OPEN PEER REVIEW REPORT 2

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Title: The role of the metabolism of branched-chain amino acids in the development of Alzheimer's disease and other metabolic disorders
Reviewer's Name: Jason Eriksen
Reviewer's country: USA
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COMMENTS TO AUTHORS

In this review, the authors provide an interesting discussion concerning alterations in branched chain amino acid metabolism in the progression of Alzheimer's disease. They suggest that because of the failure of some of the current therapies, alternative approaches must be considered.

The article is interesting and timely and covers some alternative disease targets that may have received reduced attention because of the predominance of amyloid beta and tauopathies as the putative driving agents in Alzheimer's disease. While I think this review is interesting and timely, I have some suggestions.

Page 3 lines 28 to 60: this portion of the review provides a series of different therapies that have been tried. However because these are not particularly germane to BCAA metabolism, they are more of a distraction than a benefit to the manuscript. Although these alternative approaches, many different approaches have been tried; these are not strong proof that other approaches have to be considered. It is recommended that the authors remove this section as it does not appear to advance the argument significantly.

Similarly, while the role of a beta has been diminished in Alzheimer's disease as a therapeutic target, I would be cautious about discounting the impact of tauopathy since it is clear that the presence of this pathology strongly correlates in clinical settings with cell death and cognitive deficits.

Page 5, line 46 to 59: a number of groups have looked at administration of compounds such as B6 and other vitamins. Notably, B6 was tested in clinical trials back in 2008 and a report in JAMA by Paul Aisen failed to find any protective effect of vitamin B supplementation in Alzheimer's disease. Consequently, although this correlation is interesting, there is not strong support for this particular argument.

Although BCAA supplementation has been shown in some cases to be beneficial, other reports suggest that BCAA supplementation with high-fat diet may potentially be toxic. The authors mention work by Li at al; in addition there is a another report by Tournissac et al: Alzheimers Dement (N Y). 2018; 4: 677-687. Published online 2018 Dec 10. Some of this is ascribed to differences between young and old animals and the relative paucity of information associated with BCAA metabolism. In the work by Tournissac, they suggest that BCAA administra in combination with a high-fat diet may indeed be toxic.

Given these discrepancies, it would be helpful if the authors stress these differences more clearly in order to provide appropriate context for studies that provide specific BCAA supplementation, such as the use of norvaline. These differences are somewhat apparent in the current discussion but I found myself having to tease out the distinctions.