Reviewer's report

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

Version: 2 Date: 21 November 2011

Reviewer: Richard L Doty

Reviewer's report:

Major compulsory revisions

1. This interesting study has not developed a strong rationale for why one would expect intranasal infusion of an anticholinergic agent to alter smell function more in AD than in other people. Does the olfactory epithelium contain cholinergic fibers/receptors? How much of the material enters the blood stream from the nasal spray (the nose is highly vascularized and a major route into the blood stream of numerous agents). How much (if any) actually enters the olfactory bulb? The concept, it is to have legs, needs more development in the introduction and discussion sections of the paper.

2. There is no control group for the sprayed substance. How do we not know that simply spraying warm water into the nose would not produce the same effects. A differential effect of general arousal from a nasal treatment, for example, might pick up some differences between the controls, MCI, and AD groups. This is a major problem with the design that needs rectification.

3. If one is really proposing this paradigm as a test for detecting preclinical AD, it would be useful to know its sensitivity and specificity for differentiating between controls, MCI, and AD patients. None of this critical information is provided

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I am President of, and major shareholder in, Sensonics, Inc., the manufacturer of the olfactory test used in this study. I have no conflict of interest. In fact, my suggestion of rejecting the paper would work against any real or perceived conflict of interest, since one might argue that it would be in the interests of the company if such a paper were published.