LETTER TO THE EDITOR

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TO THE EDITOR

ABSTRACT

We present a case study of scientific publishing which we base on a line of discussion we had in the official journal of the International Behavioral Neuroscience Society having the Journal Impact Factor of 8.2 as of 2022, which places it a Q1 journal in the categories of behavioural sciences (the 5th out of 54) as well as neurosciences (the 37th out of 306). Here, we quote the incorrect or inaccurate claims, check their data and comment each one by one..

KEYWORDS: BIPOLAR DISORDER, ETHICAL GUIDELINES, PEER REVIEW, SCIENTIFIC PUBLISHING

In the official journal of the International Behavioral Neuroscience Society, a review [1] stated that bipolar disorder results from contemporary Western lifestyles causing neuroinflammation. The facts as they were provided did not support this statement. We sent a commentary [2] on the review [1], to which the authors of the review [1] responded [3] with inappropriate phrases which suggested unethical intent that went beyond polite disagreement as judged by the Editor's note [4] in the end. In addition to the inappropriate phrases, the response [3] contained incorrect or inaccurate claims which were left uncorrected in the literature. Here, we quote the claims, check their data and comment each one by one.

ONE

CLAIM: "In their commentary [https://doi.org/10.1016/j.neubiorev.2021.09.039], 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."

COMMENT: The claim One is incorrect. The main piece of evidence is collected from the 1970s (Egeland, 1983) to the 2010s (Georgi et al., 2014, in which Egeland is a co-author). The three references cited by Georgi et al. (2014) in PLoS Genetics are as follows.

First, Hostetter et al. of 1983 in *American Journal of Psychiatry* studied diagnostic stability to determine validity of diagnosis, reported the agreement on 120 Amish cases, and observed the course of the illness to verify subsequent episodes of bipolar type 1 disorder and bipolar type 2 disorder.

Second, Pauls et al. of 1992 in *Archives of General Psychiatry* reported [quote]: "Active cases of mental disorder were ascertained in two ways during the period 1976 through 1987: (1) a survey of all Amish patients admitted to the psychiatric inpatient facilities serving the area; and (2) a community epidemiologic survey of all families [of the old-order Amish community of Lancaster County, Pennsylvania]. A total of 206 cases of mental illness were identified through these methods … Forty active cases were diagnosed by the psychiatric board as BP I … eight had a diagnosis of bipolar II … Total census data are available for the Amish; thus, it

is possible to estimate age- and sex-specific prevalences for each of these disorders. These rates will be underestimates of the true rates of illness to the extent that a lifetime diagnosis will be missed if no episodes of illness occurred during the time frame of this study … The number of first-degree relatives receiving each of the six diagnoses is presented in *Table 2*, together with the uncorrected and age-corrected rates for each diagnosis. These rates are comparable with others reported in the literature and are significantly higher than the age-corrected prevalence estimates [of 1.2±0.1% for bipolar type 1 disorder and 0.2±0.1% for bipolar type 2 disorder] from this population (see *Table 1*)."

Third, Egeland of 1994 is an overview entitled "An Epidemiologic and Genetic Study of Affective Disorders among the Old Order Amish" in *Genetic Studies in Affective Disorders* by Wiley-Interscience and reported [quote]: "results for a research investigation that now spans a 16-year period, and yet remains contemporary in its aims and focus … By 1980, we reported on the ascertainment of 112 "actively ill" patient cases; 71% had a major affective disorder according to the RDC (Egeland & Hostetter, 1983). A 1986 report listed 62%, or 107 of 173 patients, as actively ill with major affective disorders (Egeland, 1986). The latest diagnostic breakdown for active cases through the past 15 years [1976–1990] is given in *Table 4-1*". Of 221 individuals, 63 (28.5%) were diagnosed with bipolar type 1 disorder or bipolar type 2 disorder, and 6 (2.7%) with other bipolar (atypical/chronic) disorder.

In our commentary [2], we stated this as the best evidence currently available.

TWO

CLAIM: "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 [https://doi.org/10.1016/j.neubiorev.2020.12.031]."

COMMENT: The claim Two is inaccurate. The main field work for the Amish Study of Major Affective Disorders was done in 1976–1980, which was made possible by the more than 20 years of research activities among the Amish of the principal investigator (Egeland), and thereafter studies have been conducted. Data being derived from all this work, the prevalence has been estimated.

Already in the publication by Egeland and Hostetter (1983) in *American Journal of Psychiatry*, it reads that for a stable population of Lancaster County Amish aged 15 years or older [quote]: "the rate for major affective disorders is about 1%, which is half the usual rate of mood disorders in other [North American] populations … rates for both mental illness in general and affective disorders specifically appear to be below average".

Thereafter, in the publication by Egeland (1983) in *Comprehensive Psychiatry*, reporting the study of 1976–1982, it reads [quote]: "Since there are other active unipolar cases not yet interviewed but tagged for bipolarity, it is quite possible that the bipolar ascertainment for the Amish study will increase." Further, it reads [quote]: "The Amish population is perhaps the first in this country, and of a European origin, reporting a high proportion of bipolar compared to unipolar illness."

In the publication by Georgi et al. (2014) in *PLoS Genetics*, it reads [quote]: "Bipolar disorder type I (BPI) and bipolar disorder type II (BPII) 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 [17–19]", where the three references cited were published between 1983 and 1994, of which that of Egeland of 1994 reported the prevalence rates of bipolar disorder among the Old Order Amish for 1976–1990.

In two publications where McMahon himself was the senior author, it was reported that [quote from Hou et al., 2013, in *Trends in Genetics*]: "The presentation of major psychiatric disorders among the Amish seems to be generally similar to that in other North American populations … Large epidemiologic studies of psychiatric disorders have not, to our knowledge, been performed in this population, and therefore the true prevalence and geographic distribution of disorders are unknown", and that [quote from Dumont et al., 2020, in *Journal of Psychiatric Research*]: "44 of the 161 participants received a BEFD of BSD (27.3%), significantly higher than the 1–2% lifetime prevalence found in the general population (Ferrari et al., 2013)." Furthermore, in the latter, the distribution of bipolar spectrum disorder cases and non-cases (both healthy and diagnosed with other psychiatric disorders) revealed that bipolar spectrum disorders were more prevalent among the Amish than Mennonite or other (or unspecified) Anabaptist groups.

THREE

CLAIM: "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)."

COMMENT: The claim Three is incorrect, because there is no error in the article by Georgi et al. (2014). Since there is not any correction nor retraction, we have no reason to question the integrity of the work by Georgi et al. (2014) as published in *PloS Genetics*. The three references cited by Georgi et al. (2014) in *PloS Genetics* included the following: Hostetter et al. of 1983 in *American Journal of Psychiatry* which reported the diagnostic agreement on 120 Amish cases and observed the course of the illness to verify subsequent episodes of bipolar type 1 disorder and bipolar type 2 disorder; Pauls et al. of 1992 in *Archives of General Psychiatry*, where the prevalence rates of bipolar type 1 disorder and bipolar type 2 disorder among the first-degree relatives of Old Order Amish bipolar type 1 disorder probands were presented and compared to the age-corrected population prevalence rates of this population; and Egeland of 1994 which provided the diagnostic breakdown for 221 active cases for 1976–1990.

FOUR

CLAIM: "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)."

COMMENT: The claim Four is incorrect. The lifetime, not the 1-year, prevalence in other US populations (2.1%) being divided by the period (5-year) prevalence in the Amish (0.46%) yielded the 4.6-fold difference that we provided in our commentary [2].

Our commentary [2] was received on 19 February 2021, received in revised form on 17 September 2021, accepted on 20 September 2021, and available online on 28 September 2021. In the version we originally submitted as our commentary, we wrote [quote]: "The cited mental health study on the Amish included 8,186 participants, not 12,500, of whom 38, not 28, had bipolar disorder, yielding the prevalence rate of 0.46%, not 0.22%, for bipolar type 1 and 2 disorders till 1980. The cited World Mental Health Survey Initiative study revealed the lifetime prevalence rate of 2.1%, not 4.4%, for bipolar type 1 and 2 disorders in the USA in 2002–2003. So, the difference between the Amish and other US populations were 4.6-fold, not over 18-fold as stated, or in fact not more than 2-fold or less, because in the original report on the Amish the prevalence rate was estimated to be half the usual rate of mood disorders in other populations, or below average."

The corrigendum [5] by the authors of the review [1] was received on 24 February 2021 (five days after our commentary [2] was received and sent for peer review), received in revised form on 23 March 2021, accepted on 24 March 2021, and available online on 1 April 2021. In the corrigendum [5], the authors wrote [quote]: "There was a calculation error in [https://doi.org/10.1016/j.neubiorev.2020.12.031]. Page 30: 'A mental health study on 12,500 Amish people found that only 28 of them suffered from bipolar disorder (Egeland and Hostetter, 1983). This means that the likelihood of an Amish person having bipolar disorder is 0.22 %. Instead, 4.4 % of Americans experience this disorder (Merikangas et al., 2011). The difference between the Amish people and other Americans is therefore over 18-fold.' The authors sincerely apologize for this error. The corrected sentences should be: 'A mental health study on a population of 12,500 Amish people of which 8186 were adult found that only 38 suffered from type 1 or 2 bipolar disorder (Egeland and Hostetter, 1983). This means that the 5-year prevalence of the bipolar disorder is 0.46 %. The WHO study found that the 1-year prevalence of bipolar disorder was 1.4 % (Merikangas et al., 2011). Although it is difficult to compare the 5-year prevalence with the 1-year prevalence, one could conclude that the prevalence of the bipolar disorder is substantially lower among Older Order Amishes than in other north Americans. The true difference in prevalence is probably much larger because Egeland and Hoster (1983) noted that the "Amish interact so closely within a given district that even mild cases of emotional upset or mental disturbance cannot go undetected, and each case of mental illness was reported, on the average by 18 informants". Thus, the WHO study and other studies have not been able to detect all possible cases of mood disorders as exhaustively as Egeland and Hoster were able to do.' It is important to note that there is additional support for the environmental mismatch

hypothesis of bipolar disorder. For example, Nimgaonkar et al. (2000) found that only three out of 4286 participants met the diagnostic criteria of bipolar disorder in the Hutterites in 1950–1953."

FIVE

CLAIM: "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."

COMMENT: The claim Five is unfair. The corrigendum [5] was submitted on 24 February 2021 and thereafter published on 1 April 2021 while the peer review of our commentary [2] was still ongoing, being started on 19 February 2021. In our commentary [2], we criticized the review [1] as it had been published, and therefore we ignored none. After the two rounds of peer review and more than seven months, our commentary [2] was published on 28 September 2021.

The subsequent claim is incorrect as well, as it was in the corrigendum [5]. In the publication by Nimgaonkar et al. (2000) in *American Journal of Psychiatry*, the prevalence rates for DSM-IV psychoses, based on a one-author review of the clinical records of 252 individuals classified as psychiatrically ill in an epidemiological survey of all Hutterites living communally in the United States and Canada on January 1, 1950, were reported, and three individuals out of 252, not out of 4286, met the criteria for bipolar type 1 disorder, not including bipolar type 2 disorder nor bipolar disorder not otherwise specified. Further, the population estimates in the province of Manitoba, Canada, for 1992–1997 yielded that the prevalence rates for ICD-9 psychoses were lower in both the Hutterites and the comparison group, but the prevalence of ICD-9 neurotic disorders was higher among both the Hutterites and the comparison group (i.e., persons with one of the 19 surnames but with non-colony residential addresses that may include Prairieleut and Hutterites who left the colony and their descendants), as compared with the total Manitoba population.

SIX

CLAIM: "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 [https://doi.org/10.1016/j.neubiorev.2020.12.031]".

COMMENT: This claim Six is incorrect. In our commentary [2], we commented on what had been presented in the review [1]. We disagreed in that the causative link from low-grade inflammation to neuroinflammation was commonly known in humans, as the review [1] presented this causative link as its key and provided only one reference to its support. The reference was to an experimental model of laparotomy in mice which was to simulate the problem of some patients who suffer from cognitive dysfunction after surgery. The evidence as provided in the review [1] did not support the causative link, which we criticized in our commentary [2].

SEVEN

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

COMMENT: The claim Seven is incorrect.

In the review by Troubat et al. (2021) in *European Journal of Neuroscience*, there is a reference to one study (Moieni et al., 2015, in *Neuropsychopharmacology*), not studies, in which a single infusion, not injection, of low-dose endotoxin (derived from Escherichia coli; 0.8 ng/kg of body weight) was administered and there was no assessment of neuroinflammation.

Further, the immediate continuation of the discussion in the review by Troubat et al. (2021) including the reference to Bai et al. (2019) in *Journal of Neurology, Neurosurgery and Psychiatry*, which did not confirm the role of the

inflammatory component and thus does not support the hypothesis by the authors of the review [1], was not cited.

The discussion by Troubat et al. (2021) reads [quote]: "Interestingly, inflammation may be one of causes for the higher prevalence of depression in women, as the prevalence of autoimmune diseases (Whitacre, 2001) like depression (Grigoriadis & Robinson, 2007) is twice as high in women than in men, and these findings may reflect gender differences in basal immune activity (Chapman et al., 2009). The gender difference in terms of prevalence of MDD begins in adolescence and does not appear to be related to sex hormones (Kessler, 2003) but rather to higher sensitivity to stressful life events (Kendler, Thornton, & Prescott, 2001) or childhood psychosocial stress (Takizawa, Danese, Maughan, & Arseneault, 2015), which may be attributed to inflammation. In support of this hypothesis, women exposed to an experimental endotoxin challenge (single injection of a low dose of endotoxin from *Escherichia coli*) displayed increased levels of depressed mood and feeling of social disconnection compared to those who received placebo (Moieni et al., 2015). However, other clinical data did not confirm the potential role of this inflammatory component, as anti-inflammatory compounds (and particularly celecoxib and omega-3 fatty acids in monotherapy) were found to have no significant antidepressant effects in women, as might have been expected (Bai et al., 2019)."

EIGHT

CLAIM: "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))."

COMMENT: The claim Eight is inaccurate. In our commentary [2], we commented on what had been presented in the review [1] and wrote [quote]: "The heterogeneity in published studies means that inflammation may play a role only in a small subset of patients with bipolar disorder." The review by Benedetti et al. (2020) in *Frontiers in Psychiatry* was not included in the review [1], but it concluded that [quote]: "The objective of this review is to summarize available evidence on the connection between inflammation and BD, focusing on peripheral inflammatory markers and recent findings on their connection with other typical features of BD, to outline a general overview of the disorder. Moreover, it is meant to analyze the issues with data gathering and interpretation, given the partially contradictory and inconsistent nature of results."

NINE

CLAIM: "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 [https://doi.org/10.1016/j.neubiorev.2020.12.031]. 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."

COMMENT: The claim Nine is inaccurate. In fact, there are the four highlights in the article by Hergenhan et al. (2020) in *Journal of Molecular Biology as follows* [quote]:

- "The immune system is under control of the circadian clock.
- Circadian clock proteins act as transcription factors controlling genes of the immune system.
- Circadian clock proteins engage in direct physical interactions with inflammatory proteins.
- Immune factors also reciprocally exert control over circadian clock function."

In the article itself, it reads [quote]: "Nevertheless, all studies have shown that interruption was only temporary, for a maximum of three days, indicating that while oscillations are dampened the central clock still remains entrained to the environment during an immune response." Further, it reads [quote]: "However, in vivo the interplay between bacterial products acting directly on the SCN and indirectly via inflammatory mediators released by the immune system is not clear."

TEN

CLAIM: "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."

COMMENT: The claim Ten is incorrect. We addressed the real subject and did not replace it with a false one.

ELEVEN

CLAIM: "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."

COMMENT: The claim Eleven is incorrect. We did not try to mislead the scientific community by presenting a flawed reading of existing evidence. We criticized the evidence as it was provided in the review [1].

CONCLUSION

The current evidence does not support the premises of the environmental mismatch hypothesis as it was presented in the review [1] nor in the second commentary [3] which was given in response to our commentary [2]. Furthermore, any author should refrain from being hostile or inflammatory as well as from making libelous or derogatory personal comments or unfounded accusations.

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References

Instead of citations the direct links to the publications in question are listed below.

1. https://doi.org/10.1016/j.neubiorev.2020.12.031
2. https://doi.org/10.1016/j.neubiorev.2021.09.039
3. https://doi.org/10.1016/j.neubiorev.2022.104631
4. https://doi.org/10.1016/j.neubiorev.2022.104862
5. https://doi.org/10.1016/j.neubiorev.2021.03.027