Author's response to reviews

Title: Visual pursuit response in the severe disorder of consciousness: modulation by the central autonomic system and a predictive model.

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Author's response to reviews: see over
Dear DR. Josefino M. Rodis

I regret having missed your emails and hope my delay in complying with your requirements will be of no inconvenience to you.

The Referees’ advices were helpful and have been carefully followed. The issues raised by Referee #2 have been addressed as suggested and are in red in the ms, which has been fully revised for readability. A point-to-point response to the questions raised by Referee #2 is appended below.

We hope the paper can now meet your requirements for publication. Of course, additional changes in the text or figures/table will be promptly made if required.

Sincerely yours,
walter g Sannita, md

Questions:

1. I am not sure of the practical value of the autonomic testing as it was done simultaneously with the mirror testing for visual pursuit, which was the “gold standard” response. Would it not be worth pursing monitoring autonomic responses with simpler stimuli and perhaps spontaneous variability?

Correct. The visual pursuit response has been chosen because of its established role as an index of evolution from the VS to the MCS and a key item of the Coma-Recovery Scale. We already reported about its incidence varying within-day and over weeks (Candelieri et al. J Neurotrauma 2011, 28:2013-17). Of course, simpler stimuli are likely to be as indicative and a study on this is being completed. This sign is a prognostic index (Dolce et al. J Neurotrauma 2011, 28:1149-54), but - due to its variability- the suggestion that spontaneous variability in the sympathetic/parasympathetic balance should be monitored independently of clinical signs is correct. The issue has been addressed in the Discussion section

2. How did the authors assure wakefulness during the visual pursuit testing? Did they stimulate the patient into wakefulness (which could have altered the autonomic response without even considering the stimulus for visual pursuit)?

Subjects were tested when their eyes were open and no sign or sleep or drowsiness could be detected upon observation; in no case sensory or noxious stimuli were administered to stimulate patients into wakefulness as this would have altered the pursuit response. This is now explicit in the Methods section, where it is also specified that subjects were tested for a visual pursuit response at the time of the day when the response incidence had proven highest in a previous study (Candelieri et al, J Neurotrauma 2011, 28:2013-17).

3. Do the authors have any physiological explanation why a subcortical, presumably hypothalamic, response might correlate with recovery or preservation of pursuit responses?

Correct. There is sparse, although converging data suggesting direct/indirect functional links between HRV measures, autonomic control, and brain activation. A model network (The Central Autonomic Network; CAN) has been proposed, in which the anterior cingulate cortex and its projections to the prefrontal cortex, amigdala, hypothalamus and brainsteam are involved in the modulation of autonomic output in response to pain and emotional or behavioral stimulus conditions. There is some speculation in this model (now quoted in the Discussion section) as there is in all models, but the correlation between the sympathetic/parasympathetic balance and the pursuit response fits it quite well.