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Letter to the Editor

Exercise works for depression: bridging the implementation gap and making exercise a core component of treatment

We would like to thank Dr. Legrand and Dr. Neff for their interest in our paper, in which we discussed how the scientific community could advance further to understand the antidepressant role of exercise for individuals with depression, investigating potential sources of heterogeneities on the outcomes (1). Dr. Legrand and Dr. Neff raised several interesting points related to our suggestions (2). Their points related to our suggestions that (a) different subtypes of depression (and other biological, clinical, psychological, social characteristics) may moderate the antidepressant effects of exercise; (b) designing exercise interventions should take into account the putative biological mediators involved; and (c) more pragmatic randomised controlled trials (RCTs) are needed due their 'high external validity (outcome generalizability) by virtue of methodological features that are more closely aligned with "real life" practice norms'. Here, we wish to clarify and briefly expand on these points.

First, we suggested that, as depression exhibits heterogeneous symptomatology and biopsychosocial correlates, it is reasonable to assume that this heterogeneity will likely influence the effects of exercise on individuals with depression. Dr. Legrand and Dr. Neff argued that the source we cited to support this point 'is presented as a review article about the "moderators of response in exercise treatment or depression," but it actually included a very small number of studies (n = 11), and some of the presented conclusions have been drawn on the basis of one single study'. We would like to clarify that our point primarily reflected a theoretical postulate, namely that 'patients with similar scores on measures of depression may experience dissimilar symptoms … This heterogeneity in symptoms may reflect differences in underlying neurobiological processes …, suggesting that the same exercise prescription may be less effective for some patients and more effective for others' (p. 2) (3). Related to this postulate, we cited a review as providing 'initial evidence' suggesting that 'clinical (severity of somatic symptoms), biological [brain derived neurotrophic factor, (BDNF) and tumor necrosis factor-α], psychological (self-esteem and life satisfaction), and social factors (support and marital status) may moderate the antidepressant effects of exercise' (p. 2). We thus concur that conclusive evidence supporting our point is still lacking. In fact, we stated that, in the future, researchers can 'conduct moderator analyses to identify depressed subgroups with symptomatology and biopsychosocial characteristics associated with differential responses to exercise interventions', in order to test this assumption. Interestingly, as the publication of our initial paper, a study by Rethrost et al. (4) identified that patients with atypical depression are more likely to respond to exercise compared with patients with melancholic depression. Clearly, more research on this issue is needed.

Second, Dr. Legrand and Dr. Neff raised three points pertaining to our discussion of the challenges involved in identifying the 'optimal dose' of exercise. (a) Their first point was that 'the majority of trials that used exercise (aerobic or anaerobic) in the management of clinical depression did not quantify physical activity in terms of energy expenditure (expressed in kilocalories/week) but rather in terms of time spent at various relative intensities'. Although it is true that most reports specify the prescribed dose of exercise in terms of intensity and duration (e.g. percentage of maximal aerobic capacity for intensity and number of minutes per session for duration), this approach is essentially interchangeable with describing exercise prescriptions in terms of energy expenditure (e.g. kilocalories per week), once body mass is taken into account (p. 176) (5). (b) The second point made by Dr. Legrand and Dr. Neff was that they do not 'think that any method employed in quantifying the prescribed "dose" of physical activity will help in identifying the biological mechanisms through which exercise decreases depression'. We should clarify that we did not state that using a certain dose of exercise could provide information regarding the potential biological mechanisms. Our point was that the exercise prescription should be

designed to take advantage of the postulated mechanisms underlying the antidepressant effect. For example, to promote the upregulation of brain-derived neurotrophic factor (BDNF), as one of the biological mechanisms accounting for the antidepressant effects of exercise (6), researchers should consider the evidence on the types and doses of exercise that optimise this effect. Specifically, optimising BDNF upregulation seems to require low-intensity exercise (7). Furthermore, voluntary, self-paced exercise appears to be more effective than imposed exercise (8) and may prolong the elevation of BDNF (9). Moreover, in humans, the endocannabinoid anandamide in plasma has been found to be correlated with BDNF (10). As anandamide is closely related to affective responses to exercise (11), these findings suggest that, to upregulate BDNF and stimulate neuroplasticity, an exercise stimulus may be required that (perhaps above all else) is experienced as pleasant. Thus, it should be apparent that an exercise prescription designed to optimise the antidepressant effect may be substantially different from a typical prescription, the purpose of which has traditionally been the promotion of adaptations in the cardiovascular system. (c) The third point raised by Dr. Legrand and Dr. Neff was that 'it is doubtful that an exercise prescription can be shaped to target a specific "putative mechanism of the antidepressant effects of exercise"'. In support of this argument, they cited the study by Schmolesky et al. (12), which found no difference between 'moderate' (60% heart rate reserve) or 'vigorous' (80% heart rate reserve) and 'short' (20 min) or 'long' (40 min) exercise conditions in serum levels of BDNF in healthy men. However, Schmolesky et al. acknowledged that the increase in BDNF was highest in their lowest-intensity and shortest-duration group, albeit the difference was not statistically significant due to the low level of statistical power (see p. 507, also see their figure 1C). Moreover, it should be noted that both intensities employed in the study by Schmolesky et al. (i.e. 60% and 80% of heart rate reserve) are considered 'hard/vigorous' by the American College of Sports Medicine (this range is defined as 60–84% of oxygen uptake or heart rate reserve, or 77–93% of maximal heart rate) (5).

Lastly, Dr. Legrand and Dr. Neff commented on our proposal for more pragmatic RCTs that more accurately represent real-world clinical practice and the patients typically encountered in these circumstances. Instead, Dr. Legrand and Dr. Neff argued that 'what seems mostly needed is to develop RCTs conducted with a high degree of internal validity'. First, although internal and external validity are usually reciprocally related, it is erroneous to think of them as necessarily antithetical, fundamentally incompatible, or mutually exclusive. Instead, the challenge is to maintain balance between the two (13). Perhaps more importantly, our argument for pragmatic trials relates primarily to the current challenge of introducing exercise to treatment pathways in clinical practice. For us, the question is no longer whether exercise can demonstrate efficacy in reducing depression under optimal conditions (i.e. with select and highly motivated participants, expertly administered treatments, etc.). Recent meta-analyses have demonstrated that exercise does produce a clinically meaningful antidepressant effect under such conditions. The question now is the investigation of the antidepressant effectiveness of exercise in routine practice given the lack of pragmatic RCTs. Thus, the next step is to explore how clinical evidence can be translated into routine practice. Particularly, how current physical activity/exercise guidelines for depression can be efficiently conducted under non-optimal (pragmatic) conditions that routine practice is daily faced with (e.g. with diverse samples and non-expertly administered treatments). We believe that this is the next critical stage, so that a real difference can be made in the lives of everyday people suffering with depression. Pragmatic RCTs may hold the key to overcoming the skepticism that currently seems to preclude larger-scale implementation of exercise and physical activity in routine care.

In sum, we thank Dr. Legrand and Dr. Neff for raising these points. In many ways, we share similar views and the desire to utilise exercise as a treatment for people with depression. We hope that the demonstrated benefits of exercise for depression in robust RCTs can soon translate into broad changes in clinical practice within emerging stepped-care collaborative approaches to treatment. We maintain that pragmatic RCTs will be a vital next step in bridging the implementation gap.

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