health Organization. International Classification of Impairments, Disabilities and Handicaps. Geneva: WHO, 1980.
12. Assessment, Classification and Epidemiology Group. International Classification of Functioning and Disability (ICIDH-2) Beta-2 draft Full Version. July, 1999. Geneva: WHO.
13. Grosset KA, Grosset DG. Patient-perceived involvement and satisfaction in Parkinson's disease: effect on therapy decisions and quality of life. Movement Disorders 2005;**20**:616–619.
14. Mitchell AJ, Benito-Leon J, Gonzalez JMM et al. Quality of life and its assessment in multiple sclerosis: integrating physical and psychological components of wellbeing. Lancet Neurol 2005;**4**:556–566.
15. Dijkers M. Quality of life after spinal cord injury: a metaanalysis of the effects of disablement components. Spinal Cord 1997;**35**:829–840.
16. Taphoorn MJB, Klein M. Cognitive deficits in adult patients with brain tumors. Lancet Neurol 2004;**3**:159–168.
17. Brown PD, Buckner JC, O'Fallon JR et al. Effects of radiotherapy on cognitive function in patients with low-grade glioma measured by the Folstein Mini-Mental State Examination. J Clin Oncol 2003;**21**:2519–2524.
18. Falleti MG, Sanfilippo A, Maruff P, et al. The nature and severity of cognitive impairment associated with adjuvant chemotherapy in women with breast cancer: A meta-analysis of the current literature. Brain Cogn 2005;**59**:60–70.
19. Bartolomei F, Bosma I, Mein M et al. How do brain tumors alter functional connectivity? A magnetoencephalography study. Ann Neurol 2006;**59**:128–138.
20. Klein M, Engelberts NHJ, van der Ploeg HM, Trenite DGAKN et al. Epilepsy in low-grade gliomas: The impact on cognitive function and quality of life. Ann Neurol 2003;**54**:514–520.
21. Meyers CA, Hess KR, Yung WKA, Levin VA. Cognitive function as a predictor of survival in patients with recurrent malignant glioma. J Clin Oncol 2000;**18**:646–650.
22. Armstrong CL, Goldstein B, Shera D, Ledakis GE, Tallent EM. The predictive value of longitudinal neuropsychologic assessment in the early detection of brain tumor recurrence. Cancer 2003;**97**:649–656.
23. Meyers CA, Hess KR. Multifaceted end points in brain tumor clinical trials: cognitive deterioration precedes MRI progression. Neuro-oncol 2003;**5**:89–95.
24. Olson RA, Chhanabhai T, McKenzie M. Feasibility study of the Montreal Cognitive Assessment (MoCA) in patients with brain metastases. Support Care Cancer 2008; **16**:1273–1278.
25. Giovagnoli AR, Boiardi A. Cognitive impairment and quality-of-life in long-term survivors of malignant brain-tumors. Italian J Neurol Sci 1994;**15**:481–488.
26. Brown PD, Maurer MJ, Rummans TA et al. A prospective study of quality of life in adults with newly diagnosed high-grade gliomas: the impact of the extent of resection on quality of life and survival. Neurosurgery 2005;**57**: 495–503.
27. Osoba D, Brada M, Prados MD, Yung WKA. Effect of disease burden on health-related quality of life in patients with malignant gliomas. Neuro-oncol 2000;**2**:221–228.
28. Pelletier G, Verhoef MJ, Khatri N, Hagen N. Quality of life in brain tumor patients: the relative contributions of depression, fatigue, emotional distress, and existential issues. J Neuro-oncol 2002;**57**:41–49.
29. Giovagnoli AR, Silvani A, Colombo E et al. Facets and determinants of quality of life in patients with recurrent high grade glioma. J Neurol Neurosurg Psychiatry 2005;**76**:562–568.
30. Li J, Bentzen SM, Li JL et al. Relationship between neurocognitive function and quality of life after whole-brain radiotherapy in patients with brain metastasis. Int J Rad Oncol Biol Phys 2008;**71**:64–70.
31. Mauer ME, Bottomley A, Taphoorn MJB Evaluating health-related quality of life and symptom burden in brain tumour patients: instruments for use in experimental trials and clinical practice. Curr Opin Neurol 2008;**21**:745–753.
32. Gehring K, Sitskoorn MM, Aaronson NK et al. Interventions for cognitive deficits in adults with brain tumours. Lancet Neurol 2008;**7** 548–560.
33. Shaw EG, Rosdhal R, D'Agostino RB, Lovato J, Naughton MJ, Robbins ME, Rapp SR. Phase II study of donepezil in irradiated brain tumor patients: effect on cognitive function, mood, and quality of life. J Clin Oncol 2006;**24**:1415–1420.
34. Locke Dona EC, Cerhan JH, Wu W et al. Cognitive rehabilitation and problem-solving to improve quality of life of patients with primary brain tumors: a pilot study. J Support Oncol 2008;**6**:383–391.
35. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med 2003;**348**:1215–1222.

https://doi.org/10.1111/j.1601-5215.2009.00439.x Published online by Cambridge University Press

36. Paul SL, Sturm JW, Dewey HM, Donnan GA, Macdonell RAL, Thrift AG. Long-term outcome in the north east Melbourne stroke incidence study—predictors of quality of life at 5 years after stroke. Stroke 2005;**36**: 2082–2086.
37. Melkas S, Oksala NKJ, Jokinen H et al. Poststroke dementia predicts poor survival in long-term follow-up: influence of prestroke cognitive decline and previous stroke. J Neurol Neurosurg Psychiatry 2009;**80**:865–870.
38. Nichols-Larsen DS, Clark PC, Zeringue A, Greenspan A, Blanton S. Factors influencing stroke survivors' quality of life during subacute recovery. Stroke 2005;**36**:1480–1484.
39. Madureira S, Guerreiro M, Ferro JM. Dementia and cognitive impairment three months after stroke. Eur J Neurol 2001;**8**:621–627.
40. Patel M, Coshall C, Rudd AG et al. Post-stroke cognitive impairment: clinical determinants and its associations with long-term stroke outcomes. J Neurol Sci 2001; **187**(Suppl. 1):S23.
41. Hénon H, Durieu I, Guerouaou D et al. Poststroke dementia incidence and relationship to prestroke cognitive decline. Neurology 2001;**57**:1216–1222.
42. Tatemichi TK, Paik M, Bagiella E et al. Dementia after stroke is a predictor of long-term survival. Stroke 1994;**25**:1915–1919.
43. Fatoye FO, Komolafe MA, Eegunranti BA et al. Cognitive impairment and quality of life among stroke survivors in Nigeria. Psychol Rep 2007;**100**:876–882.
44. Moon YS, Kim SJ, Kim HC, Won MH, Kim DH. Correlates of quality of life after stroke. J Neurol Sci 2004; **224**:37–41.
45. Kwa VIH, Limburg M, de Haan RJ. The role of cognitive impairment in the quality of life after ischaemic stroke. J Neurol 1996;**243**:599–604.
46. Jonkman EJ, de Weerd AW, Vrijens NLH. Quality of life after a first ischemic stroke—long-term developments and correlations with changes in neurological deficit, mood and cognitive impairment. Acta Neurol Scand 1998;**98**:169–175.
47. Hochstenbach JB, Anderson PG, van Limbeek J, Mulder TT. Is there a relation between neuropsychologic variables and quality of life after stroke? Arch Phys Med Rehabil 2001;**82**:1360–1366.
48. Hochstenbach JB, Mulder TW. Cognitive recovery after stroke: a 2-year follow-up. Arch Phys Med Rehabil 2003;**84**:1499–1504.
49. Kauhanen ML, Korpelainen JT, Hiltunen P et al Domains and determinants of quality of life after stroke caused by brain infarction. Arch Phys Med Rehabil 2000;**81**:1541–1546.
50. Hilari K, Wiggins RD, Roy P, Byng S, Smith SC. Predictors of health-related quality of life (HRQL) in people with chronic aphasia. Aphasiology 2003;**17**:365–381.
51. Nys, GMS; van Zandvoort, MJE; van der Worp, HB et al.Early cognitive impairment predicts long-term depressive symptoms and quality of life after stroke. J Neurol Sci 2006;**247**:149–156.
52. Randhawa S, Walterfang M, Miller K et al. The development and validation of a carer questionnaire to assess cognitive function in neuropsychiatric patients. J Psychosom Res 2007;**63**:93–98.
53. te Winkel-Witlox, ACM, Post MWM, Visser-Meily JMA et al. Efficient screening of cognitive dysfunction in stroke patients: comparison between the CAMCOG and the R-CAMCOG, Mini Mental State Examination and Functional Independence Measure-cognition score. Disabil Rehabil 2008;**30**:1386–1391.
54. Tang, WK; Mok, V; Chan, SSM et al. Screening of dementia in stroke patients with Lacunar infarcts: comparison of the Mattis Dementia Rating Scale and the Mini-Mental State Examination. J Geriatr Psychiatry Neurol 2005;**18**:3–7.
55. Adunsky A, Fleissig Y, Levenkrohn S et al. Clock drawing task, mini-mental state examination and cognitive-functional independence measure: relation to functional outcome of stroke patients. Arch Gerontol Geriatr 2002;**35**: 153–160.
56. Olsson G, Sunnerhagen B, Stibrant K. Functional and cognitive capacity and health-related quality of life 2 years after day hospital rehabilitation for stroke: a prospective study. J Stroke Cerebrovasc Dis 2007;**16**:208–215.
57. Lutz MT, Helmstaedter C. EpiTrack: tracking cognitive side effects of medication on attention and executive functions in patients with epilepsy. Epilepsy Behav 2005;**7**:708–714.
58. Andersson-Roswall L, Engman E, Samuelsson H et al. Verbal memory decline and adverse effects on cognition in adult patients with pharmacoresistant partial epilepsy: a longitudinal controlled study of 36 patients. Epilepsy Behav 2004;**5**:677–686.
59. Perrine K, Hermann BP, Meador KJet al. The relationship of neuropsychological functioning to quality-of-life in epilepsy. Arch Neurol 1995;**52**:997–1003.
60. Giovagnoli AR, Avanzini G. Quality of life and memory performance in patients with temporal lobe epilepsy. Acta Neurol Scand 2000;**101**:295–300.
61. Engelberts NHJ, Klein M, van der Ploeg HM et al. Cognition and health-related quality of life in a well-defined subgroup of patients with partial epilepsy. J Neurol 2002;**249**:294–299.
62. Engelberts NHJ, Klein M, van der Ploeg HM et al. Cognition and health-related quality of life in chronic well-controlled patients with partial epilepsy on carbamazepine monotherapy. Epilepsy Behav 2002;**3**:316–321.
63. Piazzini A, Beghi E, Turner K et al. Health-related quality of life in epilepsy: findings obtained with a new Italian instrument. Epilepsy Behav 2008;**13**:119–126.
64. Meneses RF, Pais-Ribeiro JL, da Silva AM et al. Neuropsychological predictors of quality of life in focal epilepsy. Seizure-European J Epilepsy 2009;**18**:313–319.
65. Selai CE, Elstner K, Trimble MR. Quality of life pre and post epilepsy surgery. Epilepsy Res 2000;**38**:67–74.
66. Lowe AJ, David E, Kilpatrick CJ et al. Epilepsy surgery for pathologically proven hippocampal sclerosis provides long-term seizure control and improved quality of life. Epilepsia 2004;**45**:237–242.
67. Aydemir N, Ozkara C, Canbeyli R, Tekcan A. Changes in quality of life and self-perspective related to surgery in patients with temporal lobe epilepsy. Epilepsy Behav 2004;**5**:735–742.
68. Ojemann GA. Dodrill CB. Verbal memory deficits after left temporal lobectomy for epilepsy. Mechanism and intraoperative prediction. J Neurosurg 1985;**62**:101–107.
69. Joo EY, Han HJ, Lee EK et al. Resection extent versus postoperative outcomes of seizure and memory in mesial temporal lobe epilepsy. Seizure-European J Epilepsy 2005;**14**:541–551.

https://doi.org/10.1111/j.1601-5215.2009.00439.x Published online by Cambridge University Press

70. Helmstaedter C, Reuber M, Elger CCE. Interaction of cognitive aging and memory deficits related to epilepsy surgery. Ann Neurol 2002;**52**:89–94.
71. Davies KG, Bell BD, Bush AJ, Wyler AR. Prediction of verbal memory loss in individuals after anterior temporal lobectomy. Epilepsia 1998;**39**:820–828.
72. Helmstaedter C, Elger CE. Cognitive consequences of two-thirds anterior temporal lobectomy on verbal memory in 144 patients: a three-month follow-up study. Epilepsia 1996;**37**2: 171–180.
73. Helmstaedter C, Kurthen M, Lux S, Reuber M, Elger CE. Chronic epilepsy and cognition: a longitudinal study in temporal lobe epilepsy. Ann Neurol 2003;**54**: 425–432.
74. Wilson JTL, Pettigrew LEL, Teasdale GM. Emotional and cognitive consequences of head injury in relation to the Glasgow outcome scale. J Neurol Neurosurg Psychiatry 2000;**69**:204–209.
75. McCarthy ML, Dikmen SS, Langlois JA, Selassie AW, Gu JK, Horner MD. Self-reported psychosocial health among adults with traumatic brain injury. Arch Phys ed Rehab 2006;**87**:953–961.
76. Belanger HG, Curtiss G, Demery JA, Lebowitz BK, Vanderploeg RD. Factors moderating neuropsychological outcomes following mild traumatic brain injury: a meta-analysis. J Int Neuropsychol Soc 2005;**11**:215–227.
77. Kemp S, Goulding P, Spencer J et al. Unusually rapid and severe cognitive deterioration after mild traumatic brain injury. Brain Injury 2005;**19**:1269–1276.
78. Frencham KAR, Fox AM, Maybery MT. Neuropsychological studies of mild traumatic brain injury: a meta-analytic review of research since 1995. J Clin Exp Neuropsychol 2005;**27**334–351.
79. Christensen BK, Colella B, Illness E et al. Recovery of cognitive function after traumatic brain injury: a multilevel modeling analysis of canadian outcomes. Arch Phys Med Rehab 2008;**89**:S3–S15.
80. MacKenzie EJ, McCarthy ML, Ditunno JF et al. Using the SF-36 for characterizing outcome after multiple trauma involving head injury. J Trauma-Injuiry Infec Crit Care 2002;**52**:527–533.
81. Dawson DR, Levine B, Schwartz ML, Stuss DT. Acute predictors of real-world outcomes following traumatic brain injury: a prospective study. Brain Injury 2004;**18**:221–238.
82. Atchison TB, Sander AM, Struchen MA et al. Relationship between neuropsychological test performance and productivity at 1-year following traumatic brain injury. Clin Neuropsychol 2004;**18**:249–265.
83. Dijkers MP. Quality of life after traumatic brain injury: a review of research approaches and findings. Arch Phys Med Rehabil 2004;**85**(Suppl. 2):S21–S35.
84. Lannoo E, Van Rietvelde F, Colardyn F, Lemmerling M, Vandekerckhove T, Jannes C, De Soete G. Early predictors of mortality and morbidity after severe closed head injury. J Neurotrauma May 2000;**17**:403–414.
85. Tate RL, Broe GA. Psychosocial adjustment after traumatic brain injury: what are the important variables? Psychol Med 1999;**29**:713–725.
86. Wood RLL, Rutterford NA. Demographic and cognitive predictors of long-term psychosocial outcome following traumatic brain injury. J Int Neuropsychol Soc 2006;**12**: 350–358.
87. Blalock AC, McDaniel JS, Farber EW. Effect of employment on quality of life and psychological functioning in patients with HIV/AIDS. Psychosomatics 2002; **43**:400–404.
88. Blake C, Codd MB, Cassidy A, O'Meara YM. Physical function, employment and quality of life in end-stage renal disease. J Nephrol 2000;**3**:142–149.
89. Orbon KH, Schermer TR, van der Gulden JW et al. Employment status and quality of life in patients with chronic obstructive pulmonary disease. Int Arch Occup Env Health 2005;**78**:467–474.
90. Johansson U, Bernspang B. Life satisfaction related to work re-entry after brain injury: a longitudinal study. Brain Injury 2003;**17**:991–1002.
91. Ownsworth T, McKenna K. Investigation of factors related to employment outcome following traumatic brain injury: a critical review and conceptual model . Disabil Rehabil 2004;**26**:765–784.
92. Devitt R, Colantonio A, Dawson D et al. Prediction of long-term occupational performance outcomes for adults after moderate to severe traumatic brain injury. Disabil Rehabil 2006;**28**:547–559.
93. Green RE, Colella B, Hebert DA et al Prediction of return to productivity after severe traumatic brain injury: investigations of optimal neuropsychological tests and timing of assessment. Arch Phys Med Rehabil 2008;**89**(Suppl. 2):S51–S60.
94. Sherer M, Novack TA, Sander AM, Struchen MA, Alderson A, Thompson RN. Neuropsychological assessment and employment outcome after traumatic brain injury: a review. Clin Neuropsychol 2002;**16**:157–178.
95. Simpson A, Schmitter-Edgecombe M Prediction of employment status following traumatic brain injury using a behavioural measure of frontal lobe functioning. Brain Injury 2002;**16**:1075–1091.
96. Drake AI, Gray N, Yoder S, Pramuka M, Llewellyn M. Factors predicting return to work following mild traumatic brain injury: a discriminant analysis. J Head Trauma Rehabil 2000;**15**:1103–1112.
97. Ponsford J, Olver J, Ponsford M, Nelms R. Long-term adjustment of families following traumatic brain injury where comprehensive rehabilitation has been provided. Brain Injury 2003;**17**:453–468.
98. Svendsen HA, Teasdale TW The influence of neuropsychological rehabilitation on symptomatology and quality of life following brain injury: a controlled long-term follow-up. Brain Injury 2006;**20**:1295–1306.
99. Rohling ML, Faust ME, Beverly B et al. Effectiveness of cognitive rehabilitation following acquired brain injury: a meta-analytic re-examination of cicerone et al.'s (2000, 2005) Systematic teviews. Neuropsychology 2009;**23**:20–39.
100. Cicerone KD, Mott T, Azulay J et al. A randomized controlled trial of holistic neuropsychologic rehabilitation after traumatic brain injury. Arch Phys Med Rehabil 2008;**89**:2239–2249.
101. Paulsen JS, Zhao H, Stout JC et al. Clinical markers of early disease in persons near onset of Huntington's disease. Neurology 2001;**57**:658–662.
102. Helder DI, Kaptein AA, van Kempen GMJ et al. Impact of Huntington's disease on quality of life. Mov Disord 2001;**16**:325–330.

https://doi.org/10.1111/j.1601-5215.2009.00439.x Published online by Cambridge University Press

103. Ho AK, Gilbert AS, Mason SL et al. Health-related quality of life in huntington's disease: which factors matter most? Mov Disord 2009;**24**:574–578.
104. Salmon DP, Kwoonyuen PF, Heindel WC. Differentiation of Alzheimers-disease and huntingtons-disease with the dementia rating-scale. Arch Neurol 1989;**46**: 1204–1208.
105. Paulsen JS, Stout JC; TawfikReedy Z et al. The utility of the Frontal Lobe Personality Scale (FLOPS) for characterizing behavior in dementia of the Alzheimer's type (DAT) and Huntington's disease (HD). Arch Clin Neuropsychol 1996;**11**:434–435.
106. Ho AK, Robbins AOG, Walters SJ, Kaptoge S, Sahakian BJ, Barker RA. Health-related quality of life in Huntington's disease: a comparison of two generic instruments, SF-36 and SIP. Mov Disorders 2004;**19**: 1341–1348.
107. Higgins DS, Nickerson C, Molho ES, Factor SA. Health-related quality of life in Huntington disease: preliminary examination of the PDQ39. Mov Disorders 2005;**20**(Suppl. 10):S174–S174.
108. Neary D, Snowden JS, Mann DMA. Cognitive change in motor neurone disease / amyotrophic lateral sclerosis (MND/ALS).J Neurol Sci 2000;**180**:15–20.
109. Abrahams S, Leigh PN, Goldstein LH. Cognitive change in ALS—a prospective study. Neurology 2005;**64**: 1222–1226.
110. Barson FP, Kinsella GJ, Ong B, Mathers SE. A neuropsychological investigation of dementia in motor neurone disease (MND).J Neurol Sci 2000;**180**:107–113.
111. Garraux G, Salmon E, Degueldre C et al. Medial temporal lobe metabolic impairment in dementia associated with motor neuron disease. J Neurol Sci 1999;**168**: 145–150.
112. Duque P, Parama D, Borges G et al. Neuropsychological disorders in amyotrophic lateral sclerosis. Don't they exist or do they just go undetected? Rev Neurol 2003;**36**:3–8.
113. Pessin H, Rosenfeld B, Burton L, Breitbart W. The role of cognitive impairment in desire for hastened death: a study of patients with advanced AIDS. Gen Hosp Psychiatry 2003;**25**:194–199.
114. Goldstein LH, Atkins L, Leigh PN. Correlates of quality of life in people with motor neuron disease (MND). Amyotroph Lateral Scler Other Motor Neuron Disord 2002;**3**:123–129.
115. Lou JS, Reeves A, Benice T, Sexton G. Fatigue and depression are associated with poor quality of life in ALS. Neurology 2003;**60**:122–123.
116. Kubler A, Winter S, Ludolph AC, Hautzinger M, Birbaumer N Severity of depressive symptoms and quality of life in patients with amyotrophic lateral sclerosis. Neurorehabil Neural Repair 2005;**19**:182–193.
117. Epton J, Harris R, Jenkinson C. Quality of life in amyotrophic lateral sclerosis/motor neuron disease: a structured review. Amyotroph Lateral Scler Other Motor Neuron Disord 2009;**10**:15–26.
118. Rogers JM, Panegyres PK Cognitive impairment in multiple sclerosis: evidence-based analysis and recommendations. J Clin Neurosci 2007;**14**:919–927.
119. Chiaravalloti ND, DeLuca J Cognitive impairment in multiple sclerosis. Lancet Neurology 2008;**7**:1139–1151.
120. Brassington JC, Marh NV. Neuropsychological aspects of multiple sclerosis. Neuropsychol Rev 1998;**8**:43–77.
121. Shevil E, Finlayson M. Perceptions of persons with multiple sclerosis on cognitive changes and their impact on daily life. Disabil Rehabil 2006 **28**:779–788.
122. Lyon-Caen O, Jouvent R, Hauser S et al. Cognitive functions in recent-onset demyelinating diseases. Arch Neurol 1986;**43**:1138–1141.
123. Ruggieri RM, Palermo R, Vitello G, Gennuso M, Settipani N, Piccoli F. Cognitive impairment in patients suffering from relapsing-remitting multiple sclerosis with EDSS< 3.5. Acta Neurol Scand 2003;**108**:323–326.
124. Shawaryn MA, Schiaffino KM, LaRocca NG, Johnston MV. Determinants of health-related quality of life in multiple sclerosis: the role of illness intrusiveness. Mult Scler 2002;**8**:310–318.
125. Amato MP, Ponziani G, Siracusa G, Sorbi S. Cognitive dysfunction in early onset multiple sclerosis: a reappraisal after 10 years. Arch Neurol 2001;**58**:1602–1606.
126. Cutajar R, Ferriani E, Scandellari C, et al. Cognitive function and quality of life in multiple sclerosis patients. J Neurovirol 2000;**6**(Suppl):S186–S190.
127. Gold SM, Schulz H, Monch A, Schulz KH, Heesen C. Cognitive impairment in multiple sclerosis does not affect reliability and validity of self-report health measures. Mult Scler 2003;**9**:404–410.
128. O'Connor P, Lee L, Ng PT, Narayana P, Wolinsky JS. Determinants of overall quality of life in secondary progressive MS: a longitudinal study. Neurology 2001;**57**:889–891.
129. Benedict RHB, Wahlig E, Bakshic R. et al. Predicting quality of life in multiple sclerosis: accounting for physical disability, fatigue, cognition, mood disorder, personality, and behavior change. J Neurol Sci 2005;**231**:29–34.
130. Mitchell, AJ; Benito-Leon, J; Rivera-Navarro, J, et al. What degree of cognitive impairment predicts poor quality of life in multiple sclerosis?: The GEDMA study. Neurology 2006;**66**:A239–A239.
131. Patti, F; Ciancio, MR; Reggio, E, et al.The impact of outpatient rehabilitation on quality of life in multiple sclerosis. J Neurol 2002;**249**:1027–1033.
132. Martinez-Martin P. Impact of the cognitive impairment on the quality of life in patients with Parkinson's disease. Rev Neurol 2006;**43**:168–172.
133. R.H.S. Mindham & T.A. Hughes. Cognitive impairment in Parkinson's disease. Int Rev Psychiatry 2000;**12**: 281–289.
134. Aarsland D, Ballard, C, and Glenda Halliday G. Are Parkinson's Disease With Dementia and Dementia With Lewy Bodies the Same Entity? J Geriatr Psychiatry Neurol 2004;**17**:137–145.
135. Bruck A, Kurki T, Kaasinen V, Vahlberg T, Rinne JO. Hippocampal and prefrontal atrophy in patients with early non-demented Parkinson's disease is related to cognitive impairment. J Neurol Neurosurg Psychiatry **75**: 1467–1469.
136. Emre M, Aarsland D, Brown R, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord 2007;**22**:1689–1707.
137. Schrag A, Jahanshahi M, Quinn NJ. What contributes to quality of life in patients with Parkinson's disease? J Neurol Neurosurg Psychiatry 2000;**69**:308–312.
138. Croyle KL, Fields J, Lyons K, Straits-Troster K, Koller W, Pahwa R, Troster AI. Cognitive functioning predicts quality of life in Parkinson's disease. Clin Neuropsychol 2001;**15**:270–270.

https://doi.org/10.1111/j.1601-5215.2009.00439.x Published online by Cambridge University Press

139. Weintraub D, Moberg PJ, Duda JE, Katz IR, Stern MB. Effect of psychiatric and other nonmotor symptoms on disability in Parkinson's disease. J Am Geriatr Soc 2004;**52**:784–788.
140. Klepac, N; Trkulja, V; Relja, M, et al. Is quality of life in non-demented Parkinson's disease patients related to cognitive performance? A clinic-based cross-sectional study. Eur J Neurol 2008;**15**:128–133.
141. Emre M, Aarsland D, Albanese A, et al Rivastigmine for dementia associated with Parkinson's disease. New England J Med 2004;**351**:2509–2518.
142. Sinforiani E, Banchieri L, Zucchella C, Pacchetti C, Sandrini G. Cognitive rehabilitation in Parkinson's disease. Arch Gerontol Geriatr 2004;387–391.
143. Albert SM, Michaels K, Padilla M, et al. Functional significance of mild cognitive impairment in elderly patients without a dementia diagnosis American J Geriatr Psychiatry 1999;**7**:213–220.
144. Chodosh J, Petitti DB, Elliott M, Hays RD, Crooks VC, Reuben DB, Buckwalter JG, Wenger N. Physician recognition of cognitive impairment: Evaluating the need for improvement. J Am Geriatr Soc 2004;**52**:1051–1059.
145. Valcour VG, Masaki KH, Curb JD, Blanchette PL. The detection of dementia in the primary care setting. Arch Intern Med 2000;**160**:2964–2968.
146. Feil D, Marmon T, Unutzer J. Cognitive impairment, chronic medical illness, and risk of mortality in an elderly cohort. American J Geriatr Psychiatry 2003; **11**:551–560.
147. Cacciatore F, Abete P, de Santis D, Longobardi G, Ferrara N, Rengo F. Mortality and blood pressure in elderly people with and without cognitive impairment. Gerontology 2005;**51**:53–61.
148. Henon H, Durieu I, Lebert F, Pasquier F, Leys D. Influence of prestroke dementia on early and delayed mortality in stroke patients. J Neurol 2003;**250**:10–16.
149. Kiessling A, Henriksson P. Perceived cognitive function is a major determinant of health related quality of life in a non-selected population of patients with coronary artery disease - a principal components analysis. Qual Life Res 2004;**13**:1621–1631.
150. Kiessling A, Henriksson . Perceived cognitive function in coronary artery disease - An unrecognised predictor of unemployment. Qual Life Res 2005;**14**:1481–1488.
151. Rabkin JG, McElhiney M, Ferrando SJ, Van Gorp W, Hsing S. Predictors of employment of men with HIV/AIDS: A longitudinal study. Psychosom Med 2004;**66**:72–78.
152. Artero S, Touchon J, Ritchie K 2001 Disability and mild cognitive impairment: a longitudinal population-based study. International J Geriatr Psychiatry **16**: 1092–1097.
153. Possl O, Jurgensmeyer S, Karlbauer F, Wenz C, Goldenberg G. Stability of employment after brain injury: a 7-year follow-up study. Brain Injury 2001;**15**: 15–27.

https://doi.org/10.1111/j.1601-5215.2009.00439.x Published online by Cambridge University Press