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Commentary

The environmental mismatch model of bipolar disorder is supported by evidence: A response to Partonen et al.

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We thank Partonen et al. (https://doi.org/10.1016/j.neubiorev.2021.09.039) for providing a critical discussion of the environmental mismatch model for bipolar disorder which we presented in a recent article (Rantala et al., 2021) (https://doi.org/10.1016/j.neubiorev.2020.12.031).

In their commentary, Partonen and colleagues argued that the prevalence of bipolar disorder is similar in people with contemporary western lifestyles and in people with traditional lifestyles. As the main piece of evidence, they cited Georgi et al. (2014), who argued that "bipolar type 1 and 2 disorders in the Amish occur with similar prevalence, pattern of symptoms, clinical course and response to mood-stabilizing medicines as observed in the general North American population". This is clearly incorrect, because none of the three references cited by Georgi et al. (2014) to support this claim studied population prevalence of bipolar disorder (BD) among the Old Order Amish. We contacted Professor Francis J. McMahon who has led studies on genetics of BD among the Old Order Amish and he confirmed that there are no published or unpublished studies that would have recorded the prevalence of BD since the study done in 1976–1980 by Egeland and Hostetter (1983) which we originally cited.

Partonen et al. were informed twice during the review process of their commentary that the research they cited did not study BD prevalence. However, they ignored the feedback and decided to publish their commentary anyway, repeating the error in Georgi et al. (2014).

Partonen et al. calculated that the difference in BD prevalence between the Amish and other US populations would have been only 4.6-fold. This is incorrect. They were comparing the 5-year prevalence in the Amish with the 1-year prevalence in other US populations. Thus, the true differences in BD prevalence between the Old Order Amish and other North American populations can be much higher, even higher than we calculated in our corrigendum (https://doi.org/10.1016/j.neubiorev.2021.03.027).

Importantly, there is much more evidence showing that BD prevalence is higher in people with contemporary western lifestyles than in people with traditional lifestyles than we presented in our original article. Unfortunately, we are not able to provide all of it here because of limitations on the length requirements and the number of citations in the response article type. To provide one notable example, a study in the Hutterites in 1950–1953 found that only three out of 4286 participants met the diagnostic criteria of bipolar disorder, as cited in our corrigendum (https://doi.org/10.1016/j.neubiorev.2021.03.027), which Partonen et al. ignored.

Partonen and colleagues also misled readers into thinking that there is no other evidence for the link between peripheral low-grade inflammation and neuroinflammation than what we originally provided in our review article (Rantala et al., 2021). There are many more experimental studies in non-human animals and also in humans showing the causality between peripheral low-grade inflammation and neuroinflammation (for an excellent review, see Troubat et al. (2021)). In contrast to claims by Partonen et al., there are even studies that show that peripheral

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injection of proinflammatory cytokines causes neuroinflammation in humans (Troubat et al., 2021).

Partonen and colleagues criticized the idea that neuroinflammation plays a role in BD, failing to take note of recent advances in this area of research. A substantial amount of evidence shows that BD is associated with neuroinflammation (for a review, see Benedetti et al. (2020)). For example, *in vivo* positron emission tomography (PET) studies in patients with BD support the claim that these patients have neuroinflammation. Likewise, *in vivo* microglia characterization showed a significantly increased activation in the hippocampus of BD patients compared to healthy controls, suggesting the presence of neuroinflammation in BD patients. Furthermore, a direct association between microglia activation and neuronal damage in BD has been observed, suggesting a possible harmful effect of this neuroinflammatory condition (for a review, see Benedetti et al. (2020)).

It is important to note that there are more studies to support the claim that activation of the immune system (which also activates microglia cells) disrupts the functioning of the internal clock than those that we cited in our review article (Rantala et al., 2021). For example, in the highlights of their excellent review on this topic, Hergenhan et al. (2020) wrote that "[c]ircadian clock proteins engage in direct physical interactions with inflammatory proteins. Immune factors also reciprocally exert control over circadian clock function."

The criticism presented by Partonen et al. about individual variation in symptom patterns of the depressive phase in BD is a classic example of a straw man argument. In the text and Figure 1 of our review article (Rantala et al., 2021), we clearly stated that not all cases of depression in patients with BD are caused by chronic stress. Instead, there are many possible triggering factors for depression, and different triggering factors can lead to different symptom patterns—as predicted by the evolutionary psychological subtyping of depression.

Our environmental mismatch model of bipolar disorder (Rantala et al., 2021) shakes the long-held paradigm that bipolar disorder is merely a heritable disorder, with environmental factors playing a limited role. It is an essential part of scientific progress that other researchers challenge our new model—and we welcome Partonen et al.'s contribution to this discussion. This critical discussion should, however, be done to increase our collective knowledge about the topic, not to try to mislead the scientific community by presenting a flawed reading of existing evidence.

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