

Ambulatory Assessment in Neuropsychology

Applications in Multiple Sclerosis Research

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Abbreviations:

MS: Multiple Sclerosis

RRMS: Relapsing-remitting multiple sclerosis

HPA: Hypothalamus-pituitary-adrenal

PRO: Patient-reported outcome

VAS: Visual analogue scale

Gd+: Gadolinium-enhancing

MRI: Magnetic resonance imaging

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Zusammenfassung

Neuropsychologische Störungen äußern sich in unterschiedlichen Symptomen, die oft zu deutlichen funktionellen Einschränkungen des Alltagslebens führen. Forschung, Diagnostik und Behandlung sollten diesen Alltagsbezug unter Berücksichtigung von Symptomen, Persönlichkeit und Lebensumständen der betroffenen Patienten einbeziehen. Messungen mit Methoden des Ambulanten Assessment bieten dabei einen Fortschritt durch Vermeidung von retrospektiven Erinnerungsverzerrungen, durch erhöhte ökologische Validität und durch die Generierung individueller Zeitreihen, die idiographische Analysen ermöglichen. Am Beispiel der Multiplen Sklerose stellen wir in den Bereichen Erschöpfung, Stress und kognitive Funktionen dar, welche neuartigen Erkenntnisse mit Methoden des ambulanten Assessment in der Vergangenheit gewonnen wurden, und wir zeigen zukünftige diagnostische Möglichkeiten auf, die diese Methode in der Forschung und klinischen Praxis mit Multiple-Sklerose-Patienten bietet.

Schlüsselwörter: Multiple Sklerose; Ambulantes Assessment; Ecological Momentary Assessment; Erschöpfung; Stress; Cortisol; kognitive Funktionen

Abstract

Neuropsychological disorders involve a variety of symptoms that often lead to substantial functional impairments in daily life. Research, assessment, and treatment should include a reference to daily life, considering symptoms, personality, and life circumstances of the individual patient. Ambulatory assessment methodology provides progress by avoiding retrospective memory-based bias, increasing ecological validity, and by generating individual time series that permit idiographic analysis. Using multiple sclerosis as an example, we illustrate new findings generated by ambulatory assessment studies in the areas of fatigue, stress and cognitive functions, and we demonstrate future opportunities presented by ambulatory assessment methodology to research and clinical practice with multiple sclerosis patients.

Keywords: Multiple sclerosis; ambulatory assessment; ecological momentary assessment; fatigue; stress; cortisol; cognitive functions

Introduction

Neuropsychological assessment usually happens in clinical settings. This applies to the assessment of cognitive functioning, psychological stress, depressive symptoms, fatigue, pain, and negative affect, often assessed as important patient reported outcomes (PROs) in clinical research. Although clinical assessment settings benefit from a relatively high degree of control over the assessment process, it is important to note that they nevertheless have several shortcomings, such as reliance on retrospective self-reports, an artificial setting outside of the patient's daily life, and information collected at a single point in time that lacks detail on within-subject dynamics and relationships or processes that evolve over time. In recent years, methods of assessment in daily life have grown in popularity. Although these assessment methodologies come under different labels and were developed on the basis of different methodological origins (Wilhelm, Perrez, & Pawlik, 2012), they share common characteristics. The most widely-used types are Ambulatory Assessment (Ebner-Priemer & Kubiak, 2010; Fahrenberg & Myrtek, 1996; Trull & Ebner-Priemer, 2013), Ecological Momentary Assessment (Shiffman, Stone, & Hufford, 2008; Stone & Shiffman, 1994), and Experience Sampling Methodology (Csikszentmihalyi & Larson, 1992). Daily life research is characterised by its focus on real life (Reis, 2012), real time (Schwarz, 2012), and repeated assessments within subjects (Hamaker, 2012), and often explicitly incorporates data from assessment methods targeting different domains, i.e. physiological, subjective-emotional, behavioural, and cognitive (Mehl & Conner, 2012). In the following, we use the term *ambulatory assessment* to refer to the variety of daily life assessment methodologies. In clinical neuropsychology, daily life assessment methodologies generally present opportunities for a broader approach to clinical diagnosis which is likely to yield more valid results as well as interventions with much increased relevance for patients' everyday lives. Incorporating daily life assessment methodologies could be beneficial for a wide variety of questions in neuropsychological research, diagnostics, and especially for treatment. To illustrate this point, we will discuss a selection of three topics that are of high relevance for neuropsychological assessment, i.e. fatigue, psychological stress and cognitive function. Using multiple sclerosis (MS) as an example, we will illustrate how daily life assessment methods might provide highly relevant complementary information to conventional assessment methods.

Multiple sclerosis-related impairments in daily life

MS is a chronic inflammatory demyelinating disease of the central nervous system that presents itself as relapsing-remitting MS (RRMS) with recurrent episodes of symptom exacerbations and full or partial symptom recovery, secondary progressive MS with gradual clinical progression independent of exacerbations, or primary progressive MS with gradual clinical progression without exacerbations (Miller & Leary, 2007; Noseworthy, Lucchinetti, Rodriguez, & Weinstenker, 2000; Rovaris et al., 2006).

The lesions or plaques that result from damage to the myelin sheath lead to symptoms in a variety of organ systems such as tremor, loss of vision, poor balance, stiffness and painful spasms, bladder dysfunction, cognitive impairment, depression, and fatigue (Chiaravalloti & DeLuca, 2008; Compston & Coles, 2008; Krupp, Serafin, & Christodoulou, 2010; Siegert & Abernethy, 2005; Ziemssen, 2009). Due to the variety of organ systems that are affected and the severity of symptoms, MS leads to substantial functional impairments in daily life. Besides the severe impact on people with MS and members of their social network, the disease's high costs also have an indirect effect on the wider society. It has been estimated that MS was associated with costs of approximately € 14.6 billion in Europe in the year 2010 (Olesen, Gustavsson, Svensson, Wittchen, & Jonsson, 2012).

While the aetiology of MS is largely unknown, both genetic and environmental factors seem to be major causal factors (Compston & Coles, 2008). Although a number of pharmacological interventions for MS can reduce disease activity (disease modifying therapies), therapies that achieve full recovery or complete cure of the disease do not exist and are among the major aims of development of future treatments (Compston & Coles, 2008; Noseworthy, et al., 2000). Consequently, non-pharmacological interventions that might help to alleviate symptoms, moderate disease activity, or reduce the impact of symptoms on the everyday lives of MS patients would be of great importance for MS treatment. In this context it is interesting to note that recent evidence suggests that psychological stress might play a role in symptom exacerbation and relapse (Artemiadis, Anagnostouli, & Alexopoulos, 2011; Mohr, Hart, Julian, Cox, & Pelletier, 2004).

Due to the prognostic uncertainty typical of MS, patients need to be well informed about their illness (Noseworthy, et al., 2000). Broad and reliable information about MS symptoms helps patients to effectively self-manage their condition in daily life, which is often necessary due to the unpredictability and severity of symptom appearance. In addition,

health care professionals involved in MS treatment and management, i.e. physicians, clinical neuropsychologists, and expert nurses should use all information on patients' functional impairment and relevant internal and external resources available to the patient in daily life (such as coping skills or social support available to the patient) to improve the quality of life of MS patients.

Subjective symptoms

The subjective representation of symptoms is often reflected in patients' complaints and are typically assessed by psychometric scales measuring the perception of specific or broader symptoms. Fatigue is a frequently reported symptom in different clinical groups, particularly MS patients. We will therefore use MS-related fatigue as an example to discuss some of the issues related to ambulatory assessment of subjective complaints in general. Although much of the methodological knowledge generated by such research can be generalized to the assessment of other complaints, it is important to keep in mind that details of the assessment design need to be tailored to the specific phenomenon of interest. For example, decisions on the frequency of assessments, expectations on compliance rates achievable with the patients in the study, assessment devices and response scales to be used, and aggregate indicators to be derived from raw data can be very different for ambulatory assessments of fatigue, mood, balance, or other subjective complaints.

Unfortunately, there has so far been little focus on developing and utilizing ambulatory assessment techniques for fatigue measurement, not only in MS but in clinical populations in general. Typically, single-item measures have been utilised to measure momentary fatigue in those few clinical studies conducted, including modifications of the Brief Fatigue Inventory (BFI; Mendoza et al., 1999), the Rochester Fatigue Diary (Schwid, Covington, Segal, & Goodman, 2002), and other visual analogue scale (VAS) format items. Our research group, for example, has recently carried out a study in MS (Powell, Moss-Morris, Liossi, & Schlotz, in preparation) using a variation of the BFI to reflect both physical and mental fatigue in MS: "How much fatigue (tiredness, weariness, problems thinking clearly) do you feel right now?" with response by VAS ranging from 0 ("No Fatigue") to 10 ("Extreme Fatigue").

MS-related fatigue

In a large epidemiological study, 74% of 9077 MS patients obtained scores indicative of severe fatigue (Hadjimichael, Vollmer, & Oleen-Burkey, 2008) on the

Fatigue Severity Scale (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989). High prevalence of fatigue in MS (60 – 85%) has also been reported in other large-scale ($n > 500$) studies (Lerdal, Celius, & Moum, 2003; Minden et al., 2006). However, the aetiology of MS-related fatigue is uncertain, and primary disease-related mechanisms as well as secondary mechanisms have been proposed (for reviews, see Induruwa, Constantinescu, & Gran, 2012; Kos, Kerckhofs, Nagels, D'hooghe, & Ilsbrouckx, 2008; Krupp, et al., 2010). MS-related fatigue is most-frequently defined as "a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities" (Multiple Sclerosis Council for Clinical Practice Guidelines, 1998, p.2); however, multiple definitions exist (e.g., Comi, Leocani, Rossi, & Colombo, 2001; Mills & Young, 2008). Measuring fatigue is equally complex, and multiple self-report tools – of varying psychometric quality – are available to quantify subjective fatigue retrospectively in chronic illness (Whitehead, 2009).

Ambulatory assessment of MS-related fatigue

Retrospective recall necessarily requires the aggregation of phenomena over a period of time. However, MS patients typically describe fatigue as a fluctuating rather than stable and consistent phenomenon. Fatigue is typically described as being most severe in the late afternoon and sensitive to contextual effects of everyday experiences, such as psychological stress, physical and mental activity, heat and humidity, and poor sleep quality (Freal, Kraft, & Coryell, 1984; Mills & Young, 2008). This implies that the summary measures typically employed in research and clinical practice provide an incomplete representation of overall symptom experience, and lack important information about within-subject and within-day variability. Ambulatory assessment provides opportunity to prospectively examine fluctuations in fatigue severity in daily life, including diurnal fatigue patterns (fatigue changes with time) and quantifying the effects of contextual factors.

Despite its potential, only two studies have been published that utilise ambulatory assessment for the examination of MS-related fatigue in everyday life (Kim et al., 2010; Schwid et al., 2003), with the earlier study measuring fatigue within a randomised controlled trial of cooling treatment for MS symptoms (Schwid, et al., 2003). Momentary fatigue assessments have also been used elsewhere in clinic-based settings in MS populations (Claros-Salinas et al., 2010; Feys et al., 2012; Morris, Cantwell, Vowels, & Dodd, 2002), but lack the fundamental advantage of ecological validity.

Kim et al. (2010) used Actiwatch wrist devices to prompt and measure fatigue severity at 9am, 1pm, 5pm, and 9pm over 21 consecutive days in 49 MS patients. Momentary fatigue was measured using a single-item numerical rating scale (*Real-Time Digital Fatigue Score*) ranging from “Energetic, No Fatigue” (score = 0) to “Worst Possible Fatigue” (score = 10). Using multilevel (mixed-effects) modelling, incremental increases in fatigue were reported over the course of the day, indicating a relatively linear diurnal fatigue pattern and providing prospective evidence supporting previous assertions (based on qualitative interviews and simple surveys) that fatigue is worst later in the day.

Ambulatory assessment studies carried out in other clinical populations have tested hypotheses that are equally relevant in MS. For example, fatigue was associated with less concurrent and future physical activity but was not associated with prior physical activity in lagged-effects analyses in chronic fatigue syndrome and fibromyalgia (Kop et al., 2005). Testing whether similar temporal relationships exist in MS could potentially illuminate the use of all-or-nothing behaviours thought to contribute to perpetuating chronic fatigue in MS (Skerrett & Moss-Morris, 2006). Further, given the current reliance on recall measures, research and clinical practice may benefit from investigating the accuracy of and presence of bias within MS-related fatigue recall by using concurrent ambulatory assessment, as has been reported in other populations (e.g., Schneider, Stone, Schwartz, & Broderick, 2011).

Compliance

The level of compliance with measurement protocols in everyday life is a significant limitation to the study by Kim et al. (2010) and a challenge for ambulatory assessment research in general. Kim et al. (2010) reported that only 64% of wristwatch beeps elicited a response, which is possibly due to patients missing more events while fatigued or while having a heavier workload. Although multilevel modelling is robust to missed assessments (Graham, 2009), the representativeness of the sampling is threatened by relatively high levels of missing data. This highlights the importance of a careful examination of compliance when using ambulatory assessment methods. Generally speaking, compliance decreases with increasing effort, and this varies across patients. Therefore, the burden to patients needs to be kept at an acceptable individual level, while a sufficient number of assessment needs to be carried out to be able to answer the questions of interest.

Detailed targets for intervention

There is very little understanding of which facets of fatigue experience are most important. It is well-established that symptomatic fatigue has a negative impact on quality of life in MS (Amato et al., 2001; Janardhan & Bakshi, 2002); however, it is unclear whether it is characteristics such as symptom variability or periods of extreme symptom intensity that have the greatest impact on daily lives. Ambulatory assessment has the potential to contribute answers. A recent study presented several parameters that could be obtained from ambulatory assessment data of PROs: daily symptom means, variability (standard deviation), peaks (90th percentile), periods of no symptom experience (rating score = 0), and contingent-based (morning versus evening, work versus home) (Stone, Broderick, Schneider, & Schwartz, 2012). If, for example, the findings showed that periods of extreme fatigue intensity had the greatest impact on daily lives, therapies and treatments should target the lowering of 90th percentile ratings in ambulatory assessment protocols. Summary recall measures do not provide within-subject repeated measures needed for such detailed outcome assessments and, in addition, may not be sufficiently sensitive to determine an effective treatment.

Combining subjective and physiological assessments

Ambulatory assessment traditionally utilises physiological measures alongside measures of behaviour and/or internal-state subjective experience (Ebner-Priemer & Kubiak, 2010). This may include the monitoring of physical activity (Shammas et al., 2014; Yang & Hsu, 2010) and cardiac output (Pickering, Shimbo, & Haas, 2006), as well as collecting saliva samples for endocrine markers (Schlotz, 2012). The role of cortisol as a potential mediator of any association between psychological stress and fatigue in MS provides a potential avenue for future research incorporating ambulatory assessment. Although Salivary cortisol studies appear to suggest attenuated daily cortisol variability in chronic fatigue syndrome (Powell, Lioffi, Moss-Morris, & Schlotz, 2013), no association was found between salivary cortisol output and fatigue in MS in a previous study (Gold et al., 2011).

In summary, investigating fluctuations in fatigue experience seems an important future field of research which can be examined in real-time using ambulatory assessment methods. The identification of contextual and physiological factors in daily life that exacerbate fatigue severity should further our understanding of fatigue aetiology and has the potential to inform future treatment developments.

Psychological stress

The measurement of human life stress is complex (Monroe, 2008), particularly when constructs are being targeted that have little or no objective equivalent, such as perceived stress. However, subjective representation of potentially stressful situations, i.e. perceived stress, are relevant predictors of disease (Cohen, Janicki-Deverts, & Miller, 2007) and provide important information complementary to life event records. Perceived stress in neuropsychological patients can be measured by several widely-used scales such as the Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1983; Cohen & Williamson, 1988), Perceived Stress Questionnaire (PSQ; Fliege et al., 2005; Levenstein et al., 1993), or the Trier Inventory for Chronic Stress (TICS; Petrowski, Paul, Albani, & Braehler, 2012; Schulz, Schlotz, & Becker, 2004). While attempts have been made to develop short scales that measure only the major factors (e.g. Lehman, Burns, Gagen, & Mohr, 2012; Schulz, et al., 2004), such short scales neglect important domain-specific information (e.g. Morgan, Umberson, & Hertzog, 2014). Although these scales have sufficient reliability and validity as indicated by psychometric analyses, they suffer from potential memory-related bias since the reports are being assessed retrospectively. Ambulatory assessment methodology provides a relatively easy to administer and useful method to assess perceived stress with minimal or no memory-related bias during the patient's daily routine.

Although less relevant to clinical work, stress responses can be measured in a controlled environment using highly standardised stress procedures such as the Trier Social Stress Test (TSST) and related methods (Allen, Kennedy, Cryan, Dinan, & Clarke, 2014; Dickerson & Kemeny, 2004; Kirschbaum, Pirke, & Hellhammer, 1993). While laboratory stressors provide a high level of control over exposure and response assessment, this necessarily represents a relatively artificial situation and therefore has limited ecological validity. Due to high costs and the relatively high level of complexity involved in implementing laboratory stress tests, they usually cannot be applied in assessments of patients during routine clinical work, despite being useful and important tools for research projects. In addition, the lack of normative data for stress responses in such situations means that interpretation of assessment results would be difficult and of little value to the clinician for single-case diagnostics. Again, ambulatory assessment might be a feasible alternative, as a variety of physiological responses such as cortisol stress responses can in

principle be assessed contemporaneously to self-reports of perceived stress in daily life (Jacobs et al., 2007; Powell & Schlotz, 2012; Schlotz, 2012).

Stress and multiple sclerosis

The impact of psychological stress on MS has been implied for some time (Charcot, 1887) and meta-analyses have suggested that stressful life events increase the risk of symptom exacerbation in relapsing remitting MS (Artemiadis, et al., 2011; Mohr, et al., 2004). MS patients also attribute stress with the worsening of symptoms; for example, 78% of 2529 MS patients believed that a high level of stress worsens symptoms generally (Simmons, Ponsonby, van der Mei, & Sheridan, 2004) and 82% of 635 MS patients felt stress increases the severity of their fatigue (Mills & Young, 2008). In addition, it has been found that perceived stress and certain emotion-focused coping strategies such as avoidance in MS patients were associated with worse adjustment to the disease indicated by lower quality of life or more depressive symptoms (Dennison, Moss-Morris, & Chalder, 2009). Improving the understanding of stress and coping processes in MS patients therefore might have important implications for MS (self-) management.

It has been suggested that interventions for avoiding stress should be investigated in more detail for their potential to attenuate the disease process (Apel, Klauer, & Zettl, 2006). A recent randomised trial of stress management in MS patients provided evidence for a reduction of new gadolinium-enhancing (Gd+) and T2 lesions in magnetic resonance imaging (MRI) scans during the intervention, although these effects did not remain stable after treatment was finished (Mohr et al., 2012). An additional analysis of data from this study suggested that major negative stressful events, but not moderate negative stressful events and perceived stress, predicted Gd+ lesions on MRI scans carried out 1-2 months later (Burns, Nawacki, Kwasny, Pelletier, & Mohr, 2014). It is therefore unclear which type of stressor is typically relevant for MS progression, and why stress management generates clear positive effects that are nevertheless time-limited.

As mentioned above, research in psychoneuroendocrinology and psychoneuroimmunology has suggested that the dysregulations of the hypothalamus-pituitary-adrenal (HPA) axis and its end-product cortisol might be relevant for MS disease processes due to its well-known immune-suppressive effects (Heesen et al., 2007). As the HPA axis is sensitive to daily life stress, stress reactivity may play a major role in mediating potential associations between stress and MS symptoms. However, little evidence exists for this proposed

mechanism. Although the cortisol awakening responses (CAR) in daily life was found to be increased and associated with worsening of disability status in RRMS, it was not related to perceived stress (Kern et al., 2013). This suggests that daily life stress might contribute little to dysregulations of the HPA axis in MS. In contrast, HPA axis dysregulations are related to MS disease processes, and it could be speculated that up-regulation of cortisol secretion might help to reduce MS-related disability and probably other symptoms. However, despite findings of stress-relapse associations and patient-reported relevance of stress for worsening of symptoms, there is little evidence for a role of the HPA axis in this association.

Future research directions

In the future, ambulatory assessment might be used more extensively to investigate associations between daily life stress, cortisol secretion, and MS symptoms. For example, it has been suggested that the time course of stress responses might be of crucial importance for explaining a potential mediating role of HPA axis stress responses in MS exacerbations (Mohr & Pelletier, 2006). This stress resolution hypothesis suggests that the cortisol reduction after stress resolution facilitates the development of active inflammation. Since patients with RRMS often show moderate levels of ongoing inflammation not noticeable to the patient (Mohr & Pelletier, 2006; Ysraelit, Gaitán, Lopez, & Correale, 2008), a period of relatively low cortisol levels following a stress response would increase the risk for an exacerbation. Ambulatory assessment would be suitable to test this hypothesis, although relatively long observation periods would be needed.

In summary, using ambulatory assessment methodology to assess stressors, perceived stress, stress responses, and coping behaviour in daily life presents unique opportunities for the collection of ecologically valid, unbiased information from different stress response systems that are highly relevant to the MS disease processes and symptom (self-)management.

Cognitive function

Unfortunately, ambulatory assessment of cognitive functioning in daily life is far from being readily available for researchers and clinicians. Although a number of researchers are working on the development of assessments of cognitive function in daily life using mobile devices, none of them have so far been used in neuropsychological patients. However, it is noteworthy that cognitive test paradigms have been successfully used in everyday life settings using mobile

devices. For example, a reaction time test has been successfully applied using the Stroop paradigm on hand-held computer, with expected correlations between reactions times in daily life and established psychometric tests in smokers (Waters & Li, 2008); an implicit association test also showed expected effects in smokers' daily lives (Waters, Miller, & Li, 2010). Using mobile phones, performance on attention and working memory tests was shown to be impaired in a within-subject comparison of alcohol versus no alcohol consumed before assessments in daily life (Tiplady, Oshinowo, Thomson, & Drummond, 2009). Recently, a study on daily working memory and affect assessments showed that within-subject fluctuations in positive affect predicted better performance in working memory tasks independent of negative affect (Brose, Lovden, & Schmiedek, 2014). Despite these encouraging developments, it is clear that much more work is needed to further improve such tests until they reach a standard where they can be used in clinical assessment. For example, thorough psychometric analyses are needed to establish reliability and validity, usability for neuropsychological patients' needs to be established, and norm values are needed for diagnostic decisions in clinical work. Obviously, cognitive assessment in daily life is confounded by unsystematic variance due to factors such as noise, distraction of attention, or sleepiness. In addition, it has to be ascertained that patients are not exposed to any hazards in association with using mobile assessment devices in daily life (traffic; barriers; etc.). It would be best to clearly inform users how long an assessment will take and to instruct them to find a secure and relatively quiet place before starting an assessment. Finally, technological barriers need to be overcome for such tests to be readily available on mobile devices such as smartphones and tablet computer, as some of the users might be clinical experts, but technological laymen.

Ambulatory assessment of cognitive function in multiple sclerosis

Cognitive impairment can be observed in up to 70% of MS patients and often significantly affects their daily life activities and quality of life (Chiaravalloti & DeLuca, 2008). Although general intelligence and essential verbal skills appear to be only slightly affected, if affected at all, some specific cognitive functions, most notably information processing efficiency, executive functions, processing speed, and long-term memory, show significant impairment (Chiaravalloti & DeLuca, 2008). Assessment of cognitive functioning in MS should therefore be targeted to specific functions that are most strongly affected. A recommended test battery

comprises tests of word fluency, visuospatial ability, verbal memory, visuospatial memory, processing speed, working memory, and executive function (Benedict et al., 2006).

However, assessment of cognitive function using a test battery is not readily available, time consuming, and expensive, and it does not provide any information on within-subject variability or impact on daily life activities. Moreover, two frequent symptoms of MS, fatigue and depression might affect performance and therefore would ideally be assessed contemporaneously with cognitive functioning. In an attempt to make relevant cognitive tests more readily available, an internet-based assessment has been developed which showed a high level sensitivity and specificity (Younes et al., 2007). Cognitive tests in daily life using ambulatory assessment methodology and devices such as smartphones or tablet computer would be similarly available and, in addition, repeated assessments would provide information on within-subject variability and diurnal trends. Moreover, contemporaneous assessments of fatigue and depressive symptoms might reveal associations of these symptoms with cognitive functioning in MS (Feinstein, 2006), and assessments of daily life activities such as household chores or work-related activities might provide information about the impact of individual cognitive deficits on daily life activities. This information could be used to develop rehabilitative interventions targeted to the individual patient with the aim of minimizing the impact of MS symptoms on daily life. In addition, combining ambulatory cognitive tests with ambulatory assessment of perceived stress, fatigue, and salivary cortisol might reveal insights into mutual influences of these systems.

Limitations and outlook

Neuropsychological assessments and interventions involve a variety of strategies, depending on symptoms, personality, and life circumstances of the individual patient. Due to the persistent nature of many neuropsychological conditions, clinical neuropsychologists often aim at improving patients' quality of life by supporting them to manage symptoms effectively. Neuropsychological research aims at providing empirical evidence for making well-informed and effective clinical decisions, developing and evaluating innovative and effective strategies for symptom management, and understanding underlying mechanisms to minimise the negative impact of functional impairment on the patient's quality of life. For all of these targets, reliable and valid assessment of symptoms and potentially relevant contributing factors is necessary. We argued

that ambulatory assessment methodology provides opportunities to improve neuropsychological assessment due to less retrospective memory-related bias, increased ecological validity, and a series of assessments within subjects that provide opportunities for idiographic analysis. With a special emphasis on MS-related research, we discussed ambulatory assessment studies that demonstrated diurnal variability in fatigue and changes in cortisol output after awakening that might help to better understand symptoms and mechanisms. Similarly, other symptoms relevant for neuropsychology such as pain could be assessed using ambulatory methods. Although cognitive symptoms cannot yet be assessed effortlessly in daily life, future developments might provide reliable and valid ambulatory cognitive tests. However, it is clear that these early studies are just the beginning of more detailed investigations of how neuropsychological conditions in general, and MS in particular, affect daily life.

Limitations of ambulatory assessment methodology in neuropsychology

Besides the strengths of ambulatory assessment, there are a number of limitations of this methodology in neuropsychological research and interventions.

In addition to the potential negative effect of reactivity due to the relatively high number of assessments that might be perceived as a disturbance of daily life activities, disease-specific factors could limit the usability of ambulatory assessment methods. For example, cognitive, visual, and motor impairments that are very pronounced in some MS patients might limit the patients' ability to provide accurate and timely responses. However, we have recently completed a study in RRMS patients with low to moderate disability (scores on the self-administered Expanded Disability Status Scale, EDSS, between 0.0 and 6.0) all of whom were able to do the e-diary ratings as well as saliva sampling without major problems. An initial piloting with two RRMS patients using the think-aloud method showed that only slight changes to the standard setup of a handheld-based e-diary were necessary to adapt it to the needs of the patients. However, patients with greater disability due to progressive types of MS might not be able to carry out ambulatory assessment protocols. This could lead to an overrepresentation of results from RRMS patients, and raise questions about the generalizability of the results, at least in those areas where active interaction with a response device is necessary. Increased availability of automated assessment (see Bhake, Leendertz, Linthorst, & Lightman, 2013 for an example of automated cortisol sampling)

and improved assistance functions of recording devices would be necessary to avoid this imbalance in the future.

Another potential limitation of ambulatory assessment methodology is related to compliance with the sampling schedule. As repeated assessments in daily life can be quite disruptive, patients may tend to miss assessments, especially in situations in which they suffer from high levels of stress or symptom experience. However, while undisclosed low compliance certainly can be a problem with paper-pencil diaries (Stone, Shiffman, Schwartz, Broderick, & Hufford, 2002), computer-based assessment provides a much higher level of compliance monitoring.

Finally, it should be noted that assessment in daily life necessarily lacks the high degree of control that can be applied in clinical or laboratory settings. Due to the large number of potentially confounding factors, only the most relevant factors can be assessed in addition to the target assessment. For example, situational variables such as social interactions, being at work or at home, or the current activity should be recorded, either automatically or by self-report. In addition, a function to postpone assessments should be available for the patient to be able to focus their attention completely on the assessment. Nevertheless, unsystematic influences uncontrollable in daily life will unavoidably increase error variance. However, such error variance can be reduced by increasing the number of assessments, and the influence of situational variables, if recorded, can be considered when analysing the data.

Future developments

The need for minimally disruptive, maximally flexible, highly assisting and automated procedures makes clear that ambulatory assessment methodology should make use of the latest technical computing developments, such as smartphones equipped with large high-resolution displays with built-in or wireless sensors that are tailored to the patient's needs. In the future, such devices might include instant patient-therapist-communication triggered by relevant signals from momentary assessments. The fact that smartphones are increasingly becoming the standard for mobile personal communication will further help to implement ambulatory assessments as a minimally disruptive tool providing information that is highly valuable for both clinical professionals and patients. As technological innovations are being picked up by younger people with higher enthusiasm, the relatively young age of patients at first onset of MS might further support the implementation of ambulatory assessment methodology in the neuropsychology of MS.

Besides possible future developments in the ambulatory assessment of fatigue, stress, and cognitive functioning, there are a number of areas in which ambulatory assessment methods in neuropsychology could be developed with the aim of improving usability, clinical diagnostics and symptom management more generally. For example, more work is needed to establish PROs that reflect the most relevant symptom experience in patients. Repeated ambulatory assessments present the opportunity to compare different summary measures of symptom experience such as the 90th percentile, standard deviation, maximum, or number of assessments without symptoms (Stone, et al., 2012). Studies might reveal that different summary measures reflect symptom experience differently in individual patients, which might be useful information for symptom-management of individual patients.

The development of ambulatory assessment of neurocognitive functions would be of particular importance to neuropsychology. Although a few attempts have been made, much more systematic research is needed to develop ready-to-use assessments with satisfactory psychometric characteristics. Measures of working memory, attention, and emotion regulation to assess executive dysfunctions in daily life might be particularly important and suitable. When developing such ambulatory psychometric tests it has to be kept in mind that, besides a special consideration of usability, the major psychometric concepts of reliability and validity need to be extended, as the factor time adds to items and persons as a third source of variance. First suggestions and examples for more complex psychometric analyses based on generalizability theory have been given (Cranford et al., 2006; Wilhelm & Schoebi, 2007), but standards for psychometric indices or statistical parameters are lacking and need to be developed in future work.

Future developments should also aim at reducing the burden of ambulatory assessment methods on patients by further improving usability and reducing measurement reactivity of ambulatory assessments. Although this is difficult to achieve, computerised adaptive testing (CAT) might be a useful perspective here, as the number of items needed for precise assessments can be reduced when a calibrated item pool is available (Rose et al., 2012).

Finally, repeated assessments within subjects provide opportunities to investigate individual processes from an idiographic perspective and detect Granger causality in clinical research projects (see Rosmalen, Wenting, Roest, de Jonge, & Bos, 2012, for an example). For example, mutual relationships between fatigue, depressive symptoms, and cognitive

functioning in MS would be of interest to define intervention targets more precisely. Similarly, ambulatory assessment methods provide data suitable for single case experimental designs that can reveal useful information for clinical practice (Smith, 2012).

In summary, using ambulatory assessment methodology in clinical neuropsychological assessment and treatment presents the opportunity to implement multimethod-assessments in the patient's daily life, to focus on specific situations relevant to everyday life, to investigate context-effects, and to use interactive feedback for process-focused psychological intervention studies. If applied expertly, such assessments result in higher ecological validity, less biased self-reports, and higher precision, reliability, and validity of process-focused assessments. Current hardware and software already makes it possible to use ambulatory assessment strategies in assessment and treatment of MS symptoms, and future technological developments will increase the availability and usability of ambulatory assessment devices and procedures even further. These new developments present an important opportunity for clinical neuropsychologists to improve the assessment of symptoms and relevant psychological and social factors, study disease processes, support patients to self-manage their disease, evaluate pharmacological interventions in daily life using PROs, support rehabilitation programs, and develop and investigate innovative non-pharmacological interventions. If these developments in neuropsychology are being used responsibly and implemented thoroughly, they might eventually help to increase the quality of life of neuropsychological patients.

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