

**PHILIPS**

**RESPIRONICS**

Multiple sclerosis

# Applications of Actigraphy

By Jessie P Bakker MS PhD, Senior Manager Clinical Trials, Philips Respironics

## Why actigraphy?

Actigraphy is the measurement of motion used to monitor 24-hour activity patterns, usually performed with a small accelerometer contained in a watch-like device worn on the wrist or hip. The motion data time-series can be analyzed to provide a range of validated endpoints relating to activity, sleep, and circadian rhythms.

The ability to measure motion precisely and continuously throughout a clinical trial, rather than at discrete study visits, allows for the application of advanced statistical techniques to model day-by-day (or night-by-night) changes between arms and over time, increasing statistical power. Actigraphy is non-invasive, meaning that the data reflect the experiences of the study participant undergoing their usual routine in their normal environment.

## Activity patterns in multiple sclerosis

Activity patterns of those with multiple sclerosis (MS) fluctuate over time according to exacerbations and remissions,<sup>1</sup> and therefore represent an important marker of disease progression.

Several studies have demonstrated that within samples of MS patients, actigraphy endpoints correlate significantly with objective measurements such as 6-minute walk distance,<sup>2-5</sup> the timed 25-foot walk test,<sup>3-5</sup> energy expenditure,<sup>2,4-5</sup> and gait.<sup>4</sup> In 2010, Sosnoff et al. reported that both the mean value of daytime activity level, as well as the variability (standard deviation of the mean) were correlated with MS-related disability, ambulatory status, and walking impairment. Approximate entropy, a mathematical construct reflecting the regularity/complexity of a signal, also differed significantly according to ambulatory status, and correlated moderately with patient-reported measures of walking impairment.<sup>6</sup> In 2017, Ketelhut et al. found that moderate/vigorous physical activity measured by actigraphy is significantly associated with important functional outcomes of MS including leg strength, manual dexterity assessed during a 9-hole peg test, timed up-and-go test, and sit-to-stand performance.<sup>7</sup>

In cross-sectional studies, actigraphy endpoints can discriminate between MS patients and matched controls,<sup>8</sup> between MS patients at risk of falls and those not at risk,<sup>9</sup> and between active and inactive MS patients.<sup>10</sup> Thus, accelerometry measurements performed at home are significantly associated with performance-based tests in controlled environments, but have the advantage of providing greater ecological validity.<sup>11</sup>

Although actigraphy endpoints correlate with MS-specific patient reported outcomes (PROs) when analyzed cross-sectionally,<sup>5</sup> a 2014 longitudinal study found that two commonly-used PROs – the MS Walking Scale-12 and MS Impact Scale-29 – were not responsive to changes in performance, defined as actigraphy total daily activity counts.<sup>12</sup> It is possible that this disconnect is due to ‘response shift’, which describes the phenomenon in which a patient changes their conceptualization of the construct captured by a PRO, alongside an improvement or decline in health-related quality of life. Thus, it is important to capture both objective and self-reported endpoints in MS clinical trials.

### Disrupted sleep and circadian rhythms in multiple sclerosis

Aldughmi et al. demonstrated in a 2016 study that although there was no significant association between self-reported sleep quality and improvement in a 6-minute walk test in those with MS, there was a significant bivariate correlation between improvement in 6-minute walk test and the average wake bout duration measured with actigraphy.<sup>13</sup> In 2011, Merkelbach et al. reported that actigraphy-derived measurements of activity, sleep, and circadian rhythm (24-hour mean activity; the difference in amplitude between highest daytime and lowest nighttime activity; and intraday stability which quantifies robustness of circadian rhythm) were individually associated with MS severity, but not with self-reported measures of fatigue or sleepiness.<sup>14</sup> Similarly, Attarian et al. reported a high burden of sleep/circadian disruption in those with MS and fatigue.<sup>15</sup> These findings are consistent with results from a 2012 study reporting dysregulation of melatonin secretion in MS which, as a regulator of the sleep-wake cycle, may provide an underlying biological mechanism.<sup>16</sup>

...and more

Beyond conventional activity, sleep, and circadian endpoints, there is opportunity to use Philips’ Rapid Actigraphy Data Analyzer (‘RADA’) software to delve much deeper into rich and complex actigraphy datasets by investigating mathematical patterns which may be responsive to pharmacological therapy. Actigraphy datasets never ‘expire’, and can be re-analyzed quickly and easily as new algorithms are developed.

### References

1. Kasser, S.L., Goldstein, A., Wood, P.K., et al. Symptom variability, affect and physical activity in ambulatory persons with multiple sclerosis: Understanding patterns and time-bound relationships. *Disability & Health Journal* 10(2):207-213 (2017).
2. Motl, R.W., Dlugonski, D., Suh, Y., et al. Accelerometry and its association with objective markers of walking limitations in ambulatory adults with multiple sclerosis. *Archives of Physical Medicine & Rehabilitation* 91(12):1942-1947 (2010).
3. Cederberg, K.L., Motl, R.W., McAuley, E. Physical activity, sedentary behavior, and physical function in older adults with multiple sclerosis. *Journal of Aging and Physical Activity* in-press (2017).
4. Goldman, M.D., Motl, R.W., Rudick, R.A. Possible clinical outcome measures for clinical trials in patients with multiple sclerosis. *Therapeutic Advances in Neurological Disorders* 3(4):229-239 (2010).
5. Motl, R.W., Pilutti, L., Sandroff, B.M., et al. Accelerometry as a measure of walking behavior in multiple sclerosis. *Acta Neurologica Scandinavica* 127(6): 384-390 (2013).
6. Sosnoff, J.J., Goldman, M.D., Motl, R.W. Real-life walking impairment in multiple sclerosis: preliminary comparison of four methods for processing accelerometry data. *Multiple Sclerosis* 16(7):868-877 (2010).
7. Ketelhut, N.B., Kindred, J.H., Pimentel, R.E., et al. Functional factors that are important correlates to physical activity in people with multiple sclerosis: A pilot study. *Disability & Rehabilitation* in-press (2017).
8. Sandroff, B.M., Dlugonski, D., Weikert, M., et al. Physical activity and multiple sclerosis: New insights regarding inactivity. *Acta Neurologica Scandinavica* 126(4):256-262 (2012).
9. Sebastiao, E., Learmonth, Y.C., Motl, R.W. Lower physical activity in persons with multiple sclerosis at increased fall risk: A cross-sectional study. *American Journal of Physical Medicine & Rehabilitation* 96(5):357-361 (2017).
10. Klassen, L., Schachter, C., Scudds, R. An exploratory study of two measures of free-living physical activity for people with multiple sclerosis. *Clinical Rehabilitation* 22(3):260-271 (2008).
11. Motl, R.W., Sandroff, B.M., Sosnoff, J.J. Commercially available accelerometry as an ecologically valid measure of ambulation in individuals with multiple sclerosis. *Expert Review of Neurotherapeutics* 12(9):1079-1088 (2012).
12. Schwartz, C.E., Ayandeh, A., Motl, R.W. Investigating the minimally important difference in ambulation in multiple sclerosis: A disconnect between performance-based and patient-reported outcomes? *Journal of the Neurological Sciences* 347(1-2):268-274 (2014).
13. Aldughmi, M., Huisinga, J., Lynch, S.G., et al. The relationship between fatigability and sleep quality in people with multiple sclerosis. *Multiple Sclerosis Journal – Experimental, Translational, and Clinical* 2:1-9 (2016).
14. Merkelbach, S., Schulz, H., Kolmel, H.W., et al. Fatigue, sleepiness, and physical activity in patients with multiple sclerosis. *Journal of Neurology* 258(1):74-79 (2011).
15. Attarian, H.P., Brown, K.M., Duntley, S.P., et al. The relationship of sleep disturbances and fatigue in multiple sclerosis. *Archives of Neurology* 61(4):525-528 (2004).
16. Melamud, L., Golan, D., Luboshitsky, R., et al. Melatonin dysregulation, sleep disturbances and fatigue in multiple sclerosis. *Journal of the Neurological Sciences* 314(1-2):37-40 (2012).

