Author's response to reviews

Title: Pain during ice water test distinguishes clinical bladder hypersensitivity from overactivity disorders

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Author's response to reviews: see over
Sub : Response to reviewers' comments

Dear Editor,

The authors would like to thank the reviewer for the positive comments and helpful suggestions. We have taken all comments into consideration and accordingly have made revisions to improve the manuscript.

Reviewer : Mary P. P. FitzGerald

**Comment #1:** The authors are encouraged to consider revising their terminology throughout the paper. The BCR is either present or absent, not positive or negative (i.e. there is no such thing as a negative BCR). Alternatively, they could say that the ice-water test was either positive or negative. An analogy would be the Babinsky sign, which is referred to as being present when there is dorsiflexion etc of the toes. The current terminology is distracting because BCR negative doesn’t exist.

**Response:** The authors agree with the reviewer and have made appropriate changes to the text on the manuscript and figures.

**Comment #2:** The title needs to be revised, since the findings of the study are NOT that ‘the BCR distinguishes clinical bladder hypersensitivity from overactivity
disorders’, rather they found that ‘Pain during ice water test distinguishes clinical bladder hypersensitivity from overactivity disorders’ and this is a critical difference.

Response: The title of the manuscript has been revised to “Pain during ice water test distinguishes clinical bladder hypersensitivity from overactivity disorders”

Comment #3: A final, major concern is the apparently premature rush to attribute the study’s findings to the involvement of TRPM8 receptors. The authors do concede near the end of the discussion that in fact TRPM8 may not be involved, but this concession does not balance the weight of earlier discussion of possible TRPM8 involvement, which really is not supported by the data from this study. The authors should consider de-emphasizing TRPM8, including removing that label from the figures.

Response: We agree with the comment by the reviewer and have mentioned in the Background section (P4) that it is a hypothesis that the BCR is originates from specific cold receptors rather than mechanoreceptors as it is evoked by cooling the bladder wall, and is activated at bladder volumes or pressures below threshold for the ordinary voiding reflex.

In addition, we have made the following changes in the manuscript and figures-

In Background section of Abstract and manuscript text, the phrase ‘originates from menthol sensitive cold receptors in the bladder wall’ has been replaced by ‘believed to be triggered by menthol sensitive cold receptors in the bladder wall’

In the discussion section (1st Paragraph) P9, the phrase ‘that despite the increased TRPM8 nerve fibres’ has been deleted.

A ‘?’ mark has been inserted before TRPM8 in the label of ‘Control’ section of Figure 3(a) to denote the hypothesis that TRPM8 may be involved. While, ‘↑TRPM8’ has been deleted from the label of Fig 3(b-d).

Comment #4: The conclusions of the authors regarding the importance of descending inhibition in PBS patients is not supported by this study.

Response: The statement -‘but no reflex motor response / detrusor contraction results as there is preserved central inhibition’ has been omitted from the discussion on P11.

Comment #5: Page 5: second paragraph – C-fibre afferent ‘activation’ in various ways ‘may be associated with functional changes such as increased urination frequency and urgency, as well as suprapubic pain’ – what evidence do the authors have for this statement? Please supply references.

Response: References (Yoshimura et. al, 2002, Wyndaele and De Wachter, 2003) have been added to the statement in the manuscript.

Comment #6 : Page 7: last paragraph – ‘cold sensation in the suprapubic region, presumably referred from the bladder’ – could this sensation actually be referred from the urethra?
Response: ‘Presumably referred from the bladder’ from the results section on P7 has been deleted and ‘presumably referred from the bladder or urethra’ has been added in the Discussion section P10-11, Paragraph on thermal perception from the bladder mucosa.

Comment #7 : Page 9: Discussion – ‘None of our PBS patients had a positive BCR, indicating that despite the increased TRPM8 nerve fibres, the inhibitory signals from higher centres being preserved, result in a negative BCR’ – another implication might be that in these patients, TRPM8 is not involved in the BCR. 
Response: In the discussion section (1st Paragraph) P9, the phrase ‘that despite the increased TRPM8 nerve fibres’ has been deleted.

Comment #8 : Page 11: again, the pain of the ice water test does not evoke the BCR … one conclusion might be that the pain of the ice water test is just not due to involvement of TRPM8. 
Response: We agree with the point raised by the reviewer, and the phrase ‘alternative molecular mechanisms, that do not involve TRPM8, are also possible’ is mentioned in the discussion, last sentence of paragraph on P11-12.

Comment #9 : Please explain why the PBS patients in this study had such low levels of bladder pain at the start of urodynamics – levels of about 1/10 seem to be prevalent, and this seems to be too low for this group of patients. Perhaps this would be clarified by more clinical information about this group of patients? 
Response: In the PBS patients, Pain was recorded on a Visual Analogue Scale (VAS) for worst, least and average pain during the last 24 hours before the bladder cooling reflex study. The Mean (range) of the worst’ for worst, least and average pain scores (VAS) of our PBS patients was 4.7 (2 to 9), 0.4 (0 to 3) and 3.4 (2 to 6) respectively. This statement has been included in the methods (Patient selection) section as a separate paragraph, P6. Most of the PBS patients reported relief of pain after bladder emptying, and hence our baseline pain scores before urodynamics (after bladder emptying) ranged from 0 to 3 with a mean of 0.64.

Reviewer : Gerard Amarenco  

Comment #1 : the order of urodynamic investigation (normal saline at room temperature vs cold test) was not randomized. Thus the results, (comparison of VAS in the groups) must be discussed with caution. This point must be taken into account in discussion chapter … all the more so that, the hypothesis of a peripheral and/or central sensitisation in PBS (since report of pain in PBS is more important) is interesting. 
Response: We agree with the comment by the reviewer on this limitation of the study, thus the statement ‘One of the limitations of the study was that the order of urodynamic investigation (normal saline at room temperature vs cold saline) was not randomized.’ has been included in the discussion, P11.
Additional changes

The Bladder cooling reflex study has been on-going since the time of the original submission. In these 3 months, we have increased the number of patients from 50 to 64. The increased numbers has not made any significant changes in the results or its interpretation, but increases the confidence in our results. Thus, the data has been updated in the text, tables and figures.

We hope that this manuscript now conforms to the Journal’s format requirements and is acceptable for publication.

Yours sincerely,

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Professor of Clinical Neurology