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What's in a delayed bathyphase? Letter to the Editor (re: McCall WV. A rest-activity biomarker to predict response to SSRIs in major depressive disorder)

Stephen F. Smagula, PhD

University of Pittsburgh, School of Medicine, Western Psychiatric Institute and Clinic, Phone: 412-246-5744

Stephen F. Smagula: sfs26@pitt.edu

TO THE EDITOR

Mounting evidence, including the recent paper by McCall (2015), suggests rest-activity rhythms are prognostic indicators of health. Recent research demonstrates that rest- activity rhythm disturbances predict future depression (Smagula et al., 2015a), dementia (Tranah et al., 2011), cardiovascular disease (Paudel et al., 2011), and mortality (Paudel et al., 2010; Zuurbier et al., 2015). Prior research also demonstrates that rest-activity rhythm disturbances might explain the statistical association between sleep disturbances and depression (Luik et al., 2015).

To my knowledge, the article by McCall (2015) is the first to suggest that rest-activity rhythms hold clinical prognostic value in a pharmacological depression treatment setting. Because the rest-activity rhythm is easily and objectively measured via actigraph recording, the McCall paper highlights a potentially important tool that may, in the future, aid psychiatrists and other mental health professionals in targeting treatments. McCall deserves praise for his succinct exposition and inclusion of prediction metrics (the cut-point of 260.2 minutes bathyphase has a positive predictive value (for treatment response) of 0.75 and negative predictive value of 0.88). The limitations of McCall's paper also serves-well to highlight several areas of rest-activity rhythm research that are currently under-developed.

First, the meaning of a bathyphase delay remains unclear, and may differ among patients with depression but no insomnia. McCall is clear to point out that the presented findings are preliminary and based upon a small sample; indeed, selection bias may limit the external validity of the study (the 12 with and 17 without a "favorable [delayed] bathyphase" from whom the main finding was revealed had major depressive disorder co-morbid with insomnia). As the authors point out, phase delays or "eveningness" have been previously associated with more severe depression (Courtet and Olie, 2012), and more severe depression is typically associated with treatment resistance (e.g. see Joel et al. (2014)). Thus, McCall's findings were tantalizing, and led to the question "what's in a delayed bathyphase?" and further "does it differ by insomnia status?"

Second, most literature on rest-activity rhythms (as is the case in sleep research (Smagula et al., 2015b)) focuses on the rest-activity rhythm as a predictor, with very little empirical evidence regarding the predictors of rest-activity rhythms. Given the now-established relevance of rest- activity rhythms to health outcomes in community (see above) and clinical settings (the McCall paper), a fruitful future direction may be to understand the determinants of rest-activity rhythm characteristics. In the case of the McCall paper, examining the clinical characteristics of the patients with and without a “favorable [delayed] bathyphase” may have been productive. For example, are the patients with a less “favorable [delayed] bathyphase” burdened with greater severity of early morning awakening complaints? It would also be interesting to know whether patients with major depressive disorder, insomnia, and a less “favorable [delayed] bathyphase” differ from similar patients with a more “favorable [delayed] bathyphase” in terms of the predominate depressive symptoms expressed pre-treatment or, residually, after treatment.

One final future direction of note has to do with McCall’s main finding not benefiting from the placebo-controlled study design. Therefore, patients with relatively delayed bathyphase may have benefited from either enhanced fluoxetine efficacy or a more pronounced placebo effect. Future randomized studies should test whether delayed bathyphase is indeed a moderator of fluoxetine efficacy.

McCall has done a great service to researchers focused on rest-activity rhythms in depression, and I sincerely look forward to the author’s future work (that may already be planned to further advance the field by addressing these limitations). With use of activity monitoring technology becoming more widespread and less expensive, it is possible in the not-too-distant future, mental health practitioners will benefit from the rich data offered by continuous and ecologically valid remote activity monitoring. To understand the meaning of such data, future large-scale studies including patients with major depressive disorder, both with and without co-morbid insomnia, are necessary. To fully understand relations between rest-activity rhythms, mood, and treatment responsiveness, future studies will likely need to integrate markers of circadian biology (dim light onset melatonin) and the biosignatures of depression (i.e. using MRI or blood biomarkers).

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