February 10, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 8145_Review.doc).

**Title:** FMRI contributions to addressing autobiographical memory impairment in temporal lobe pathology

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**Name of Journal:** *World Journal of Radiology* (Special Issue "fMRI: Experimental studies, prevention, diagnosis, treatment, and evidence-based medicine")

**ESPS Manuscript NO:** 8154

We are very pleased by the reviewer's note that our manuscript is "well written and referenced". While noting these positive comments, the reviewers also raised some concerns, which we have answered in this revised submission. Chief among the reviewers' comments were the need of clarifications of the aim of the review and note of the link between AM and other pathological conditions (the revisions are noted in blue in the manuscript). We are grateful for the thoughtful feedback provided by the reviewers. As a result of addressing the reviewers' comments, our manuscript has been strengthened. We very much hope that our manuscript is now suitable for publication in *World Journal of Radiology* in the Special Issue "fMRI: Experimental studies, prevention, diagnosis, treatment, and evidence-based medicine".

The manuscript has been improved according to the suggestions of reviewers:

**Reviewer 00727503**

1. We now included a paragraph discussing the link between traumatic brain injury and autobiographical memory. Please see page 13: "Traumatic Brain Injury (TBI) has been usually associated with impaired AM [125-127] together with diffuse axonal injury mainly affecting the connection between frontal and temporal regions [126, 128]. Given the diffuse nature of damage, TBI presents a challenge in understanding impairment of AM, which might be linked to a more general deficit in executive functions and alteration of the sense of self. Recent single-case fMRI investigation [129] of a TBI patient, ML (initially reported by Levine et al., 1998 [125]), revealed decreased involvement of the medial prefrontal and posterior cortices for recently encoded personal events, which retrieval is lacking specificity and autonoetic awareness [125]. This finding underscores the link between autonoetic awareness and medial PFC, which can be involved as a compensatory mechanism only when autonoetic awareness is relatively preserved".

2. We replaced nerve with neuronal (please see page 9 toward the end).

**Reviewer 02682003**

3. We now clearly stated the aim of the review. Please see page 3: "In the context of the broader issue under consideration in this special topic (with focus on functional Magnetic Resonance Imaging, fMRI), the present review aims at discussing emerging research that highlights the usefulness of fMRI in the examination of AM in patients with damage to the core memory structures in the medial temporal lobe (MTL). The emphasis of this review is, therefore, on fMRI investigations of AM impairments due to neurological conditions affecting the MTL. The decision to focus on the MTL is driven by evidence that MTL plays a pivotal role in normal AM functioning and its damage typically leads to amnesia for past events [6-9] (but see also [10]) and that fMRI examinations of AM in neurological patients, which to date are in a limited number, have been more often reported in the case of patients with damage to the MTL".
Please see also page 7 for clarification on the inclusion criteria: "The purpose of the review is not to provide an exhaustive literature review of memory impairment due to brain-damage and its assessment with neuroimaging in general (for more general reviews on human memory disorders and the application of neuroimaging, we refer the readers to [65, 67, 68]). Rather the aim is to present and discuss examples of studies that have used fMRI in particular (as the most advanced neuroimaging method and targeted by the scope of the present special topic) to investigate AM impairment in patients with damage to the MTL regions, because of their critical importance for retrieval of specific autobiographical events as highlighted by functional neuroimaging research in normal subjects and lesion research (although the latter continues still to debate the long-life involvement of the hippocampus). Therefore, below, we will discuss studies that use fMRI protocols to investigate AM in patients with different neurological conditions

affecting the MTL and hence, shed light on the functionality of damaged MTL and the potential reorganisation of the AM network. We selected the studies based on that they examine AM through fMRI in pathologies with overt damage to the MTL".

4. The presentation of the fMRI studies of normal AM is now part of the introduction. Please see page 4.
We have this section because we believe that "fMRI investigations of AM in normal conditions have been very informative in establishing what is called the AM brain network, which can be used as a framework for investigation and better understanding of neural correlates of AM deficits" (please see page 6).

5. We added a Table summarizing the presented studies. Please see Table 1.

6. We considered also other pathologies affecting the medial temporal lobe, in which AM was investigated through fMRI. Please see page 8: "**Hypoxia (in adulthood)** Deprivation of oxygen supply (hypoxia) in adulthood leads also to damage to the MTL, specifically hippocampus, and severe deficit in memory of past events [74-76]. By comparison to patients with developmental amnesia, patients with hypoxic MTL damage in adulthood showed much severe pattern of memory impairment. In an fMRI examination, Maguire et al. (2005) [77] investigated memory in a patient, VC (initially reported by Cipolotti et al., 2001 [75]), who had MTL damage due to hypoxia in late adulthood. Given that VC did not have reliable memory of personal past events to be investigated in a functional neuroimaging procedure [78, 79], only his memory for personal facts and general knowledge were examined. In the context of broadly comparable to age-matched controls memory network, VC exhibited increased activity in lateral temporal regions compared to controls, and did not show any activity in the residual hippocampi, while hippocampal activations were revealed in controls as well as in developmental amnesic patient Jon for personal facts. Those findings suggest that in the case of hypoxic MTL damage in adulthood, deficit of AM are much severe and could be due to the absence of residual functionality in lesioned hippocampi. Overall, combined together findings from developmental and adult-acquired amnesia due to hypoxia point to the importance of age at which damage occurs, which is of great importance for reorganisation and compensatory brain mechanisms and this issue clearly needs further investigation by systematic fMRI examination of patients with damage occurring at different period of life".
Please see also pages 11 and 12: "**Encephalitis** Encephalitis is a neurological condition characterised by an acute inflammation of the brain, generally caused by a virus or autoimmunity (e.g., herpes encephalitis, limbic encephalitis). There is usually an extensive damage to the temporal lobes, including the medial temporal regions [114-116] and extending to the PFC [117, 118] although not necessary [119], and a severe memory impairment [114]. More specifically, neuropsychological research provides evidence of retrograde amnesia, particularly for autobiographical events [116, 120-123]. Despite evidence that encephalitis severely affects retrograde memory, especially AM and may lead to interesting dissociations in relation to the side of damage [120], fMRI investigations of

AM in encephalitic patients are very rare [124]. In a single-case fMRI study, Berry et al. (2009) [124] examined the neural correlates underlying rehearsed personal episodes in a woman, Mrs B, diagnosed with limbic encephalitis five years before the neuroimaging investigation and presenting impaired memory for autobiographical events. The patient used a wearable camera, SenseCam (Microsoft Research, Cambridge) to recode images during personal events, and then reviewed the images approximately every two days during three weeks. During scanning, Mrs B viewed rehearsed SenseCam images, together with never rehearsed and new images as well as events recorded in written diary and also rehearsed every two days during three weeks. At the behavioural level, the patients showed better performance for rehearsed SenseCam images, which at the neural level was associated with increased activity in the left ventro-lateral PFC, lateral temporal, parietal and occipital regions in the absence of MTL activations. This study suggests a potentially effective way of alleviating AM deficit with a rehearsal-based training using visual material and supported by frontal and posterior activations, which very likely reflect more general recognition of the event rather than detailed specific recollection, especially given that during scanning events were not remembered in details, but just recognised (as known or familiar). Further investigation involving detailed recollection of personal events would help better understand the effects of training procedures on AM brain network".
For completeness, we also mentioned that fMRI could be useful in other pathologies associated with impaired AM (please see pages 13 and 14).

7. We linked egocentric and allocentric representations to recollection of context in AM and underlying neural correlates. Please see page 6: "For instance, precuneus because of its role in egocentric (view-dependant, relative to the observer) representation of a place, has been thought critical for autonoetic awareness in remembering events from first-person perspective [63]. This is by comparison to MTL, which is involved in allocentric (view-independent) representations [64], but only those that are rich instead of schematic [7]" and Page 11: "It could be also speculated that precuneus involvement could reflect retrieval processes that are based on a more egocentric representations and greater reliance on a self-referential perspective during recollection".

**Editor**

8. References and formatting were corrected.

Thank you for your consideration and we look forward to hearing your decision regarding our manuscript.

Sincerely yours,

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