Author's response to reviews

Title: An olfactory 'stress test' may detect preclinical Alzheimer's disease.

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Author's response to reviews: see over
Dear Editors,

We thank you for the opportunity of responding to Dr Richard Doty’s critique of our manuscript.

1). Rationale. We have expanded the introduction to make this clearer. We emphasize even more the basic science that speaks to the importance of the cholinergic system for olfaction and we now make reference to clinical studies that indicate that individuals with AD exhibit heightened sensitivity to interventions that involve the cholinergic system. We state our belief that this vulnerability likely extends to the olfactory system.

Throughout, we make plain our belief that the atropine effect is a centrally mediated phenomenon (i.e. not at the level of olfactory epithelium). The question of how much of the intranasal atropine gets to the olfactory bulb is not answerable from our data or the existing literature, but we cite a review which outlines the general principles that determine which drugs are likely to concentrate in olfactory bulb. This material, we believe, justifies our expectation of olfactory bulb uptake of intranasally-delivered atropine. Nevertheless, in the discussion, we now acknowledge that this remains somewhat speculative however we note that more diffuse uptake of atropine into the CNS from the blood could also explain our findings.

2.) Absence of a control group i.e. failure to include a pharmacologically inert nasal spray in the study. We identify this as an uncertainty/limitation of the study and state that we will in future studies include such an experimental arm, but we believe that the coherent, consistent and highly significant associations between the atropine effect and the three other potential markers of AD-risk make a ‘chance’ association, or one lacking any relevant biological explanation, very implausible.

3). Lack of analyses on the sensitivity and specificity of the Olfactory Stress Test (OST) relative to clinical categorization. We have added nothing on this to our manuscript revisions because we believe to do so would achieve nothing but conceptual confusion. The three clinical groups in our study are defined by their performance on cognitive tests. But a central theme -- indeed the motivation-- for our study is the now well-established fact that cognitive performance is an imprecise and potentially highly inaccurate guide to the presence of underlying AD pathology in the brain (a point we make in the very first sentence of the paper), the detection of which is the goal of biomarker application. To elevate the clinical diagnosis as the ‘Gold Standard’ against which to judge the sensitivity/specificity of the OST would be to ignore this central point and threaten the coherence of the paper.

We have made several other small changes in the body of the work, and have provided better quality figures.

Many thanks again for considering our work.

Yours sincerely,

Peter Schofield