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1 **TITLE:** In search of a naturalistic neuroimaging approach: Exploration of general feasibility  
2 through the case of VR-fMRI and application in the domain of episodic memory

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10 **ABSTRACT**

11 LENORMAND D. and P. Piolino. In search of a naturalistic neuroimaging approach:  
12 Exploration of general feasibility through the case of VR-fMRI and application in the domain  
13 of episodic memory. NEUROSCI BIOBEHAV REV XX(X) XXX-XXX, 2021. Virtual Reality  
14 (VR) is an increasingly widespread tool for research as it allows the creation of experiments  
15 taking place in multimodal and daily-life-like environments, while keeping a strong  
16 experimental control. Adding neuroimaging to VR leads to a better understanding of the  
17 underlying brain networks or regions activated during a naturalistic task, whether for research  
18 purposes or rehabilitation. The present paper focuses on the specific use of concurrent VR and  
19 fMRI and its technical challenges and feasibility, with a brief examination of the general  
20 existing solutions. Following the PRISMA guidelines, the review investigates the particular  
21 case of how VR-fMRI has explored episodic memory so far, with a comparison of object- and  
22 place-based episodic memory. This review confirms the involvement of cerebral regions well-  
23 known to be implicated in episodic memory, but also unravels other regions devoted to narrative  
24 and body self-referential processes, promoting new avenues of research in the domain of

1 naturalistic episodic memory. Future studies should develop more immersive and interactive  
2 virtual neuroimaging features to increase ecological and embodied neurocognition aspects.

### 3 **KEYWORDS**

4 Virtual reality, fMRI, naturalistic material, ecological approach, virtual environments,  
5 episodic memory, spatial memory, PRISMA

### 6 **LIST OF ABBREVIATIONS**

- 7 BOLD: blood-oxygen-level dependent  
8 DLPFC: dorsolateral prefrontal cortex  
9 EC: entorhinal cortex  
10 EEG: electroencephalography  
11 EM: episodic memory  
12 EPI: echo planar imaging  
13 fMRI: functional magnetic resonance imaging  
14 fNIRS: functional near infrared spectroscopy  
15 GLM: general linear model  
16 HD: head direction  
17 HMD: head-mounted display  
18 HPC: hippocampus  
19 MEG: magnetoencephalography  
20 MTL: medial temporal lobe  
21 PFC: prefrontal cortex  
22 PHG: parahippocampal gyrus  
23 pmEC: posteromedial entorhinal cortex  
24 PTSD: post-traumatic stress disorder  
25 rIPFC: right lateral PFC

- 1 RSC: retrosplenial cortex
- 2 VE: virtual environments
- 3 VR: virtual reality
- 4 VRISE: virtual reality induced symptoms and effects

1 **MAIN TEXT**

2

3 **INTRODUCTION**

4 As real-life experiences involve complex and not yet fully understood brain networks, more  
5 naturalistic experiments have increasingly been needed in the wake of Neisser’s ecological  
6 approach advocating “a commitment to the study of variables that are ecologically important”  
7 (Neisser, 1976). As opposed to traditional tasks using pictures or lists of words, films were first  
8 introduced as a more naturalistic material, leading to some new insights into brain functions,  
9 such as the dependence upon a long narrative structure for the engagement of higher cortical  
10 regions, multisensory integration, the concepts of temporal windows, social and affective  
11 processing, etc. (Sonkusare et al., 2019). More recently, 360° videos were proposed as a tool to  
12 improve immersion, an egocentric view and realism (Serino and Repetto, 2018); wearable  
13 cameras such as SenseCam offered the opportunity to implement recalls of real-life experiences  
14 (see for instance Milton et al. (2011)). In this context, Virtual Reality (VR) has thus emerged  
15 as a tool for cognitive neuroscience research and neuropsychological assessment (Bohil et al.,  
16 2011; Parsons et al., 2017; Plancher and Piolino, 2017; Shamay-Tsoory and Mendelsohn, 2019;  
17 Valladares-Rodríguez et al., 2016).

18

19 **a. DESIGNING VR PARADIGMS**

20 VR is a technology that allows human beings to immerse themselves in and interact with  
21 “near-realistic” computer-generated three-dimensional environments in real time using  
22 integrated computer components to deliver a multisensory experience (Fuchs, 2017). VR  
23 systems can be classified on two orthogonal axes, immersion and interaction (Fuchs et al., 2011;  
24 La Corte et al., 2019). Immersion can be full or partial: a full immersion entails challenging and  
25 often complex devices, for instance head-mounted displays (HMD) with head-movement

1 tracking, allowing sensory-motor contingency, while a lower immersion uses only a screen, for  
2 example, to display the VE. Interaction makes the participant either more active, e.g., with  
3 tracking sensors and gloves, or less active, with only a remote control or buttons. The sense of  
4 presence in the VE results in the combination of both immersion and interaction: “*presence*  
5 refers to the phenomenon of behaving and feeling as if we are in the virtual world created by  
6 computer displays” (Sanchez-Vives and Slater, 2005). Embodiment, which comprises the sense  
7 of self-location, the sense of agency and body ownership, emerges “when [a body]’s properties  
8 are processed as if they were the properties of one’s own biological body” (Kilteni et al., 2012).  
9 To make the VE as realistic as possible, one of the most important parameters to take into  
10 account is the sense of presence. This factor is not often considered in traditional laboratory  
11 settings, while in real-life scenarios, where the sense of presence is assumed to be high, there  
12 is a clear lack of experimental control, limiting the feasibility of such paradigms. Besides  
13 lacking experimental control and entailing more risks, real-life scenarios might lead to different  
14 experiences for each participant, making comparison difficult. The grounds for the use of VR  
15 in research lie at the crossroads of these concepts.

16 Compared to classical laboratory settings (see Table 1 for a comparison of some validity  
17 criteria and general characteristics), VR allows the experimenter to design precise, diverse,  
18 ecological and realistic experiments, while keeping more experimental control than in  
19 traditional settings (Parsons, 2015). The main advantage of VR experimental paradigms is their  
20 *ecological validity* which lies on the *verisimilitude* of stimuli and activities with real-life and  
21 *veridicality* in terms of correspondence with functional outcome and behavioural observation.  
22 The potential tests and tasks are thus multiplied. Situations that were previously impossible in  
23 the lab become commonplace: Virtual Environments (VE) can be a city with different streets  
24 (Plancher et al., 2010), a jungle (Lorenzetti et al., 2018) or a park (Felnhofer et al., 2015), but

1 also indoor environments such as a museum, a supermarket or a flat (Boller et al., 2021; Marín-  
2 Morales et al., 2019).

3 At first sight, VR immersion and interaction seem useful to study cognitive functions that  
4 specifically occur in a determined, naturalistic environment, such as selective attention,  
5 working memory, spatial memory, episodic memory, decision-making, and social interactions  
6 (Sonkusare et al., 2019). To use VR to enlarge the body of knowledge concerning a cognitive  
7 function, its specific feasibility and ecological validity should first be assessed. This issue has  
8 been reviewed in many cognitive functions (Valladares-Rodríguez et al., 2016) including  
9 episodic memory (for reviews, see for instance Plancher and Piolino (2017), Smith (2019) or  
10 Tuena et al. (2019)). Besides, thanks to its ecological validity, VR is also increasingly used in  
11 psychotherapy (Kellmeyer, 2018; Morina et al., 2015; Riva, 2005), and in neuropsychological  
12 assessment and training (Neguț et al., 2016; Rizzo et al., 2004), especially in neurodegenerative  
13 disorders such as mild cognitive impairments (Weniger et al., 2011), Alzheimer's (Serino et al.,  
14 2017) and Parkinson's diseases (Shine et al., 2013a). Importantly, VE trigger the same  
15 physiological and psychological reactions as their real-life counterparts (Regenbrecht et al.,  
16 1998). Studies that recreated VE close to real-life conditions found that the same self-  
17 experience was generated in individuals. For instance, Armougum et al. (2019), in a study  
18 conducted in a Paris underground station and its VR reproduction, showed that the cognitive  
19 load impact on behavioural and physiological measures was the same in both situations.  
20 Freeman et al. (2008), in a VR environment that reproduced a London subway ride, reached the  
21 same conclusion concerning paranoid reactions. Likewise, there appears to be a good  
22 correspondence between the spatial knowledge of an environment acquired in the real world  
23 and a model of that environment in VR, as shown by Arthur et al. (1997), Regian and Yadrick  
24 (1994) and Witmer et al. (1996). More recently, Hejtmanek et al. (2020) confirmed the transfer  
25 effect in spatial memory from immersive VR to reality. Virtual navigation learning translates

1 well to its real-world counterpart. Clemenson et al. (2020) found the same results but  
2 highlighted that VR-learning leads to a less flexible cognitive map. Lastly, the efficiency of VR  
3 technology is also significantly close to, or even better than, traditional cognitive behavioural  
4 therapy and neuropsychological training, especially regarding transfer to real-life and  
5 prediction of everyday behaviours (Morina et al., 2015; Neğu et al., 2016).

6 By adding neuroimaging, VR enables the examination of cerebral networks during a given  
7 task similar to a real-life situation (Wiederhold and Wiederhold, 2008). Compared with  
8 experimental paradigms using for instance digital cameras (e.g., SenseCam) to capture  
9 autobiographical-like memories (Milton et al., 2011; Rissman et al., 2016) or learning a route  
10 in real life before testing (Schinazi and Epstein, 2010), the implementation of VR is less risky  
11 and less complex. The participants remain in a controlled environment, where interfering  
12 stimuli can be accounted for and dealt with. The task can also be more easily adapted to the  
13 cognitive function of interest. Besides, VR allows the exploration of brain activations during  
14 the task itself: recording fMRI activation during a real-life event is not an option in the  
15 foreseeable future. Adding neuroimaging to VR paradigms also contributes to confirming the  
16 ecological validity of VR, i.e., its capability to simulate reality and create experimental  
17 conditions that are similar to a real-world setting, while sometimes even adding a therapeutic  
18 or diagnostic value. Even more compellingly, VR adds an ecological dimension to traditional  
19 fMRI paradigms, which focus more on static images, films without interaction or lists of  
20 pictures or images, whereas VR appears to be able to activate similar brain regions as in real-  
21 life situations, for instance for emotions, fears or perception (Peñate et al., 2019; Sonkusare et  
22 al., 2019). As it is quite difficult to assess brain activation for actual real-life situations, this  
23 comparison is still limited.



1       The present paper focuses on the methodological feasibility of the specific acquisition of  
2 fMRI data with concomitant VR and how to design a VE for fMRI that will be as appealing as  
3 possible.

4

#### 5       **b. NEUROIMAGING AND VR: case study of fMRI**

6       To further explore the neural bases of behavioural VR results, electroencephalography  
7 (EEG) is a prevalent and widespread tool. In recent years, the feasibility and signal quality of  
8 the concomitant use of VR and EEG (on June 8<sup>th</sup>, 2021, 245 articles were found on PubMed  
9 using the combination of the keywords “virtual reality” and “EEG”) have been confirmed (see  
10 for instance Hertweck et al. (2019) or Slobounov et al. (2015)). The combination of these  
11 techniques was used to investigate for instance cognitive workload (Tremmel et al., 2019),  
12 language processing (Tromp et al., 2018), attention (Magosso et al., 2019) and stress (Fadeev  
13 et al., 2020), while some studies focused on the therapeutic aspects (Steinisch et al., 2013;  
14 Tarrant et al., 2018; Vourvopoulos et al., 2019). Magnetoencephalography (MEG) and  
15 functional near infrared spectroscopy (fNIRS) are also increasingly used (on June 8<sup>th</sup>, 2021, 11  
16 articles were found on PubMed using the combination of the keywords “virtual reality” and  
17 “MEG”; 38 articles were found on PubMed using the combination of the keywords “virtual  
18 reality” and “fNIRS”). MEG is still relatively rarely used concurrently with VR, and primarily  
19 for somatosensation (Bhattacharjee et al., 2020), visual action feedback (Limanowski et al.,  
20 2020) and spatial navigation (Cornwell et al., 2010; Pu et al., 2017, 2018). New, more portable  
21 MEG devices are being developed that should help the combination of the two techniques  
22 become more commonplace (Roberts et al., 2019). fNIRS is already used to study optic flow  
23 and postural control (Basso Moro et al., 2014; Herold et al., 2017; Hinderaker et al., 2020;  
24 Hoppes et al., 2018) and driving-related issues (Scheunemann et al., 2018; Stojan and Voelcker-  
25 Rehage, 2020; Xu et al., 2017), as well as cognitive workload (Putze et al., 2019) or prospective

1 memory (Dong et al., 2019). The combination of VR and fNIRS is also implemented for  
2 therapeutic goals (Hudak et al., 2017; Landowska et al., 2018; Maidan et al., 2018).

3 Compared to these mostly portable and user- and participant-friendly techniques, the  
4 implementation of functional magnetic resonance imaging (fMRI) presents some challenges,  
5 especially in the context of VR paradigms. fMRI is used to acquire brain images in VR  
6 experiments at different times: “(1) having participants actively engage in VR experiences in  
7 the scanner while functional neuroimaging data are acquired, (2) scanning participants as they  
8 are prompted to retrieve information previously acquired in a VE, and (3) identifying structural  
9 or functional correlates of behavioural metrics obtained through the use of VR” (Reggente et  
10 al., 2018). Hence, fMRI is often added to VR paradigms to confirm any beneficial therapeutic  
11 effects, and activations during cognitive functions, by contrasting the neural networks before  
12 and after the task or the procedure and comparing them to those obtained with more traditional  
13 methods.

14 In this integrative review, we focused on the challenges faced when implementing  
15 concomitant VR-fMRI where the participants actively engage in VR experiences in the scanner  
16 while functional neuroimaging data are acquired. This type of VR-fMRI experimental paradigm  
17 is of particular interest, as it presents the most challenges, as both fMRI and VR have their own  
18 technical specificities.

19

## 20 **i. Technical challenges of concomitant VR-fMRI**

21 When considering the concomitant use of fMRI and VR in an experimental paradigm, the  
22 key constraints of each technology need to be addressed. Typically, the design of VR paradigms  
23 requires specific software to build the VE (for instance Unity3D or Blender), and hardware  
24 (such as the VR helmets), to implement the experiment. VE need a fast and concurrent  
25 execution: this is a constraint especially regarding the graphics card and processing power. The

1 main points to consider are thus usability, flexibility and testability (Beck et al., 2007). On the  
2 other hand, the fMRI tools have to be compatible with the VR software. There must be enough  
3 repetitions of the events to yield sufficient statistical power, and the VR signal (events and  
4 exploration of the VE) has to be carefully synchronised with the fMRI acquisition, so as to  
5 ensure correspondence between events in the VE and responses in the brain. Additionally,  
6 because of the electromagnetic fields in the scanner, only specialised VR hardware can be used,  
7 and this may limit what is possible or not in such an experimental design. Last but not least,  
8 movement is very restricted in an MRI scanner: this means that no head tracking is possible as  
9 the participant cannot move their head. Tracking systems have to take into account the  
10 limitations of both the electromagnetic fields of the scanner and the restricted movements of  
11 the participant. Steel et al. (2020) commented on the study by Huffman and Ekstrom (2019) in  
12 which the role of idiothetic cues in spatial mental representations was investigated. In this  
13 experiment, the VE was explored before the subsequent recall tasks in the MRI scanner. As a  
14 matter of fact, Steel et al. (2020) pointed out that navigation suffers from several issues when  
15 explored via concomitant VR and fMRI. Defining very precisely which process is monitored  
16 during the study is of the utmost importance: there is a clear distinction between physical tasks,  
17 for instance physical navigation, and mental or virtual ones, for instance when someone moves  
18 through a nonphysical space. As fMRI deprives the subject of their movements, a thorough  
19 understanding of the mechanisms underlying specifically strict physical navigation is not  
20 possible, even though physical and mental navigation may partially rely on shared neural  
21 networks (it is also noteworthy that fMRI still allows navigation with joysticks, buttons or  
22 gloves, that are also regularly used for non-fMRI experiments). Taube et al. (2013) further  
23 detailed the limits of such an exploration of navigation with fMRI. Whereas active movement,  
24 vestibular functions and the motor signal play a prominent role in real-life navigation,  
25 exploration while lying supine in the scanner deprives the subject, at least partially, of these

1 items. Tracking head direction (HD) also becomes an issue, as HD cells are always active, but  
2 their firing could be altered with the 90° rotation of the body. Likewise, otolith organs, a  
3 structure in the inner ear in the vestibular system, usually point to the real-world position of the  
4 subject (supine in the scanner) rather than their position in the VE (e.g., standing, walking) –  
5 though a dual representation could be possible. A careful analysis of fMRI images seems thus  
6 mandatory in such paradigms, and specific care should be taken when interpreting head  
7 direction related activations. This discrepancy between the real-world idiothetic cues and task  
8 allocentric reference frames appears to be one of the biggest difficulties in adapting VR to  
9 fMRI, particularly for navigation. As a result, some tasks seem to be more easily adaptable to  
10 the concomitant use of VR and fMRI, for instance memory or attention tasks, where  
11 interpretation of the activated brain areas is not as open to discussion, such as the subsequent  
12 memory effect (SME). Keeping in mind what is possible or not in fMRI will strengthen its use.  
13 Thus, precisely defining the task, the mental process and how it is identified in the contrasts  
14 during the analyses makes such an experimental paradigm possible.

15 Concomitant VR-fMRI has already been used with therapeutic intent for several disorders:  
16 programs were designed to treat pain in burn patients (Hoffman et al., 2004), smoking cravings  
17 (Lee et al., 2005), to evaluate driving behaviour (Calhoun et al., 2005) or study fear conditioning  
18 (Alvarez et al., 2008). Naturally, VR is also used in rehabilitation and neuroimaging proves to  
19 be particularly useful in combination with VR in these cases (Ansado et al., 2020). VR-fMRI  
20 is even used to study specific features of pathologies, such as freezing of gait in Parkinson's  
21 disease (for recent reviews, see Bluett et al. (2019) and Gilat et al. (2019)), spatial learning in  
22 bulimia nervosa (Cyr et al., 2016) and in schizophrenia (Salgado-Pineda et al., 2016), or fear  
23 learning for post-traumatic stress disorder (PTSD) (for a review see Glenn et al. (2018)). Some  
24 interesting points have already been highlighted thanks to VR, for example grid-cell-like  
25 representations in spatial cognition in human beings (Doeller et al., 2010); however, there is no

1 standard solution for the VR-fMRI combination. Besides the lack of unity in VE design, the  
2 hardware differs vastly, ranging from screens to the most state-of-the-art HMD (head-mounted  
3 display) with movement-tracking gloves (see Table 2 for some examples of VR-fMRI studies).  
4 Hence, the VEs displayed in the scanner differ in immersion but also in interaction. In the low  
5 interaction and low immersion category, only a screen or a mirror is available to the participant  
6 who lies passively in the scanner, merely watching the VE in front of them. On the contrary, it  
7 is possible to have high immersion and high interaction by equipping the subject with an HMD  
8 and a glove or a joystick provided to the subject to carry out actions in the VE while in the  
9 scanner.

10

## 11 **ii. General operational solutions**

12 Despite the technical challenges of concomitant VR-fMRI, some solutions have already  
13 been successfully implemented. The Table 2 lists some studies carried out in recent years with  
14 various technological and programming solutions. These studies were selected using the  
15 combined keywords “Virtual Reality” and “fMRI”. We excluded studies that used VR outside  
16 the scanner, such as those studies describing the use of VR for surgery and anatomy (these  
17 studies did not use concomitant VR-fMRI, rather focusing on building anatomically correct  
18 body parts for educational or training purposes). We also excluded studies that used fMRI as a  
19 means to assess the results obtained through the VR experiment, without VR being carried out  
20 in the scanner. For this part of our review, only studies with enough methodological details  
21 regarding VR (what was used for both hardware – presentation of the VE – and/or software –  
22 construction of the VE) are reported, with a focus on the last five years (2016 to 2021). The  
23 main goal of this non-systematic, integrative part of the review is to provide the reader with  
24 some hindsight on the methodological aspects of concomitant VR-fMRI and on the operational  
25 solutions that have already been implemented. As this is a growing field of interest, the reader

1 may find other relevant studies fitting this subject and is welcome to compare them to those  
2 already listed.

3 First, regarding the technological implementation in the MRI scanner, specially adapted  
4 hardware is required. MRI-compatible VR helmets have been developed that are designed to  
5 answer the specific needs of VR-fMRI, ensuring immersion in the VE. For instance, among  
6 others, Andoh et al. (2020), Limanowski et al. (2017), Siemerkus et al. (2012), Suthana et al.  
7 (2011) and Weniger et al. (2013) reported the use of the head-mounted display by Resonance  
8 Technology Inc., respectively with a 3-T Siemens Allegra scanner for Suthana et al. (2011) and  
9 a 3-T Siemens Magnetom Trio for Andoh et al. (2020), Siemerkus et al. (2012) and Weniger et  
10 al. (2013) and a 3-T Siemens Tim Trio for Limanowski et al. (2017). Duarte et al. (2014)  
11 reported the use of stereoscopic glasses by Avotec Inc. in a 3-T Siemens Magnetom Trio,  
12 Salgado-Pineda et al. (2016) fMRI-safe VR glasses developed by VisuaStim Digital,  
13 Resonance Technology Inc., used in a 1.5-T scanner (General Electric Medical Systems). In  
14 addition, MRI-compatible gloves, joystick, buttons, and keypads can also be used to keep the  
15 VE interactive. Noise cancelling earphones help reduce the noise of the scanner, while still  
16 letting through any necessary auditory stimulus, and head padding makes the experience a little  
17 more comfortable, on top of reducing head movement for the subsequent data pre-processing.  
18 Over time, the hardware available for VR-fMRI has evolved considerably. Besides joysticks  
19 and buttons, motion-capture gloves are increasingly used for instance, either custom-made or  
20 purchased commercially (see the 5DT Data Glove 5 MRI by 5DT Inc., Irvine, CA, USA; or  
21 custom-made solutions for instance Diers et al. (2015)). However, the use of HMD is still  
22 limited, as goggles and 3D glasses or mirrors and screens seem to be much more common. In  
23 their study, Forlim et al. (2019) found that, as contrasted to screen, goggle presentation involved  
24 higher connectivity when focusing on the visual and default mode network. They also found

1 stronger connectivity when considering stereoscopic vs. google monoscopic goggles. If these  
2 results are confirmed, this could provide some clues as to what is best to be used in VR-fMRI.

3 Second, regarding the acquisition, different possibilities have been implemented for the  
4 signal synchronisation. The first possibility is to define onsets, for instance when an active  
5 trigger signal is sent by the MRI before the start of each scan (Beck et al., 2010). Another option  
6 is to acquire fMRI data in blocks (see for instance Adamovich et al. (2009), Mueller et al.  
7 (2012), Salgado-Pineda et al. (2016) or Modroño et al. (2019)). Lastly, it is possible to  
8 continuously acquire data. In this case, the start of the stimulus sequence is synchronised to the  
9 start of the fMRI scan, matching brain activity and VR experiences and making an event-related  
10 analysis possible (Burgess et al., 2001; Hoffman et al., 2004; Lee et al., 2016; Limanowski and  
11 Blankenburg, 2017; Saleh et al., 2016). This technique is also used in rt-fMRI for subsequent  
12 functional analyses (Lorenzetti et al., 2018; Skouras et al., 2020). EPI (echo planar imaging)  
13 images of brain activity are usually acquired around every 3 seconds, as was the case for  
14 example in Hoffman et al. (2004), Doeller et al. (2010) or Skouras et al. (2020).

15 Finally, many options make it possible to adapt immersion and optimise the sense of  
16 presence in the VE in fMRI. Granted, to adapt immersion, a good real-time performance is  
17 required (Mueller et al., 2012) and to enhance realism, a qualitative game such as Unity 3D is  
18 an asset. The view of the VE has to be adjusted in real-time as the subject evolves through it by  
19 calculating the interactions and/or navigation between the subject and the VE, and the computer  
20 used for the VE should not lose any performance or data over time. However, this is not enough,  
21 as the subject is lying down in a scanner and their movements are thus restricted, despite the  
22 fact that the phenomenon known as Visual Field Motion helps the subject know their posture  
23 relative to the environment (Slobounov et al., 2006). The sense of presence is then optimised  
24 by generalising interactions with the VE: e.g., by moving objects (Kalpouzos et al., 2010), aim  
25 and shoot (Hoffman et al., 2004); by creating events of different natures to keep the attention

1 of the participant at an optimal level; by reducing the discrepancy between proprioception and  
2 sensory data (for a recent review of the possibilities for this point, linked with the notion of  
3 cybersickness, see for instance Caserman et al. (2021): using the latest HMD such as Oculus  
4 Rift or HTC Vive, and matching stimuli, seem to help to achieve this goal). To increase realism,  
5 embodiment can be partially achieved through a first-person point of view with an avatar (e.g.,  
6 as an arm or a full body). Some basic features can also be implemented. For instance, cortical  
7 regions seem to be more strongly recruited when the hand of the participant is represented in a  
8 complete, realistic way for feedback, rather than by an incomplete or abstract hand (Brand et  
9 al., 2020). Interestingly, some studies, mainly on Parkinson's disease and freezing of gait, added  
10 foot pedals to simulate walking while in the scanner (Ehgoetz Martens et al., 2018; Gilat et al.,  
11 2017; Matar et al., 2019; Shine et al., 2013b). The probability and intensity of VR-induced  
12 symptoms and effects appear to increase with the duration of the VR session (Sharples et al.,  
13 2008). To limit these unwelcome effects, the sessions should not exceed 55 to 70 minutes  
14 (Kourtesis et al., 2019). The intensity of VR-ISE (virtual reality induced symptoms and effects)  
15 has not been thoroughly explored in VR-fMRI paradigms yet. The application of the different  
16 technical solutions should nonetheless help reduce the disadvantages that arise in the  
17 concomitant use of VR and fMRI.

18

## 19 **SYSTEMATIC REVIEW: VR-fMRI FOR EPISODIC MEMORY**

20 To further explore VR-fMRI, we reviewed how episodic memory (EM) was explored using  
21 concomitant VR-fMRI. VR-fMRI seems particularly interesting for EM as this long-term  
22 memory focuses on the memory of events associated with their encoding context (Tulving,  
23 2002) which is quite rich, with phenomenological elements as well as spatial components.  
24 Given the current scarcity of VR-fMRI studies in the specific domain of EM, we focused on



1 EM itself but also on spatial memory, as the two are often considered to be closely related  
2 (Moscovitch et al., 2005; Robin, 2018; Tuena et al., 2020).

3

#### 4 **a. ELEMENTS OF EM**

5 The concept of EM refers to a system of long-term memory that encodes, stores and recalls  
6 information related to personally experienced events in a particular spatial and temporal context  
7 (e.g., remembering what happened last Sunday and where, the day one's first child was  
8 born). EM is crucial to ensure new learning and ground our sense of self and temporal  
9 continuity (Tulving, 2002). It is a unique neurocognitive system that underlies the conscious  
10 recall of specific events in daily life or particular autobiographical episodes through a subjective  
11 mental time travel and auto-noetic state of consciousness (consciousness involving the self)  
12 allowing them to be re-experienced virtually (Tulving, 1985). A vivid episodic memory  
13 involves both the subject ("the traveller"), his subjectivity and the most objective attempt to  
14 recollect all the details of the lived situation. This system intervenes in the learning and  
15 distinctiveness of the memory trace, it allows the individual to build a sense of continuity and  
16 identity and participates in his autonomy and well-being in daily life. The richness of the  
17 episodic memory trace is defined by the ability to associate several types of information related  
18 to an event: the target information (What), its external context (Where and When) and its  
19 internal context (How), which includes the integration of sensory-motor information (e.g.,  
20 visual, auditory, and tactile), phenomenological information (e.g., emotions, thoughts, self-  
21 reference), and idiosyncratic aspects of this event. Long-lasting EMs, also called episodic  
22 autobiographical memories, are particularly relevant for the self and can be remembered across  
23 decades (Conway, 2005; Piolino et al., 2009). EM differs from semantic memory that stores  
24 general knowledge about the world (concepts, words, facts) without contextual reference,  
25 although it relies on the latter during encoding (Tulving, 1972). Semantic memory also

1 encompasses generic components of autobiographical memory or personal semantics (Cermak  
2 and O'Connor, 1983; Kopelman et al., 1989; Martinelli et al., 2013; Renoult et al., 2016), and  
3 its retrieval is accompanied by a sense of familiarity devoid of recollection.

4 EM is very close to the concept of spatial memory (Burgess et al., 2002; Moscovitch et al.,  
5 2005; O'Keefe and Nadel, 1979; Tuena et al., 2019), when the latter concerns detailed and  
6 specific spatial information encoded during navigation that helps the person memorize the route  
7 of an unfamiliar environment, locate objects or landmarks and memorize their position. In this  
8 case, the retrieval consists in re-experiencing the environment with its perceptual details as one  
9 takes a mental walk through it, a spatial analogue of mental time travel, and recalling or  
10 recognizing its various specific attributes on formal tests. Another interesting example of the  
11 link between spatial memory and EM concerns the Method of Loci (i.e., MoL is a method of  
12 memorizing lists of items by mentally placing each item to be remembered at a point along a  
13 familiar space and an imaginary journey). As highlighted by Reggente et al. (2020), the  
14 implementation of “memory palaces” using VR is more efficient when the objects are placed  
15 in space: 28% more objects were recalled in the MoL experimental condition. Hence, what-  
16 where binding seems to be a contributing factor to the effect of the MoL, further confirming  
17 the link between what-where binding and successful EM encoding. In general, spatial  
18 information can be either egocentric (subject-to-object, route) or allocentric (object-to-object,  
19 map) information including spatial information about the location of the individual in the  
20 environment (turn right at the bakery) or about the position of objects relative to each other (are  
21 the buildings far from each other), respectively (Colombo et al., 2017). The egocentric frame  
22 of reference leads to the creation of spatial information with reference to the self (body-centered  
23 representations) which is considered as one of the major characteristics of EM. Generally, most  
24 authors agree that successful navigation requires the ability to switch and combine the two  
25 frames, the route (sequential record of spatial information) and the map (spatial relations of

1 landmarks to one another) (Burgess, 2006; Colombo et al., 2017). However, spatial memory  
2 can also result from generic (schematic) spatial information (e.g., a frequent journey from a  
3 starting point to an end point). In sum, detailed perceptual–spatial representations of  
4 experienced environments correspond to EM while schematic representations of the topography  
5 of familiar environments correspond to semantic memory (Moscovitch et al., 2005; Rosenbaum  
6 et al., 2005).

7        Figures 2 and 3 highlight the main brain regions traditionally activated for navigation, EM  
8 and autobiographical memory, showing a gradual engagement of memory and of the self, with  
9 Table 3 listing the correlations with tasks. These figures were obtained with the automatic tool  
10 linkRbrain (Mesmoudi et al., 2015), using the main tasks “navigation”, “episodic memory” and  
11 “autobiographical memory” for the three sets of data.

12        EM and spatial memory develop slowly during childhood and decline in aging, are sensitive  
13 to distortions, and are altered in many neurological and psychiatric pathologies, particularly  
14 Alzheimer’s disease, of which they are the most frequent preclinical symptoms. EM and spatial  
15 disorders significantly limit autonomy in the activities of daily life. Thus, the quality of the  
16 evaluation of episodic and spatial memory, and in particular its predictive value of functioning  
17 in daily life and large-scale environments, is one of the issues that is attracting growing interest  
18 among researchers and clinicians.

19        However, most experimental EM studies still use a relatively simplistic lab material (lists  
20 of words or images) compared to its definition and its complex expression in daily life. VR  
21 enables EM to be studied in more naturalistic conditions involving a rich and dynamic spatio-  
22 temporal continuum and active behaviour. Interestingly, it involves the sense of self, especially  
23 through presence and embodiment (for instance through first-person perspective or self-  
24 location), which is crucial for EM. The usefulness of VR to study naturalistic event memory  
25 (e.g., recall of witnessing a car accident, attending a street show, shopping in stores and markets,

1 responding to someone who asks us for directions during a walk in a virtual city...) has been  
2 assessed on feature binding processes (what-where-when) and sense of recollection (autonoetic  
3 consciousness). This VR paradigm provided an insightful way of investigating age effects on  
4 EM with children, adolescents, young adults and healthy elderly adults (Abichou et al., 2021a;  
5 Abichou et al., 2019; Abichou et al., 2021b; Jebara et al., 2014; Picard et al., 2015; Plancher et  
6 al., 2010). Some compelling EM research results have already been obtained thanks to VR  
7 (Smith, 2019; Tuena et al., 2019). For instance, VR highlighted the role of action (Jebara et al.,  
8 2014; Plancher et al., 2012) and first-person visual co-perception of one's own body (Brechet  
9 et al., 2020; Brechet et al., 2019; Tuena et al., 2017) during the encoding of dynamic visual  
10 scenes in enhancing EM. It also provided a way to analyse the effects of attention (Blondé et  
11 al., 2021), working memory (Plancher et al., 2018) and cognitive load (Armougum et al., 2020;  
12 Armougum et al., 2019).

13

## 14 **b. METHODS**

### 15 **i. Search strategy**

16 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)  
17 guidelines were followed (Moher et al., 2009). Three databases were investigated for the  
18 research, all years considered: PubMed, Web of Science and PsycInfo (last search conducted  
19 on March 16, 2021). The following combinations of keywords were used: ["episodic memory"]  
20 AND ["virtual reality"] AND [fMRI]; ["spatial memory"] AND ["virtual reality"] AND  
21 [fMRI]. These strings were adapted to fit the different databases. In PubMed the Title/Abstract  
22 was searched (no other criterion), in Web of Science the Topic (all databases, all years), and in  
23 PsycInfo the Abstract (no other criterion).

24

### 25 **ii. Selection criteria**

1 For the selection step, the abstracts were screened. The main criterion considered to select  
2 the relevant studies was the concomitant use of VR and fMRI to study either episodic or spatial  
3 memory on humans. Studies that did not meet this criterion were excluded. We excluded  
4 articles for which the full text was not available or could not be found by any means, as well as  
5 reviews, editorial material, dissertation abstracts, meeting and conference abstracts. One study  
6 was excluded as it was not published in English, one study used EEG instead of fMRI and  
7 another one MEG.

8

### 9 **iii. Eligibility criteria**

10 For eligibility, we focused on the following criteria: studies should have a strict  
11 concomitance between VR and fMRI (for instance, picture viewing during recollection is not  
12 enough; paired-associate learning of words does not fit this criterion either), and assess memory  
13 performance, and they should not use fMRI only for resting-state. Studies about strict  
14 navigation skills were also excluded; for instance, we excluded the study by Graham et al.  
15 (2003) that primarily focused on spatial navigation. The studies that met these criteria are  
16 reported, even when some information is missing (about the VR hardware for instance).

17

### 18 **c. RESULTS**

19 The initial search for “episodic memory” resulted in 7 articles for PubMed, 23 articles for  
20 Web of Science and 2 articles for PsycInfo; for “spatial memory” in 20 articles for PubMed, 40  
21 articles for Web of Science and 19 articles for PsycInfo. Duplicates were removed (both  
22 automatically and by manual verification) and a total of 65 records were considered for  
23 screening. 3 articles that did not appear in the PRISMA search (found while researching  
24 naturalistic memory with VR-fMRI) were added, bringing the total to 68. After screening, 41  
25 articles were assessed for eligibility. 25 studies were finally included in the present review (see

1 Figure 1 for an overview of the process). All eligible papers are summarised in Table 4 with  
2 the following main clusters of interest: the target population, the virtual apparatus (software  
3 and hardware), the experimental conditions and controls, the memory tasks and assessments,  
4 the primary outcomes.

5

#### 6 **i. Population included**

7 Most experiments included mainly young adults or students. Age means and ranges varied  
8 between experiments, and sometimes age information (Burgess et al., 2001; Demanuele et al.,  
9 2015; Nau et al., 2020) or gender distribution information (Astur et al., 2005) was missing.  
10 Participants were mostly healthy, though we counted one study with a group of bulimia nervosa  
11 patients (Cyr et al., 2016), one study with ketamine users (Morgan et al., 2014), two studies  
12 with schizophrenia patients (Salgado-Pineda et al., 2016; Siemerkus et al., 2012), one study  
13 with athletes with mild traumatic brain injuries (Slobounov et al., 2010), one study with cocaine  
14 dependent patients (Tau et al., 2014), and one study with patients with childhood abuse  
15 (Weniger et al., 2013). However, all these studies included one matching healthy control group.  
16 Considering the results obtained with the control group makes the comparison possible with  
17 other studies with healthy participants only. However, in our search we found one study with  
18 amnesic mild cognitive impairment patients (aMCI) (Migo et al., 2016). This group and the  
19 healthy controls were much older than the participants of the other studies. We thus cautiously  
20 compared the results of this study with the others.

21 Table 4 contains a summary of the population included, study by study.

22

#### 23 **ii. Virtual apparatus**

24 As stated before, the virtual apparatus for concomitant VR-fMRI experiments has to be  
25 adapted to the particular experimental conditions of the electromagnetic scanner. Specific

1 hardware exists and was used for the studies in the present review (see figure 4.1). To immerse  
2 participants in the VE, they mostly used MRI-compatible goggles or HMD (Cyr et al., 2016;  
3 Duarte et al., 2014; Kalpouzos et al., 2010; Salgado-Pineda et al., 2016; Siemerikus et al., 2012;  
4 Suthana et al., 2011; Tau et al., 2014; Weniger et al., 2013; Weniger et al., 2010). We could not  
5 find any hardware-related information for two studies (Bellmund et al., 2016; Nau et al., 2020),  
6 but the rest used either a projector and screen (Antonova et al., 2011; Astur et al., 2005; Burgess  
7 et al., 2001; Gomez et al., 2014; Javadi et al., 2019; Migo et al., 2016; Parslow et al., 2004;  
8 Slobounov et al., 2010; Sutton et al., 2010; Wolbers et al., 2004) or a screen and mirrors on  
9 goggles (Lee et al., 2016).

10       Regarding the interaction in the VE, most studies (13) used custom-made joysticks, while  
11 some others (7) used MRI-compatible buttons. More occasionally, keypads (Burgess et al.,  
12 2001; Iglói et al., 2015; Morgan et al., 2014; Sutton et al., 2010), keys (Doeller et al., 2010;  
13 Hartley et al., 2003; Suthana et al., 2011), fibre optic response pads (Demanuele et al., 2015)  
14 and tracker balls were used (Migo et al., 2016). All studies reported the use of a device of some  
15 kind in the VE inside the scanner; it was used either for interaction in the VE or to answer test  
16 questions.

17       Interaction varied across the studies. All used navigation through the VE (see figure 4.3 for  
18 examples of existing VE): in a town (Burgess et al., 2001; Hartley et al., 2003; Salgado-Pineda  
19 et al., 2016; Suthana et al., 2011), a park (Demanuele et al., 2015; Doeller et al., 2010; Migo et  
20 al., 2016; Morgan et al., 2014), a maze (Astur et al., 2005; Cyr et al., 2016; Iglói et al., 2015;  
21 Javadi et al., 2019; Siemerikus et al., 2012; Tau et al., 2014; Weniger et al., 2013; Weniger et  
22 al., 2010), a room (Antonova et al., 2011; Duarte et al., 2014; Parslow et al., 2004; Sutton et  
23 al., 2010), a corridor (Slobounov et al., 2010), and from one building to the next (Lee et al.,  
24 2016). Two studies (Gomez et al., 2014; Wolbers et al., 2004) reported no interaction in the  
25 VE, which was explored through videos with fixed points of view. This passive exploration of

1 the VE is in contrast with the active navigation of the other studies. Some studies reported the  
2 additional pressing of a button when recognising an object (Burgess et al., 2001; Lee et al.,  
3 2016; Suthana et al., 2011; Wolbers et al., 2004) or to point towards a pre-learned direction  
4 (Gomez et al., 2014; Wolbers et al., 2004). Some studies involved a higher level of interaction  
5 and activity of the subject, e.g., by replacing objects on top of navigation as a specific action  
6 (Doeller et al., 2010; Duarte et al., 2014; Morgan et al., 2014; Nau et al., 2020; Steemers et al.,  
7 2016; Sutton et al., 2010).

8 This interaction was realised without embodying an avatar (full body or partial body) for  
9 all the studies except Steemers et al. (2016). All the studies reported the use of a ground-level,  
10 first-person perspective except Gomez et al. (2014) and Suthana et al. (2011). The former  
11 specifically explored the influence of the point of view and the latter included a map view  
12 during encoding.

13

### 14 **iii. Types of memory assessment**

15 VR assessment of memory depended on the type of memory assessed and on the type of  
16 experimental task (see figure 4.2 for examples of existing tasks). These constraints led to  
17 assessing memory through, for instance, accuracy of the reported position (Antonova et al.,  
18 2011; Bellmund et al., 2016; Doeller et al., 2010; Duarte et al., 2014; Javadi et al., 2019; Morgan  
19 et al., 2014; Nau et al., 2020; Parslow et al., 2004; Steemers et al., 2016; Sutton et al., 2010;  
20 Wolbers et al., 2004). Optimality of the reported trajectory, with either speed or accuracy, was  
21 also used as an indicator of memory performance (Hartley et al., 2003; Iglói et al., 2015; Javadi  
22 et al., 2019; Salgado-Pineda et al., 2016; Slobounov et al., 2010), sometimes by using the angle  
23 of the reported direction (Bellmund et al., 2016; Gomez et al., 2014; Lee et al., 2016). Other  
24 assessments were the number of memory errors (Astur et al., 2005; Burgess et al., 2001;  
25 Demanuele et al., 2015; Migo et al., 2016; Siemerikus et al., 2012; Weniger et al., 2013; Weniger



1 et al., 2010), the improvement over runs (Cyr et al., 2016; Suthana et al., 2011), the reaction  
2 time (Lee et al., 2016; Migo et al., 2016), and the time spent on the task (Migo et al., 2016;  
3 Siemerikus et al., 2012). Some studies also used report protocols with interviews or  
4 questionnaires outside the scanner (Burgess et al., 2001; Iglói et al., 2015; Lee et al., 2016;  
5 Siemerikus et al., 2012; Weniger et al., 2013; Weniger et al., 2010).

6 The investigation of EM requires an encoding phase followed by a retrieval phase.  
7 Generally preceded by a familiarisation or training phase, the encoding was largely intentional  
8 and different aspects of EM are tested and measured, though some studies also used an  
9 incidental encoding which is closer to every-day encoding situations (see for instance Bellmund  
10 et al. (2016), Doeller et al. (2010), Hartley et al. (2003), Nau et al. (2020) or Salgado-Pineda et  
11 al. (2016)). What-where binding was largely predominant in studies focusing on EM, with only  
12 Burgess et al. (2001) presenting a what-where-who binding with perception elements. The  
13 spatial component was usually measured by the proximity of the replace or direction or  
14 trajectory response to the correct object location; Salgado-Pineda et al. (2016) used a specific  
15 measure of spatial navigation and memory performance including the time spent on the task,  
16 the final distance to the goal, and the total distance travelled.

17

#### 18 **iv. Investigation of the mechanisms of memory with VR**

19 Investigating memory with VR while in an fMRI scanner involves challenges in the task  
20 design and implementation. Such experiments nevertheless provide significant results and  
21 interesting conclusions. In the present review, we thus focus on EM and its spatial component  
22 (see figure 2.2).

23 **When investigating EM**, studies focused on retrieving information associated with specific  
24 items such as everyday objects or buildings. However, the information retrieved is almost  
25 always the spatial localisation. This makes the comparison between sheer spatial memory, as

1 previously described, and spatial memory as associated with EM, possible. In this review, we  
2 thus describe EM through its spatial component with objects, and with buildings (well-defined  
3 landmarks). One study by Burgess et al. (2001) explored EM exhaustively, with both context-  
4 dependent and -independent elements: spatial context (place questions), control for nonspatial  
5 context-dependent memory (person questions), context independent memory (object  
6 questions), with a perceptual part controlling for memory. This study tested the memory for the  
7 spatial context of controlled, lifelike events. Participants had to retrieve objects from avatars  
8 around the VE, and then answered questions about the pre-learned objects (where they had been  
9 encoded, whom the participants had received them from, recognition of old versus new objects,  
10 pure perception). With this paired forced choice recognition paradigm, different networks were  
11 activated for each type of memory. The memory for spatial context, as seen by contrasting place  
12 with perceptual (width, nonmemory) conditions, activated the parietal and prefrontal areas, and  
13 the medial temporal areas. Four broad anatomical regions played a role: a continuous activation  
14 from the precuneus to the bilateral PHG (parahippocampal gyri) via the parieto-occipital sulcus  
15 and RSC, with the left HPC (hippocampus); the bilateral posterior parietal cortex; the anterior  
16 and mid cingulate; and the bilateral dorsolateral, ventrolateral and anterior PFC (prefrontal  
17 cortex). The person versus perception contrast activated a similar network, without the PHG,  
18 HPC and ventrolateral PFC and anterior cingulate, and with less activation in the RSC.  
19 Contrasting with object instead of perception led to the same results (with place, left HPC  
20 activation fell below the threshold and with person, left ventrolateral PFC and anterior cingulate  
21 were above the threshold, right dorsolateral PFC below). The recognition of new versus old  
22 objects, as contrasted with the non-memory condition, led to much weaker activation in the  
23 precuneus and parieto-occipital sulcus and additional activation in the right fusiform gyrus.  
24 Other regions were activated in object versus person (right inferior temporal gyrus) and in  
25 object versus place (right intra parietal sulcus). Interestingly, the memory for spatial context as

1 opposed to the memory for person, seen in the place versus person contrast, involved the  
2 bilateral posterior PHG and RSC, the lateral posterior parietal area and the parieto-occipital  
3 sulcus.

4 **Eight studies explored EM through the retrieval of the spatial component associated**  
5 **with the memory of an object:** Doeller et al. (2010), Duarte et al. (2014), Gomez et al. (2014),  
6 Javadi et al. (2019), Lee et al. (2016), Morgan et al. (2014), Nau et al. (2020), and Sutton et al.  
7 (2010). Subjects had to encode objects with their respective spatial location that was retrieved  
8 later. For instance in the study by Doeller et al. (2010), on which were based Morgan et al.  
9 (2014) and Nau et al. (2020), the participants had to collect objects by running over them in the  
10 VE. Then, pictures of the objects were presented, and the participants had to move to where  
11 they thought the object had been in the VE. The other studies involved the same type of memory  
12 assessment, with chairs for Duarte et al. (2014) or other various objects in the other studies.  
13 The HPC was also involved in this type of task. In the study by Duarte et al. (2014), the posterior  
14 third of the HPC was activated for 3D visual spatial encoding and slightly less for retrieval,  
15 with an anterior-posterior asymmetrical activation (antagonistic BOLD coupling). Gomez et al.  
16 (2014) reported a differentiated activation of the HPC: the right HPC activated for self-location  
17 chances in self-related conditions, and, as a whole, the HPC supported spatial processing  
18 (egocentric-updating and allocentric, landmark-based, processing). Lee et al. (2016) also  
19 reported a differentiated activation: the activity shifted from left to right HPC as additional  
20 spatial components such as place memory or spatial navigation were required for the task, the  
21 BOLD signals correlating with efficiency of retrieval for object-place memory and spatial  
22 memory. Other studies involved both the HPC and the PHG: Javadi et al. (2019), Morgan et al.  
23 (2014), Nau et al. (2020), Sutton et al. (2010). Sutton et al. (2010) also reported the activation  
24 of MTL (medial temporal lobe) during encoding and retrieval. The entorhinal cortex (EC) also  
25 played a role in two studies. In the study by Doeller et al. (2010), orientationally aligned grid-

1 cell firing was reported in the EC, with a significant activation in the right EC for fast runs. The  
2 activation in this region correlated with memory performance. For Nau et al. (2020), the  
3 accuracy was also reflected in the EC, more precisely with the posteromedial entorhinal cortex  
4 (pmEC), but also in the RSC. The models using voxels from pmEC predicted virtual head  
5 direction well when participants had a high memory error: the authors concluded that the pmEC  
6 reflected how well the participants managed to report the location of objects in the VE. Other  
7 studies reported the activation of the RSC: Gomez et al. (2014) (in the self-related condition for  
8 orientation changes) and Javadi et al. (2019). Only Javadi et al. (2019) reported the specific  
9 activation of frontal areas: medial frontal gyrus; superior and lateral PFC for detours, and right  
10 lateral PFC, rIPFC, for false shortcuts. Here, the PFC seems to have a role in resolving path  
11 conflicts for the superior PFC and predicting errors for rIPFC. This paradigm involved a  
12 changing VE where the maze could change with deleted paths (creating detours) or created  
13 paths (shortcuts or false shortcuts), thus introducing the notion of choice-making. Javadi et al.  
14 (2019) reported an exclusive correlation of activity in the caudate nucleus bilaterally with the  
15 change in path distance for all events, that is, detours. The caudate was also involved in Morgan  
16 et al. (2014) to update spatial memory. The occipito-parieto-temporal network was involved in  
17 the studies by Gomez et al. (2014) (spatial encoding), Lee et al. (2016) (shift from early visual  
18 information processing areas, such as the middle occipital gyrus, to higher information  
19 processing areas, such as the superior and middle temporal gyri, as the task changed from object  
20 recognition to object-cued place recognition and navigation) and Nau et al. (2020) (visual  
21 regions).

22 **Six studies used buildings as landmarks for item-cued spatial memory in EM:**  
23 Bellmund et al. (2016), Hartley et al. (2003), Salgado-Pineda et al. (2016), Steemers et al.  
24 (2016), Suthana et al. (2011) and Wolbers et al. (2004). These studies mostly report the  
25 activation of the HPC. Hartley et al. (2003) found that the activity in the right HPC was

1 associated with accurate wayfinding between buildings. By opposing three main experimental  
2 conditions, namely finding one's way in a VE based on pre-learned spatial information,  
3 following a pre-learned route in the VE and following a designated trail, they highlighted two  
4 different mechanisms for navigation. The first one, response learning, as seen before, involved  
5 the head of the caudate nucleus for action-based representation (route following), while the  
6 second one, place learning, relied on the HPC to form flexible cognitive maps (wayfinding). In  
7 the study by Bellmund et al. (2016), where participants when in the scanner imagined directions  
8 in a virtual city between building locations pre-learnt before entering the scan (incidental spatial  
9 training and intentional learning of building names), the PHG was also implicated in  
10 representing the directional aspect of imagined views with a resolution of 30°. Likewise, both  
11 HPC and PHG were activated in Salgado-Pineda et al. (2016). More precisely, Steemers et al.  
12 (2016) showed that, in response to gradual, linear changes in the background of the VE, the  
13 neural activity pattern in the HPC followed nonlinear response patterns matching the  
14 behavioural response pattern. In other words, the divergence of orthogonal or competing  
15 representations in the HPC translates into mnemonic decisions (putative attractor dynamics). In  
16 the study by Suthana et al. (2011), where subjects passively viewed videos of navigation and  
17 then viewed old or new videos which they had to discriminate during recognition, multiple  
18 regions were activated, for instance the MTL, the dentate gyrus (for encoding) and the right  
19 subiculum (for retrieval). Furthermore, Bellmund et al. (2016) reported a grid-like-activity  
20 during imagined movement in the EC, alongside a high correlation between the behavioural  
21 performance during the direction imagination task, the navigation success and the accuracy of  
22 direction estimates during training, and the performance during a post-scan map test. Activation  
23 in the RSC and the PFC was reported in the studies by Salgado-Pineda et al. (2016) and Wolbers  
24 et al. (2004). In the latter study, the left medial frontal gyrus, left RSC and bilateral posterior  
25 inferior parietal cortices were activated.

1 We identified **three main types of tasks to explore spatial memory without EM**  
2 **assessment**: exploration of a maze to find rewards, going to a pre-learned, pre-defined location  
3 and route-following. The studies in this section are devoid of any episodic element as they focus  
4 on the sole memory of locations or pathways, without any idea of binding, temporality, or  
5 auto-noetic consciousness. By definition, spatial memory for EM concerns detailed and specific  
6 spatial information encoded during a navigation that enables the person to memorize the route  
7 of an unfamiliar environment, locate objects or landmarks and memorize their position.  
8 Retrieval consists in re-experiencing the environment with its perceptual details as one takes a  
9 mental walk through it, a spatial analogue of mental time travel, and recalling or recognizing  
10 its various specific attributes on formal tests. The following tasks focused solely on the spatial  
11 component without any notion of episodicity. The details of the activated regions can be found  
12 in Table 4, study by study, limited to those of the healthy controls.

13 **Eight studies focused their main task on finding rewards in a maze** (Astur et al., 2005;  
14 Cyr et al., 2016; Demanuele et al., 2015; Migo et al., 2016; Siemerkus et al., 2012; Tau et al.,  
15 2014; Weniger et al., 2013; Weniger et al., 2010). For this type of task, during the experiment,  
16 the participant had to explore the VE and look for rewards in the arms of the maze without re-  
17 entering arms that they had already explored. The control conditions differed a little: Astur et  
18 al. (2005) used an experimental condition with each arm containing a reward vs. a control  
19 condition where only four arms had a reward. Cyr et al. (2016) and Tau et al. (2014) prevented  
20 spatial learning in the control condition with a randomised layout of extra-maze spatial cues,  
21 and the same mean number of arm visits as in the learning condition. Similarly, Demanuele et  
22 al. (2015) used a control condition with determined maze arms to be visited. Migo et al. (2016)  
23 opted for a visual control (passive viewing of an image). Siemerkus et al. (2012) and Weniger  
24 et al. (2013) used the “BASELINE” as control, that is, the mean confound or intersect of their  
25 General Linear Model (GLM) based on the time courses of the experimental condition. This

1 model also provided their predictor of interest (DECIDE) that corresponded to the moments  
2 when the subject had to decide which way to go at the intersections in the maze. In this type of  
3 task, one main region was activated, namely the HPC and neighbouring PHG. During  
4 navigation in the mazes while trying to find the right maze arms, the HPC (Cyr et al., 2016),  
5 anterior HPC (Astur et al., 2005), right HPC (Migo et al., 2016) as well as the PHG (Migo et  
6 al., 2016; Siemerkus et al., 2012; Weniger et al., 2013; Weniger et al., 2010) and MTL (Tau et  
7 al., 2014) were activated. Specific learning of the spatial layout involved the right anterior HPC  
8 (Cyr et al., 2016). Frontal regions were also activated during navigation: the dorsolateral  
9 prefrontal cortex (DLPFC) (Demanuele et al., 2015), left DLPFC (Migo et al., 2016), left  
10 superior frontal gyrus and right subgyral frontal (Astur et al., 2005), inferior frontal gyrus (Cyr  
11 et al., 2016), and frontal regions (Tau et al., 2014). The precuneus was activated in several  
12 studies during navigation (Demanuele et al., 2015; Migo et al., 2016; Siemerkus et al., 2012;  
13 Weniger et al., 2013). The parietal cortex was sometimes activated during navigation: superior  
14 parietal cortex (Cyr et al., 2016), posterior parietal cortex (Migo et al., 2016), inferior parietal  
15 cortex (Weniger et al., 2013). Besides, Siemerkus et al. (2012) reported the activation of the  
16 cuneus during virtual learning. Other regions contributed to the signal during navigation, albeit  
17 more rarely: lingual and fusiform gyri (Cyr et al., 2016), left supramarginal gyrus and caudate  
18 nucleus (Migo et al., 2016), left postcentral gyrus and left anterior insula (Weniger et al., 2010),  
19 cingular cortex (Weniger et al., 2013). Some studies also noticed the activation of  
20 somatosensory-motor and visual areas, for instance during navigation (Demanuele et al. (2015)  
21 or Migo et al. (2016), the latter only for the visual cortex). The retrosplenial cortex (RSC) was  
22 involved in some studies (Migo et al., 2016; Siemerkus et al., 2012; Weniger et al., 2013), as  
23 well as the parietooccipital sulcus (Siemerkus et al., 2012; Weniger et al., 2013). Interestingly,  
24 Tau et al. (2014) reported the activation of ventral and dorsal visual streams for visual

1 processing and attention during search, and of the cingulo-opercular network for goal-directed  
2 behaviour.

3 **Six studies explored spatial memory by asking participants to go to a pre-learned, pre-**  
4 **defined position in the VE** (Antonova et al., 2011; Iglói et al., 2015; Parslow et al., 2004;  
5 Salgado-Pineda et al., 2016; Slobounov et al., 2010; Wolbers et al., 2004). The participant  
6 needed to replace a location in the VE, that is, they had to go back to a given, specific place in  
7 the VE which they had learned earlier. HPC was activated alongside PHG for Antonova et al.  
8 (2011) (during activation), Parslow et al. (2004) (for both viewer-independent and -dependent  
9 conditions; HPC and PHG were involved mainly in allocentric processing during encoding)  
10 and Salgado-Pineda et al. (2016). The HPC was also activated in Iglói et al. (2015) (right HPC  
11 for place-based responses; left HPC for sequence-based egocentric responses) and in Slobounov  
12 et al. (2010) (bilateral HPC during encoding). In Parslow et al. (2004), both conditions activated  
13 the superior temporal regions. Most studies also reported the activation of the parietal cortex:  
14 Antonova et al. (2011) (lateral and medial parietal cortex during activation), Parslow et al.  
15 (2004) (parietal cortex for both conditions), Iglói et al. (2015) (medial parietal cortex),  
16 Slobounov et al. (2010) (bilateral parietal cortex during encoding and parietal cortex during  
17 retrieval), Wolbers et al. (2004) (bilateral posterior inferior parietal cortices during route  
18 learning; the only activity that increased across learning sessions in this study). Some activation  
19 was found in frontal regions: DLPFC (Antonova et al., 2011), right DLPFC (Slobounov et al.  
20 (2010) during encoding), medial PFC (Iglói et al., 2015), PFC (Salgado-Pineda et al., 2016),  
21 medial frontal and inferior frontal gyri (Parslow et al., 2004), left medial frontal gyrus (Wolbers  
22 et al. (2004) during route learning). Both Parslow et al. (2004) (for both viewer-dependent and  
23 independent conditions) and Slobounov et al. (2010) found activation in the occipital regions,  
24 while only Slobounov et al. (2010) found activation in the somatosensory and visual regions,  
25 namely activation in the lateral extrastriate visual cortex extending into V2 during encoding



1 and activation in the premotor cortex during retrieval. Other regions involved regions include  
2 the thalamic and cerebellar areas (Antonova et al., 2011; Parslow et al., 2004), with a  
3 differentiated activation in the cerebellum for Iglói et al. (2015) (left cerebellum for place-based  
4 responses; right cerebellum for sequence-based egocentric responses); RSC (Salgado-Pineda et  
5 al., 2016; Wolbers et al., 2004); precuneus (during both encoding and retrieval for Slobounov  
6 et al. (2010)); anterior cingulate and precentral gyri (Parslow et al., 2004). Furthermore, Iglói  
7 et al. (2015) noted that the two networks they observed were activated during training  
8 sequences.

9 **Three studies focused on route-following.** This task was mostly used as a control  
10 condition, as in Hartley et al. (2003), Javadi et al. (2019) and Salgado-Pineda et al. (2016). The  
11 activations for this condition were used during analyses for contrasts but the absolute  
12 activations still provide information about the regions involved in navigation in a VE. Hartley  
13 et al. (2003) noted activation in the head of the right caudate, for navigation via the same well-  
14 learned route. Javadi et al. (2019) reported activations in HPC, bilateral PHG, RSC and medial  
15 frontal areas, though less than in the active condition. As could be expected, the route-following  
16 condition in Salgado-Pineda et al. (2016) was directly incorporated in the contrasts for the  
17 neuroimaging analysis.

18

## 19 **DISCUSSION**

20 The present review examined VR-fMRI paradigms used to construct more ecological and  
21 valid experiments to explore human cognition and highlight their constraints, benefits, and the  
22 limitations. To illustrate VR-fMRI and reflect on what is already possible, we chose EM as this  
23 cognitive function benefits from VR experiments and VR navigation given its multi-modal  
24 definition. The. The activation of the canonical regions of EM and spatial memory (Robin,  
25 2018) – namely HPC and PHG, EC and RSC, PFC and the occipital-parieto-temporal network

1 – validates VR as a tool to explore these cognitive functions. Although the existing VR-fMRI  
2 EM paradigms are not highly immersive or interactive, and use a first-person perspective in the  
3 VE without any complete or partial body avatar, a larger network of activation is found, for  
4 instance in the medial PFC, the cerebellum or insula, or in movement-related aspects of  
5 navigation (for instance the caudate nucleus for speed, Maguire et al. (1998)). We discuss these  
6 issues and limitations of the existing VR-fMRI EM paradigms and suggest new perspectives.

7

8 • **REPLICATION OF MAIN ACTIVATED REGIONS FOR EM AS EXPLORED**  
9 **WITH VR-fMRI**

10 The present review focused on EM and the correlated spatial memory, with a focus on  
11 human data. The richness of EM depends on the interplay between the median temporal lobe  
12 and the neocortical and sub-cortical structures of the brain. The **role of the HPC** has been  
13 investigated in several studies and key reviews (Burgess et al., 2002; Moscovitch et al., 2016;  
14 Tulving and Markowitsch, 1998) that point to its key role in episodic and autobiographical  
15 memory (Miller et al., 2020; Moscovitch et al., 2005; Piolino et al., 2009). Most particularly,  
16 the HPC is presumed to mediate recollection by relying on relational information, including the  
17 temporal-spatial context of the memory (Moscovitch et al., 2005). It intervenes specifically in  
18 the encoding phase in the association mechanisms (“binding”) between the content of the  
19 experience and the spatial and temporal context in which it occurred and their transformation  
20 into a coherent and temporally organised memory trace, and in the recall phase by ensuring the  
21 reactivation of brain structures allowing a long-lasting revival of the event in its context  
22 (Moscovitch et al., 2016). The HPC is also considered crucial for memorising new routes and  
23 maintaining and operating on cognitive maps necessary for navigation, whether the maps are  
24 old or newly formed (Burgess et al., 2002; O’Keefe and Nadel, 1979), but no more for  
25 navigation of familiar environments (Moscovitch et al., 2005; Rosenbaum et al., 2000). Medial

1 temporal regions at large are involved in updating spatial representations after self-motion, thus  
2 updating spatial memory. Burgess et al. (2002) highlighted three main components of spatial  
3 memory in which the HPC region is involved: spatial frameworks, dimensionality, and  
4 orientation. The left HPC is reported to store relationships between entities as narratives, though  
5 not necessarily verbal ones, thus supporting episodic and autobiographical memory, while the  
6 right HPC focuses on spatial relationships for locations and wayfinding in environments  
7 (allocentric) (Maguire et al., 1998). In the VR-fMRI studies reported in this review, the HPC  
8 was activated during spatial learning and retrieval for spatial memory tasks and EM tasks,  
9 mainly bilaterally with the PHG, with few studies reporting a lateralised activation. The PHG  
10 is required for object-location memory and the representation of scenes, and to process the  
11 spatial information in visual scenes (e.g. extracting the distance to the nearest landmark), with  
12 an additional activation of HPC for locations in 3D space (Burgess et al., 2002). Most notably,  
13 Cyr et al. (2016) Iglói et al. (2015), and Migo et al. (2016) reported a specific activation in the  
14 right hippocampus for place-based memory. Although almost every study focusing on EM in  
15 this review reported the activation of the HPC, interestingly, some studies reported a  
16 differentiated activation. Duarte et al. (2014) highlighted differences between posterior and  
17 anterior HPC; Burgess et al. (2001), Lee et al. (2016) and Gomez et al. (2014) showed a space-  
18 related activation of the right HPC, with a more autobiographic-related activation of the left  
19 HPC, as seen in previous literature. According to the cognitive map theory, the hippocampus  
20 supports the allocentric processing of space, contrary to other brain regions such as the parietal  
21 cortex, that support egocentric processing (O'Keefe and Nadel, 1979). Few studies specifically  
22 focused on that aspect, though Gomez et al. (2014) and Parslow et al. (2004) noted activation  
23 in the HPC for allocentric processing (with the former also noting activation in the HPC for  
24 egocentric-updating). Depending on the test type (for instance, learning an environment from a

1 two-dimensional map versus learning an environment by navigating in it), the HPC and the  
2 parietal cortex are thus differently activated.

3 The **parietal cortex** contributes directly to EM, as part of a network that is also active for  
4 the processing of non-episodic information (Rugg and King, 2018). The ventral parietal cortex  
5 is thought to have mnemonic functions related to attention and stimulus representation (Davis  
6 et al., 2018), the posterior parietal lobe has a role in generic (schematic) representations of  
7 topography needed for navigation and egocentric frame, and as a whole, the parietal cortex  
8 seems to play a key role during memory processes (Kim, 2018). The parietal cortex was highly  
9 involved in the studies of this review reporting on spatial memory, for all tasks (for tasks in  
10 mazes, see for instance Cyr et al. (2016), Migo et al. (2016) and Weniger et al. (2013); for  
11 location-specific tasks, see for instance Antonova et al. (2011), Iglói et al. (2015), Parslow et  
12 al. (2004), Slobounov et al. (2010) and Wolbers et al. (2004)). Burgess et al. (2001) highlighted  
13 the role of the parietal cortex in EM as one of the main activated areas. However, the studies in  
14 this review focusing on EM did not report any major activation in this region, except for Gomez  
15 et al. (2014). This could imply that VR-fMRI EM studies are not yet sufficiently sensitive to  
16 self-engagement since the temporal-parietal junction has been thought to play an important role  
17 in multisensory integration mechanisms, especially those involved in body self-awareness  
18 (Blanke et al., 2015; Ionta et al., 2011).

19 As part of the posteromedial cortex (Zilles et al., 2003), which seems to support memory  
20 encoding and retrieval demands (E/R flip) (Amlien et al., 2018), the **RSC** is involved in path  
21 integration and location tracking alongside the HPC (Chrastil et al., 2015). Accordingly, studies  
22 with location-related tasks (finding and remembering one's location in a maze, finding a pre-  
23 learned location) reported the activation of the RSC (Migo et al., 2016; Salgado-Pineda et al.,  
24 2016; Siemerkus et al., 2012; Weniger et al., 2013; Wolbers et al., 2004). Likewise, Gomez et  
25 al. (2014) reported activation in the RSC for orientation changes for the self. The RSC is thus

1 involved in spatial memory through its role in the learning of spatial landmarks, the  
2 consolidation and retrieval of spatial memory, but also the transformation between allocentric  
3 and egocentric spatial frames: Serino et al. (2015) showed that the RSC seems to be involved  
4 in translating allocentric reference frames to egocentric ones by providing a small-scale map of  
5 the environment when remembering the correct path. This leads to considering its implication  
6 in EM (Mitchell et al., 2018), and in learning and encoding behaviourally relevant cues (Smith  
7 et al., 2018). Burgess et al. (2001) reported the RSC in the main activated network in EM;  
8 likewise, the RSC was activated for EM-related spatial memory for objects (Javadi et al., 2019;  
9 Nau et al., 2020) and landmarks (Salgado-Pineda et al., 2016; Wolbers et al., 2004).

10 Furthermore, while also taking into account other dimensions of the task at hand (Ekstrom  
11 and Ranganath, 2018), the HPC integrates information coming from frontal lobes (Desgranges  
12 et al., 1998; Preston and Eichenbaum, 2013) (for contextual binding see for instance Yonelinas  
13 et al. (2019)). The **PFC** is involved in encoding and retrieval of EM: the DLPFC is associated  
14 with mentoring encoding and retrieval processes, while the ventrolateral PFC is associated with  
15 strategic retrieval and information selection and triggering autobiographical memory by  
16 synchronising emotional and factual components of the personal past. The ventromedial PFC  
17 integrates the emotional part of memories while the dorsomedial PFC processes self-references  
18 (for a review see for instance Brand and Markowitsch (2008)). In this review, only Burgess et  
19 al. (2001) and Javadi et al. (2019) reported PFC activation in EM. However, almost all the  
20 studies investigating spatial memory almost all reported activation in the PFC (DLPFC, left  
21 DLPFC, right PFC, superior PFC, inferior PFC, medial PFC), though Salgado-Pineda et al.  
22 (2016) notably reported a decreased DLPFC activity for schizophrenic patients.

23

1 • **ENLIGHTENING SPECIFIC REGIONS ACTIVATED FOR EM THROUGH VR-**  
2 **fMRI EXPLORATION: ON THE TRAIL OF “TRUE” EM RELATED TO THE**  
3 **SELF**

4 Naturalistic episodic memory (true EM) records specific events experienced by oneself  
5 (Tulving, 1985, 2002). The self as the subject of conscious experience is thus critical in  
6 determining the idiosyncratic nature of EM and associated self-awareness (Bergouignan et al.,  
7 2014; Makowski et al., 2017). It grounds the self-reference processing in memory which  
8 consists in linking the new to-be-remembered piece of information to the self (Klein, 2012).  
9 This link emerges either via its narrative component (e.g., self-relevance, self-description, self-  
10 esteem, personal intention and future goals, autobiographical memories) or its minimal  
11 component (e.g., the “I” that is experiencing “here and now” or body self) (Gallagher, 2000).  
12 Recent research has revealed that body self-awareness, that is, the implicit and pre-reflexive  
13 experience of being the subject of a given experience, is based on multisensory brain  
14 mechanisms underlying the integration of bodily signals (for a review, see Blanke et al. (2015)).  
15 These mechanisms contribute to EM and auto-noetic consciousness (Bergouignan et al., 2014;  
16 Brechet et al., 2020; Brechet et al., 2019) since EM involves indeed the naturalistic viewing of  
17 one’s own body during encoding from the first-person perspective. As previously mentioned,  
18 VR not only introduces new possibilities to investigate behaviour in realistic, naturalistic  
19 environments, but also increases the level of immersion, self-engagement, sense of embodiment  
20 and presence in experiments. Bergouignan et al. (2014) studied the impact of congruent and  
21 incongruent self-location (first- vs third-person perspective) with VR during a scene encoding  
22 and its subsequent recall, showing a lower level of temporal, spatial and emotional details as  
23 well as a weaker sense of recollection in participants in the out-of-body condition, which is  
24 coherent with a reduced activity in the left posterior HPC during recall. One recent resting-state  
25 fMRI study investigated how first-person body view during encoding in immersive VR

1 modulates EM and auto-noetic consciousness (Gauthier et al., 2020). This study interestingly  
2 showed that body view at encoding enhanced EM thanks to connectivity between the right HPC  
3 and the sensorimotor fronto-parietal network, comprising the primary somatosensory and motor  
4 cortices.

5 Remarkably, despite the current limitations of concurrent VR and fMRI in terms of  
6 interaction and embodiment and immersion, several regions have been identified in addition to  
7 the cerebral networks that are already well known to sustain EM. Indeed, the present review  
8 highlights that some regions that are not directly connected to EM when using traditional  
9 material but that are related to self-awareness and the processing of multisensory bodily signals  
10 are activated: the medial PFC, the cerebellum, the insula, and the motor areas.

11 The **medial PFC** is related to the core of autobiographical memory (see for instance Oddo  
12 et al. (2010)) and the self-memory system (Martinelli et al., 2013). It is part of the cortical  
13 midline (Summerfield et al., 2009) related to self-referential processes (Northoff et al., 2006).  
14 Self-referential processing of information provides an EM advantage, known as the self-  
15 reference effect, and is characterised by a greater activation of the ventromedial PFC (Martinelli  
16 et al., 2013; Northoff et al., 2006). This region was involved in several studies, more for EM  
17 than for spatial memory (for EM: Doeller et al. (2010), Gomez et al. (2014), Hartley et al.  
18 (2003), Javadi et al. (2019), Wolbers et al. (2004); for spatial memory: Iglói et al. (2015),  
19 Parslow et al. (2004), Siemerikus et al. (2012)). It is noteworthy that some of the studies, mostly  
20 in spatial memory, reported a deactivation rather than an activation (for EM: Duarte et al.  
21 (2014); for spatial memory: Astur et al. (2005), Salgado-Pineda et al. (2016), Weniger et al.  
22 (2010)). The proportion of studies reporting a deactivation was higher when the immersion was  
23 high (goggles, HMD...) compared to when it was lower (screen, mirror...). This functional  
24 activation limit of the medial PFC, which is critical for the self-reference effect on memory  
25 encoding, could indicate that, most of the time, immersion in VR-fMRI is not sufficient to

1 involve all the cognitive, emotional, and sensory components of the narrative self. It is thus  
2 necessary to develop tasks and devices that enhance the sense of self in the VE in the scanner.

3 In addition, other cerebral areas were activated that are involved in the minimal or body  
4 aspects of the self, and that may reveal their contribution to EM encoding and retrieval  
5 (Bergouignan et al., 2014; Brechet et al., 2019; Gauthier et al., 2020; Tuena et al., 2017).

6 The **cerebellum** was activated, much more when immersion was low (for EM: Gomez et  
7 al. (2014), Hartley et al. (2003); for spatial memory: Antonova et al. (2011), Astur et al. (2005),  
8 Iglói et al. (2015), Parslow et al. (2004)) than when it was high (Tau et al. (2014), spatial  
9 memory). The cerebellum is considered to be primarily involved in the coordination of body  
10 movement control and the facilitation of implicit learning of motor skills such as those involved  
11 in walking. Some fMRI studies already emphasised its role in both the encoding and retrieval  
12 of EM (Andreasen et al., 1999; Fliessbach et al., 2007), as well as autobiographical memory  
13 (Addis et al., 2016). It is now viewed as a hub serving a higher level of brain functions beyond  
14 movement, including the implicit part of complex thought and cognitive processes such as  
15 intuition or imagination (Ito, 2008) (for a recent review, see Kawato et al. (2021)).

16 The **insula** was equally activated for low immersion (for EM: Hartley et al. (2003), Javadi  
17 et al. (2019), Lee et al. (2016), Sutton et al. (2010); for spatial memory: Iglói et al. (2015), Migo  
18 et al. (2016), Parslow et al. (2004)) versus high immersion (only for spatial memory: Siemerkus  
19 et al. (2012), Tau et al. (2014), Weniger et al. (2013), Weniger et al. (2010)). Last but not least,  
20 the **motor area** was activated in several studies, involving the precentral gyri (for EM: Doeller  
21 et al. (2010), Gomez et al. (2014), Hartley et al. (2003), Javadi et al. (2019), Sutton et al. (2010);  
22 for spatial memory: Demanuele et al. (2015), Iglói et al. (2015), Migo et al. (2016), Parslow et  
23 al. (2004), Siemerkus et al. (2012), Slobounov et al. (2010), Tau et al. (2014), Weniger et al.  
24 (2013), Weniger et al. (2010)), the supplementary motor area (only for EM: Hartley et al.  
25 (2003)) or the motor cortex itself (only for EM: Doeller et al. (2010), Hartley et al. (2003),



1 Sutton et al. (2010)). However, since the level of interaction in the scanner remains limited,  
2 these supplementary motor activations were mostly smaller and less intense, and for highest  
3 interaction only. Furthermore, the insula and the premotor area (as well as the tempo-parietal  
4 junction) have been thought to play an important role in the multisensory integration involved  
5 in the proprioceptive drift as observed in the rubber hand illusion (Tsakiris, 2010) or in bodily  
6 self-awareness (Blanke et al., 2015).

7 Bodily self-awareness is assumed to consist of three distinct components: the experience of  
8 owning a body (body ownership), the experience of being a body at a given location within an  
9 environment (self-location), and the experience of taking a first-person, body-centred  
10 perspective on the environment (first perspective). It includes body-centred perception  
11 (proprioception, visual body-related information and embodiment) and involves spatio-  
12 temporal mechanisms integrating multisensory bodily stimuli within peri-personal space  
13 (Blanke et al., 2015). Recently, embodied immersive VR studies showed that body self-  
14 awareness enhances EM, emphasizing its critical role in creating idiosyncratic self-related  
15 memory (Bergouignan et al., 2014; Brechet et al., 2020; Brechet et al., 2019; Gauthier et al.,  
16 2020; Tuena et al., 2017). A neurocognitive assumption proposes that body ownership arises  
17 as an interaction between the current multisensory input and the internal models of the body.  
18 The insula is especially considered a key area for subjective experience and awareness of the  
19 internal physiological states of the body or interoception involved in the sense of body  
20 ownership, as illustrated in the rubber hand illusion. On the other hand, the premotor area is  
21 also involved in interoception as well as exteroception such as touch and can thus contribute to  
22 the sense of agency. These findings pave the way for future concomitant VR-fMRI research  
23 exploring the role of the self and the bodily self in the formation of EM and specifically  
24 idiosyncratic details and autothetic consciousness.

25

1 • **LIMITS, RECOMMENDATIONS, FUTURE DIRECTIONS, AND CONCLUSION**

2 The major asset of VR-fMRI paradigms consists in the exploration of human behaviour in  
3 naturalistic and daily-life-like environments. However, to our knowledge, there is no fixed,  
4 standardised experimental framework for concomitant VR-fMRI despite the increasing  
5 availability of MRI-compatible equipment. The VR-fMRI paradigms are not fully optimised  
6 yet as the properties of VR are not used to their full extent, especially embodiment (e.g., sense  
7 of body-ownership or agency). As pointed out by Taube et al. (2013), the supine position in the  
8 scanner could be an issue especially for head direction. The difference between the real-world  
9 input, where the subject is lying down, and the VR input, in which the subject can be walking  
10 in an environment, sends mixed, competing signals to head-direction cells in the brain that  
11 could fire for either one input, or for both if holding multiple reference frames proves to be  
12 possible. Brain recordings can therefore be influenced by both a conflicting otolith signal and  
13 the adaptation between two reference frames (real-world and VR). Future studies should take  
14 this point into careful consideration, especially when interpreting zones of activation in the  
15 brain. The sense information processing that leads to the sense of presence in the VE should  
16 also be optimised, and the level of immersion and interaction adjusted accordingly (see  
17 Berthiaume et al. (2021)). As a matter of fact, high interaction for VR-fMRI means, at the most  
18 at the moment, keys, buttons or a joystick for the subject to evolve in the VE. Interaction could  
19 be further enhanced in the scanner with movement-tracking gloves and with specific actions to  
20 be carried out in the VE, or even with pedals to simulate real walking, as some studies already  
21 do. Eye-tracking would add useful elements of proof for the involvement of the participants in  
22 the VE. The use of goggles or HMD could also be more systematic to improve immersion and  
23 embodiment in an avatar. To acquire fMRI data with tasks in conditions as close as possible to  
24 real life using VR, we suggest designing VE in which the participant can freely interact with  
25 some objects. Some equipment seems better fitted to do so, such as gloves or pedals (see Table

1 5 for a comparison of the main existing equipment regarding interaction, immersion, potential  
2 cybersickness, naturalistic complexity). Considering the main criteria that we think are essential  
3 to design a VE, that is, the facility for researchers, the existence of plug-ins for additional  
4 external devices and the capacity to manage VR devices, Unity 3D seems to be the best software  
5 yet. We recommend that future VR-fMRI studies should include at least one experimental  
6 condition with active interaction, while controlling for any signs of cyber-sickness (Kourtesis  
7 et al., 2019). This should allow an easier task-by-task evaluation of the efficiency of interaction  
8 and thus a better understanding of the actual effect of interacting in a real-world environment.  
9 These are general guidelines to enhance the ecological validity of VR experiments with an  
10 added fMRI dimension, to which future studies will likely add.

11 Furthermore, the present review has shown that studies combining VR and fMRI in the  
12 domain of EM are promising, but still scarce in comparison with those on spatial memory. The  
13 synthesis of the data on EM and its neural correlates highlights regions similar to those of more  
14 conventionally designed studies using standard experimental material, but also more specific  
15 regions related to self-referential processes. It underlines the importance of this approach to  
16 study EM in a naturalistic context and to better understand its formation mechanisms. However,  
17 although there are already well-established VR EM paradigms that allow the investigation of  
18 the memory of specific events, considering the richness of their context (what, where, when  
19 and perceptual details) and the sense of remembering (e.g. Plancher et al. (2012); Jebara et al.  
20 (2014); Abichou et al. (2019); Abichou et al. (2021a)), only Burgess et al. (2001) appear to  
21 have explored EM with its feature binding (what, who, and where) with both VR and fMRI.  
22 Given technical advances, we believe further explorations could be timely. Adding more daily-  
23 life elements to the paradigms, such as emotional events (with different valences and  
24 intensities) and self-relevance, would be very interesting. Likewise, combining the first  
25 perspective with an avatar (full or partial body) in the VE would increase the precision of VR

1 as well as the feeling of presence. As the dimensions of immersion and interaction are of the  
2 utmost importance when considering EM VR paradigms (Smith, 2019), we recommend that  
3 future VR-fMRI research on the formation of naturalistic EM should comprise the assessment  
4 of complex feature binding, idiosyncratic details and auto-noetic consciousness, in interaction  
5 with different components of the self. This includes the development of virtual devices that  
6 allow viewing one's own body from a first-person perspective during encoding of naturalistic  
7 events in the scanner. Additionally, exploring paradigms with different points of view, such as  
8 the third-person perspective described by Barra et al. (2012) (slanted or oblique), would help  
9 to shed some more light on the cognitive functions that can be explored with concomitant VR-  
10 fMRI. For instance, these technical advances should lead memory research to consider an  
11 integrative framework of EM comprising its neurocognitive mechanisms underlying  
12 retrospection (long-lasting autobiographical memory, see Moscovitch et al. (2005) or Piolino  
13 et al. (2009)) and prospection (Atance and O'Neill, 2001; Szpunar et al., 2014), prospection  
14 being a broad concept that has been used to characterise a wide variety of future-oriented  
15 cognition, including episodic future thinking (Addis et al., 2008). Prospective memory has also  
16 already been explored in VR (for instance by Debarnot et al. (2015) or Lecouvey et al. (2019)  
17 or La Corte et al. (2021); for a review in neurological assessments and rehabilitation, see Knight  
18 and Titov (2009)), even considering VR-fMRI (Kalpouzos et al., 2010). Therefore, exploring  
19 one specific cognitive function with concomitant VR-fMRI is possible and still perfectible.  
20 These considerations could be expanded to include other cognitive functions for which such  
21 neuroimaging results would prove useful.

22 All things considered, VR proves to be a powerful tool to explore human behaviour in  
23 naturalistic and daily-life-like environments. By adapting experimental paradigms and adding  
24 a virtual component to fMRI scanning, the studies increasingly resemble real-life situations,  
25 and the VR-fMRI combination represents an increasingly compelling paradigm thanks to its

- 1 ecological value and therapeutic applications. The technical challenges of these paradigms are
- 2 quite interesting as they appear to be relevant for other ones, such as the combination of VR
- 3 and EEG.

1 **AUTHOR CONTRIBUTIONS**

2 DL conceptualised the PRISMA study and wrote the original draft of the manuscript while  
3 PP wrote specific parts. PP and DL reviewed and edited its content.

4

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8

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## 1 REFERENCES

- 2
- 3 Abichou, K., La Corte, V., Gaston-Bellegarde, A., Nicolas, S., Piolino, P., 2021a. How Rich are False Memories  
4 in a Naturalistic Context in Healthy Aging? *Memory*.
- 5 Abichou, K., La Corte, V., Hubert, N., Orriols, E., Gaston-Bellegarde, A., Nicolas, S., Piolino, P., 2019. Young  
6 and Older Adults Benefit From Sleep, but Not From Active Wakefulness for Memory Consolidation of What-  
7 Where-When Naturalistic Events. *Front. Aging Neurosci.* 11.
- 8 Abichou, K., La Corte, V., Sperduti, M., Gaston-Bellegarde, A., Nicolas, S., Piolino, P., 2021b. The production  
9 of false recognition and the associated state of consciousness following encoding in a naturalistic context in  
10 aging. *Conscious. Cogn.* 90, 103097.
- 11 Adamovich, S.V., August, K., Merians, A., Tunik, E., 2009. A virtual reality-based system integrated with fmri  
12 to study neural mechanisms of action observation-execution: a proof of concept study. *Restor. Neurol. Neurosci.*  
13 27, 209-223.
- 14 Addis, D.R., Moloney, E.E.J., Tippett, L.J., P. Roberts, R., Hach, S., 2016. Characterizing cerebellar activity  
15 during autobiographical memory retrieval: ALE and functional connectivity investigations. *Neuropsychologia*  
16 90, 80-93.
- 17 Addis, D.R., Wong, A.T., Schacter, D.L., 2008. Age-related changes in the episodic simulation of future events.  
18 *Psychol. Sci.* 19, 33-41.
- 19 Alvarez, R.P., Biggs, A., Chen, G., Pine, D.S., Grillon, C., 2008. Contextual fear conditioning in humans:  
20 cortical-hippocampal and amygdala contributions. *J. Neurosci.* 28, 6211-6219.
- 21 Amlien, I.K., Sneve, M.H., Vidal-Pineiro, D., Walhovd, K.B., Fjell, A.M., 2018. The Lifespan Trajectory of the  
22 Encoding-Retrieval Flip: A Multimodal Examination of Medial Parietal Cortex Contributions to Episodic  
23 Memory. *J. Neurosci.* 38, 8666-8679.
- 24 Andoh, J., Milde, C., Diers, M., Bekrater-Bodmann, R., Trojan, J., Fuchs, X., Becker, S., Desch, S., Flor, H.,  
25 2020. Assessment of cortical reorganization and preserved function in phantom limb pain: a methodological  
26 perspective. *Sci. Rep.* 10, 11504-11504.
- 27 Andreasen, N.C., O'Leary, D.S., Paradiso, S., Cizadlo, T., Arndt, S., Watkins, G.L., Ponto, L.L., Hichwa, R.D.,  
28 1999. The cerebellum plays a role in conscious episodic memory retrieval. *Hum. Brain Mapp.* 8, 226-234.
- 29 Ansado, J., Chasen, C., Bouchard, S., Northoff, G., 2020. How brain imaging provides predictive biomarkers for  
30 therapeutic success in the context of virtual reality cognitive training. *Neurosci. Biobehav. Rev.*
- 31 Antonova, E., Parslow, D., Brammer, M., Simmons, A., Williams, S., Dawson, G.R., Morris, R., 2011.  
32 Scopolamine disrupts hippocampal activity during allocentric spatial memory in humans: an fMRI study using a  
33 virtual reality analogue of the Morris Water Maze. *J Psychopharmacol* 25, 1256-1265.
- 34 Armougum, A., Gaston-Bellegarde, A., Marle, C.J.-L., Piolino, P., 2020. Expertise reversal effect: Cost of  
35 generating new schemas. *Comput. Human Behav.* 111, 106406.
- 36 Armougum, A., Orriols, E., Gaston-Bellegarde, A., Marle, C., Piolino, P., 2019. Virtual reality: A new method to  
37 investigate cognitive load during navigation. *J. Environ. Psychol.* 65, 101338.
- 38 Arthur, E.J., Hancock, P.A., Chrysler, S.T., 1997. The perception of spatial layout in real and virtual worlds.  
39 *Ergonomics* 40, 69-77.
- 40 Astur, R.S., St Germain, S.A., Baker, E.K., Calhoun, V., Pearlson, G.D., Constable, R.T., 2005. fMRI  
41 hippocampal activity during a virtual radial arm maze. *Appl. Psychophysiol. Biofeedback* 30, 307-317.
- 42 Atance, C.M., O'Neill, D.K., 2001. Episodic future thinking. *Trends Cogn. Sci.* 5, 533-539.
- 43 Barra, J., Laou, L., Poline, J.B., Lebihan, D., Berthoz, A., 2012. Does an oblique/slanted perspective during  
44 virtual navigation engage both egocentric and allocentric brain strategies? *PLoS One* 7, e49537.
- 45 Basso Moro, S., Bisconti, S., Muthalib, M., Spezialetti, M., Cutini, S., Ferrari, M., Placidi, G., Quaresima, V.,  
46 2014. A semi-immersive virtual reality incremental swing balance task activates prefrontal cortex: a functional  
47 near-infrared spectroscopy study. *Neuroimage* 85 Pt 1, 451-460.
- 48 Beck, L., Wolter, M., Mungard, N., Kuhlen, T., Sturm, W., 2007. Combining Virtual Reality and Functional  
49 Magnetic Resonance Imaging (fMRI): Problems and Solutions, in: Holzinger, A. (Ed.), *HCI and Usability for  
50 Medicine and Health Care*. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 335-348.
- 51 Beck, L., Wolter, M., Mungard, N.F., Vohn, R., Staedtgen, M., Kuhlen, T., Sturm, W., 2010. Evaluation of  
52 spatial processing in virtual reality using functional magnetic resonance imaging (fMRI). *Cyberpsychol Behav  
53 Soc Netw* 13, 211-215.
- 54 Bellmund, J.L.S., Deuker, L., Schroder, T.N., Doeller, C.F., 2016. Grid-cell representations in mental  
55 simulation. *Elife* 5.
- 56 Bergouignan, L., Nyberg, L., Ehrsson, H.H., 2014. Out-of-body-induced hippocampal amnesia. *Proceedings of  
57 the National Academy of Sciences* 111, 4421.
- 58 Berthiaume, M., Corno, G., Nolet, K., Bouchard, S., 2021. A Novel Integrated Information Processing Model of  
59 Presence. *PRESENCE: Virtual and Augmented Reality* 27, 378-399.

1 Bhattacharjee, A., Kajal, D.S., Patrono, A., Li Hegner, Y., Zampini, M., Schwarz, C., Braun, C., 2020. A Tactile  
2 Virtual Reality for the Study of Active Somatosensation. *Front. Integr. Neurosci.* 14, 5.

3 Blanke, O., Slater, M., Serino, A., 2015. Behavioral, Neural, and Computational Principles of Bodily Self-  
4 Consciousness. *Neuron* 88, 145-166.

5 Blondé, P., Makowski, D., Sperduti, M., Piolino, P., 2021. In Medio Stat Virtus: intermediate levels of mind  
6 wandering improve episodic memory encoding in a virtual environment. *Psychol. Res.* 85, 1613-1625.

7 Bluett, B., Bayram, E., Litvan, I., 2019. The virtual reality of Parkinson's disease freezing of gait: A systematic  
8 review. *Parkinsonism Relat. Disord.* 61, 26-33.

9 Bohil, C., Alicea, B., Biocca, F., 2011. Virtual reality in neuroscience research and therapy. *Nature reviews.*  
10 *Neuroscience* 12, 752-762.

11 Boller, B., Ouellet, É., Belleville, S., 2021. Using Virtual Reality to Assess and Promote Transfer of Memory  
12 Training in Older Adults With Memory Complaints: A Randomized Controlled Trial. *Front. Psychol.* 12,  
13 627242.

14 Brand, J., Piccirelli, M., Hepp-Reymond, M.-C., Eng, K., Michels, L., 2020. Brain Activation During Visually  
15 Guided Finger Movements. *Front. Hum. Neurosci.* 14, 309-309.

16 Brand, M., Markowitsch, H.J., 2008. Chapter 3.5 The role of the prefrontal cortex in episodic memory, in: Dere,  
17 E., Easton, A., Nadel, L., Huston, J.P. (Eds.), *Handbook of Behavioral Neuroscience*. Elsevier, pp. 317-619.

18 Brechet, L., Hausmann, S.B., Mange, R., Herbelin, B., Blanke, O., Serino, A., 2020. Subjective feeling of re-  
19 experiencing past events using immersive virtual reality prevents a loss of episodic memory. *Brain Behav* 10,  
20 e01571.

21 Brechet, L., Mange, R., Herbelin, B., Theillaud, Q., Gauthier, B., Serino, A., Blanke, O., 2019. First-person view  
22 of one's body in immersive virtual reality: Influence on episodic memory. *PLoS One* 14, e0197763.

23 Brihmat, N., Tarri, M., Quidé, Y., Anglio, K., Pavard, B., Castel-Lacanal, E., Gasq, D., De Boissezon, X.,  
24 Marque, P., Loubinoux, I., 2018. Action, observation or imitation of virtual hand movement affect differently  
25 regions of the mirror neuron system and the default mode network. *Brain Imaging Behav.* 12, 1363-1378.

26 Burgess, N., 2006. Spatial memory: how egocentric and allocentric combine. *Trends Cogn. Sci.* 10, 551-557.

27 Burgess, N., Maguire, E.A., O'Keefe, J., 2002. The Human Hippocampus and Spatial and Episodic Memory.  
28 *Neuron* 35, 625-641.

29 Burgess, N., Maguire, E.A., Spiers, H.J., O'Keefe, J., 2001. A Temporoparietal and Prefrontal Network for  
30 Retrieving the Spatial Context of Lifelike Events. *Neuroimage* 14, 439-453.

31 Calhoun, V.D., Carvalho, K., Astur, R., Pearlson, G.D., 2005. Using Virtual Reality to Study Alcohol  
32 Intoxication Effects on the Neural Correlates of Simulated Driving. *Appl. Psychophysiol. Biofeedback* 30, 285-  
33 306.

34 Caserman, P., Garcia-Agundez, A., Gámez Zerban, A., Göbel, S., 2021. Cybersickness in current-generation  
35 virtual reality head-mounted displays: systematic review and outlook. *Virtual Reality* 25, 1153-1170.

36 Cermak, L.S., O'Connor, M., 1983. The anterograde and retrograde retrieval ability of a patient with amnesia  
37 due to encephalitis. *Neuropsychologia* 21, 213-234.

38 Chrastil, E.R., Sherrill, K.R., Hasselmo, M.E., Stern, C.E., 2015. There and Back Again: Hippocampus and  
39 Retrosplenial Cortex Track Homing Distance during Human Path Integration. *J. Neurosci.* 35, 15442-15452.

40 Clemenson, G.D., Wang, L., Mao, Z., Stark, S.M., Stark, C.E.L., 2020. Exploring the Spatial Relationships  
41 Between Real and Virtual Experiences: What Transfers and What Doesn't. *Frontiers in Virtual Reality* 1, 17.

42 Colombo, D., Serino, S., Tuena, C., Pedroli, E., Dakanalis, A., Cipresso, P., Riva, G., 2017. Egocentric and  
43 allocentric spatial reference frames in aging: A systematic review. *Neurosci. Biobehav. Rev.* 80, 605-621.

44 Conway, M.A., 2005. Memory and the self. *Journal of Memory and Language* 53, 594-628.

45 Cornwell, B.R., Salvatore, G., Colon-Rosario, V., Latov, D.R., Holroyd, T., Carver, F.W., Coppola, R., Manji,  
46 H.K., Zarate, C.A., Jr., Grillon, C., 2010. Abnormal hippocampal functioning and impaired spatial navigation in  
47 depressed individuals: evidence from whole-head magnetoencephalography. *Am. J. Psychiatry* 167, 836-844.

48 Cyr, M., Wang, Z., Tau, G.Z., Zhao, G., Friedl, E., Stefan, M., Terranova, K., Marsh, R., 2016. Reward-Based  
49 Spatial Learning in Teens With Bulimia Nervosa. *J. Am. Acad. Child Adolesc. Psychiatry* 55, 962-971.e963.

50 Davis, S.W., Wing, E.A., Cabeza, R., 2018. Contributions of the ventral parietal cortex to declarative memory.  
51 *Handb. Clin. Neurol.* 151, 525-553.

52 Debarnot, U., Crépon, B., Orriols, E., Abram, M., Charron, S., Lion, S., Roca, P., Oppenheim, C., Gueguen, B.,  
53 Ergis, A.M., Baron, J.C., Piolino, P., 2015. Intermittent theta burst stimulation over left BA10 enhances virtual  
54 reality-based prospective memory in healthy aged subjects. *Neurobiol. Aging* 36, 2360-2369.

55 Demanuele, C., Böhner, F., Plichta, M.M., Kirsch, P., Tost, H., Meyer-Lindenberg, A., Durstewitz, D., 2015. A  
56 statistical approach for segregating cognitive task stages from multivariate fMRI BOLD time series. *Front. Hum.*  
57 *Neurosci.* 9.

58 Desgranges, B., Baron, J.C., Eustache, F., 1998. The functional neuroanatomy of episodic memory: the role of  
59 the frontal lobes, the hippocampal formation, and other areas. *Neuroimage* 8, 198-213.



1 Diers, M., Kamping, S., Kirsch, P., Rance, M., Bekrater-Bodmann, R., Foell, J., Trojan, J., Fuchs, X., Bach, F.,  
2 Maass, H., Cakmak, H., Flor, H., 2015. Illusion-related brain activations: a new virtual reality mirror box system  
3 for use during functional magnetic resonance imaging. *Brain Res.* 1594, 173-182.

4 Doeller, C.F., Barry, C., Burgess, N., 2010. Evidence for grid cells in a human memory network. *Nature* 463,  
5 657-661.

6 Dong, D., Wong, L.K.F., Luo, Z., 2019. Assess BA10 activity in slide-based and immersive virtual reality  
7 prospective memory task using functional near-infrared spectroscopy (fNIRS). *Appl Neuropsychol Adult* 26,  
8 465-471.

9 Duarte, I.C., Ferreira, C., Marques, J., Castelo-Branco, M., 2014. Anterior/posterior competitive  
10 deactivation/activation dichotomy in the human hippocampus as revealed by a 3D navigation task. *PLoS One* 9,  
11 e86213.

12 Ehgoetz Martens, K.A., Hall, J.M., Georgiades, M.J., Gilat, M., Walton, C.C., Matar, E., Lewis, S.J.G., Shine,  
13 J.M., 2018. The functional network signature of heterogeneity in freezing of gait. *Brain* 141, 1145-1160.

14 Ekstrom, A.D., Ranganath, C., 2018. Space, time, and episodic memory: The hippocampus is all over the  
15 cognitive map. *Hippocampus* 28, 680-687.

16 Fadeev, K.A., Smirnov, A.S., Zhigalova, O.P., Bazhina, P.S., Tumialis, A.V., Golokhvast, K.S., 2020. Too Real  
17 to Be Virtual: Autonomic and EEG Responses to Extreme Stress Scenarios in Virtual Reality. *Behav. Neurol.*  
18 2020, 5758038.

19 Faul, L., Stjepanović, D., Stivers, J.M., Stewart, G.W., Graner, J.L., Morey, R.A., LaBar, K.S., 2020. Proximal  
20 threats promote enhanced acquisition and persistence of reactive fear-learning circuits. *Proceedings of the*  
21 *National Academy of Sciences* 117, 16678.

22 Felnhofer, A., Kothgassner, O.D., Schmidt, M., Heinzle, A.-K., Beutl, L., Hlavacs, H., Kryspin-Exner, I., 2015.  
23 Is virtual reality emotionally arousing? Investigating five emotion inducing virtual park scenarios. *Int. J. Hum.*  
24 *Comput. Stud.* 82, 48-56.

25 Fliessbach, K., Trautner, P., Quesada, C.M., Elger, C.E., Weber, B., 2007. Cerebellar contributions to episodic  
26 memory encoding as revealed by fMRI. *Neuroimage* 35, 1330-1337.

27 Forlim, C.G., Bittner, L., Mostajeran, F., Steinicke, F., Gallinat, J., Kühn, S., 2019. Stereoscopic Rendering via  
28 Goggles Elicits Higher Functional Connectivity During Virtual Reality Gaming. *Front. Hum. Neurosci.* 13, 365-  
29 365.

30 Freeman, D., Pugh, K., Antley, A., Slater, M., Bebbington, P., Gittins, M., Dunn, G., Kuipers, E., Fowler, D.,  
31 Garety, P., 2008. Virtual reality study of paranoid thinking in the general population. *Br. J. Psychiatry* 192, 258-  
32 263.

33 Fuchs, P., 2017. *Virtual Reality Headsets - A Theoretical and Pragmatic Approach*, 1st ed. ed. CRC Press.

34 Fuchs, P., Moreau, G., Guitton, P., 2011. *Virtual Reality: Concepts and Technologies*.

35 Gallagher, S., 2000. Philosophical conceptions of the self: implications for cognitive science. *Trends Cogn. Sci.*  
36 4, 14-21.

37 Gauthier, B., Brechet, L., Lance, F., Mange, R., Herbelin, B., Faivre, N., Bolton, T.A.W., Van De Ville, D.,  
38 Blanke, O., 2020. First-person body view modulates the neural substrates of episodic memory and autonoetic  
39 consciousness: A functional connectivity study. *Neuroimage* 223.

40 Gilat, M., Bell, P.T., Ehgoetz Martens, K.A., Georgiades, M.J., Hall, J.M., Walton, C.C., Lewis, S.J.G., Shine,  
41 J.M., 2017. Dopamine depletion impairs gait automaticity by altering cortico-striatal and cerebellar processing in  
42 Parkinson's disease. *Neuroimage* 152, 207-220.

43 Gilat, M., Dijkstra, B.W., D'Cruz, N., Nieuwboer, A., Lewis, S.J.G., 2019. Functional MRI to Study Gait  
44 Impairment in Parkinson's Disease: a Systematic Review and Exploratory ALE Meta-Analysis. *Curr. Neurol.*  
45 *Neurosci. Rep.* 19, 49.

46 Glenn, D.E., Risbrough, V.B., Simmons, A.N., Acheson, D.T., Stout, D.M., 2018. The Future of Contextual Fear  
47 Learning for PTSD Research: A Methodological Review of Neuroimaging Studies. *Curr. Top. Behav. Neurosci.*  
48 38, 207-228.

49 Gomez, A., Cerles, M., Rousset, S., Rémy, C., Baciú, M., 2014. Differential hippocampal and retrosplenial  
50 involvement in egocentric-updating, rotation, and allocentric processing during online spatial encoding: an fMRI  
51 study. *Front. Hum. Neurosci.* 8, 150.

52 Graham, S.J., Quintin, G., Mraz, R., Hong, J., Zakzanis, K.K., 2003. Combining virtual reality experiments with  
53 functional magnetic resonance imaging: Initial work assessing human spatial navigation. *Annual Review of*  
54 *CyberTherapy and Telemedicine* 1, 83-97.

55 Hartley, T., Maguire, E.A., Spiers, H.J., Burgess, N., 2003. The well-worn route and the path less traveled:  
56 Distinct neural bases of route following and wayfinding in humans. *Neuron* 37, 877-888.

57 Hejtmanek, L., Starrett, M., Ferrer, E., Ekstrom, A.D., 2020. How Much of What We Learn in Virtual Reality  
58 Transfers to Real-World Navigation? *Multisens Res* 33, 479-503.

59 Herold, F., Orłowski, K., Börmel, S., Müller, N.G., 2017. Cortical activation during balancing on a balance  
60 board. *Hum Mov Sci* 51, 51-58.

1 Hertweck, S., Weber, D., Alwanni, H., Unruh, F., Fischbach, M., Latoschik, M., Ball, T., 2019. Brain Activity in  
2 Virtual Reality: Assessing Signal Quality of High-Resolution EEG While Using Head-Mounted Displays.  
3 Hinderaker, M., Sylcott, B., Williams, K., Lin, C.C., 2020. Aging Affects the Ability to Process the Optic Flow  
4 Stimulations: A Functional Near-Infrared Spectrometry Study. *J Mot Behav* 52, 466-473.  
5 Hoffman, H.G., Richards, T.L., Coda, B., Bills, A.R., Blough, D., Richards, A.L., Sharar, S.R., 2004.  
6 Modulation of thermal pain-related brain activity with virtual reality: evidence from fMRI. *Neuroreport* 15,  
7 1245-1248.  
8 Hoppes, C.W., Sparto, P.J., Whitney, S.L., Furman, J.M., Huppert, T.J., 2018. Functional near-infrared  
9 spectroscopy during optic flow with and without fixation. *PLoS One* 13, e0193710.  
10 Hudak, J., Blume, F., Dresler, T., Haeussinger, F.B., Renner, T.J., Fallgatter, A.J., Gawrilow, C., Ehlis, A.C.,  
11 2017. Near-Infrared Spectroscopy-Based Frontal Lobe Neurofeedback Integrated in Virtual Reality Modulates  
12 Brain and Behavior in Highly Impulsive Adults. *Front. Hum. Neurosci.* 11, 425.  
13 Huffman, D.J., Ekstrom, A.D., 2019. A Modality-Independent Network Underlies the Retrieval of Large-Scale  
14 Spatial Environments in the Human Brain. *Neuron* 104, 611-622.e617.  
15 Iglói, K., Doeller, C.F., Paradis, A.L., Benchenane, K., Berthoz, A., Burgess, N., Rondi-Reig, L., 2015.  
16 Interaction Between Hippocampus and Cerebellum Crus I in Sequence-Based but not Place-Based Navigation.  
17 *Cereb. Cortex* 25, 4146-4154.  
18 Ionta, S., Heydrich, L., Lenggenhager, B., Mouthon, M., Fornari, E., Chapuis, D., Gassert, R., Blanke, O., 2011.  
19 Multisensory mechanisms in temporo-parietal cortex support self-location and first-person perspective. *Neuron*  
20 70, 363-374.  
21 Ito, M., 2008. Control of mental activities by internal models in the cerebellum. *Nat. Rev. Neurosci.* 9, 304-313.  
22 Javadi, A.-H., Patai, E.Z., Marin-Garcia, E., Margolis, A., Tan, H.-R.M., Kumaran, D., Nardini, M., Penny, W.,  
23 Duzel, E., Dayan, P., Spiers, H.J., 2019. Prefrontal Dynamics Associated with Efficient Detours and Shortcuts:  
24 A Combined Functional Magnetic Resonance Imaging and Magnetoencephalography Study. *J. Cogn. Neurosci.*  
25 31, 1227-1247.  
26 Jebara, N., Orriols, E., Zaoui, M., Berthoz, A., Piolino, P., 2014. Effects of enactment in episodic memory: a  
27 pilot virtual reality study with young and elderly adults. *Front. Aging Neurosci.* 6, 338.  
28 Ju, U., Wallraven, C., 2019. Manipulating and decoding subjective gaming experience during active gameplay: a  
29 multivariate, whole-brain analysis. *Neuroimage* 188, 1-13.  
30 Kalpouzos, G., Eriksson, J., Sjölie, D., Molin, J., Nyberg, L., 2010. Neurocognitive systems related to real-world  
31 prospective memory. *PLoS One* 5, e13304-e13304.  
32 Kawato, M., Ohmae, S., Hoang, H., Sanger, T., 2021. 50 Years Since the Marr, Ito, and Albus Models of the  
33 Cerebellum. *Neuroscience* 462, 151-174.  
34 Kellmeyer, P., 2018. Neurophilosophical and Ethical Aspects of Virtual Reality Therapy in Neurology and  
35 Psychiatry. *Camb. Q. Healthc. Ethics* 27, 610-627.  
36 Kilteni, K., Groten, R., Slater, M., 2012. The Sense of Embodiment in Virtual Reality. *Presence Teleoperators*  
37 *& Virtual Environments* 21.  
38 Kim, H., 2018. Parietal control network activation during memory tasks may be associated with the co-  
39 occurrence of externally and internally directed cognition: A cross-function meta-analysis. *Brain Res.* 1683, 55-  
40 66.  
41 Kirlic, N., Aupperle, R.L., Misaki, M., Kuplicki, R., Alvarez, R.P., 2017. Recruitment of orbitofrontal cortex  
42 during unpredictable threat among adults at risk for affective disorders. *Brain Behav* 7, e00757-e00757.  
43 Klein, S.B., 2012. Self, memory, and the self-reference effect: an examination of conceptual and methodological  
44 issues. *Pers. Soc. Psychol. Rev.* 16, 283-300.  
45 Knight, R.G., Titov, N., 2009. Use of Virtual Reality Tasks to Assess Prospective Memory: Applicability and  
46 Evidence. *Brain Impair.* 10, 3-13.  
47 Kopelman, M.D., Wilson, B.A., Baddeley, A.D., 1989. The autobiographical memory interview: a new  
48 assessment of autobiographical and personal semantic memory in amnesic patients. *J. Clin. Exp. Neuropsychol.*  
49 11, 724-744.  
50 Kourtesis, P., Collina, S., Dumas, L.A.A., MacPherson, S.E., 2019. Validation of the Virtual Reality  
51 Neuroscience Questionnaire: Maximum Duration of Immersive Virtual Reality Sessions Without the Presence of  
52 Pertinent Adverse Symptomatology. *Front. Hum. Neurosci.* 13.  
53 Ku, J., Mraz, R., Baker, N., Zakzanis, K., Lee, J., Kim, I., Kim, S., Graham, S., 2003. A Data Glove with Tactile  
54 Feedback for fMRI of Virtual Reality Experiments. *Cyberpsychology & behavior : the impact of the Internet,*  
55 *multimedia and virtual reality on behavior and society* 6, 497-508.  
56 La Corte, V., Ferrieux, S., Abram, M., Bertrand, A., Dubois, B., Teichmann, M., Piolino, P., 2021. The role of  
57 semantic memory in prospective memory and episodic future thinking: new insights from a case of semantic  
58 dementia. *Memory* 29, 943-962.  
59 La Corte, V., Spereduti, M., Abichou, K., Piolino, P., 2019. Episodic Memory Assessment and Remediation in  
60 Normal and Pathological Aging Using Virtual Reality: A Mini Review. *Front. Psychol.* 10, 173.

1 Landowska, A., Roberts, D., Eachus, P., Barrett, A., 2018. Within- and Between-Session Prefrontal Cortex  
2 Response to Virtual Reality Exposure Therapy for Acrophobia. *Front. Hum. Neurosci.* 12, 362.

3 Lecouvey, G., Morand, A., Gonneaud, J., Piolino, P., Orriols, E., Pélerin, A., Ferreira Da Silva, L., de La  
4 Sayette, V., Eustache, F., Desgranges, B., 2019. An Impairment of Prospective Memory in Mild Alzheimer's  
5 Disease: A Ride in a Virtual Town. *Front. Psychol.* 10, 241-241.

6 Lee, C.-H., Ryu, J., Lee, S.-H., Kim, H., Lee, I., 2016. Functional cross-hemispheric shift between object-place  
7 paired associate memory and spatial memory in the human hippocampus. *Hippocampus* 26, 1061-1077.

8 Lee, J.-H., Lim, Y., Wiederhold, B.K., Graham, S.J., 2005. A Functional Magnetic Resonance Imaging (fMRI)  
9 Study of Cue-Induced Smoking Craving in Virtual Environments. *Appl. Psychophysiol. Biofeedback* 30, 195-  
10 204.

11 Limanowski, J., Blankenburg, F., 2017. Posterior parietal cortex evaluates visuoproprioceptive congruence based  
12 on brief visual information. *Sci. Rep.* 7, 16659-16659.

13 Limanowski, J., Kirilina, E., Blankenburg, F., 2017. Neuronal correlates of continuous manual tracking under  
14 varying visual movement feedback in a virtual reality environment. *Neuroimage* 146, 81-89.

15 Limanowski, J., Litvak, V., Friston, K., 2020. Cortical beta oscillations reflect the contextual gating of visual  
16 action feedback. *Neuroimage* 222, 117267.

17 Lorenzetti, V., Melo, B., Basílio, R., Suo, C., Yücel, M., Tierra-Criollo, C.J., Moll, J., 2018. Emotion Regulation  
18 Using Virtual Environments and Real-Time fMRI Neurofeedback. *Front. Neurol.* 9.

19 Magosso, E., De Crescenzo, F., Ricci, G., Piastra, S., Ursino, M., 2019. EEG Alpha Power Is Modulated by  
20 Attentional Changes during Cognitive Tasks and Virtual Reality Immersion. *Comput. Intell. Neurosci.* 2019,  
21 7051079.

22 Maguire, E.A., Burgess, N., Donnett, J.G., Frackowiak, R.S., Frith, C.D., O'Keefe, J., 1998. Knowing where and  
23 getting there: a human navigation network. *Science* 280, 921-924.

24 Maidan, I., Nieuwhof, F., Bernad-Elazari, H., Bloem, B.R., Giladi, N., Hausdorff, J.M., Claassen, J., Mirelman,  
25 A., 2018. Evidence for Differential Effects of 2 Forms of Exercise on Prefrontal Plasticity During Walking in  
26 Parkinson's Disease. *Neurorehabil. Neural Repair* 32, 200-208.

27 Makowski, D., Sperduti, M., Nicolas, S., Piolino, P., 2017. "Being there" and remembering it: Presence  
28 improves memory encoding. *Conscious. Cogn.* 53, 194-202.

29 Manuweera, T., Yarossi, M., Adamovich, S., Tunik, E., 2019. Parietal Activation Associated With Target-  
30 Directed Right Hand Movement Is Lateralized by Mirror Feedback to the Ipsilateral Hemisphere. *Front. Hum.*  
31 *Neurosci.* 12, 531-531.

32 Marín-Morales, J., Higuera-Trujillo, J.L., Greco, A., Guixeres, J., Llinares, C., Gentili, C., Scilingo, E.P.,  
33 Alcañiz, M., Valenza, G., 2019. Real vs. immersive-virtual emotional experience: Analysis of psycho-  
34 physiological patterns in a free exploration of an art museum. *PLoS One* 14, e0223881.

35 Martinelli, P., Sperduti, M., Piolino, P., 2013. Neural substrates of the self-memory system: new insights from a  
36 meta-analysis. *Hum. Brain Mapp.* 34, 1515-1529.

37 Matar, E., Shine, J.M., Gilat, M., Ehgoetz Martens, K.A., Ward, P.B., Frank, M.J., Moustafa, A.A., Naismith,  
38 S.L., Lewis, S.J.G., 2019. Identifying the neural correlates of doorway freezing in Parkinson's disease. *Hum.*  
39 *Brain Mapp.* 40, 2055-2064.

40 Mesmoudi, S., Rodic, M., Cioli, C., Cointet, J.P., Yarkoni, T., Burnod, Y., 2015. LinkRbrain: multi-scale data  
41 integrator of the brain. *J. Neurosci. Methods* 241, 44-52.

42 Migo, E.M., O'Daly, O., Mitterschiffthaler, M., Antonova, E., Dawson, G.R., Dourish, C.T., Craig, K.J.,  
43 Simmons, A., Wilcock, G.K., McCulloch, E., Jackson, S.H., Kopelman, M.D., Williams, S.C., Morris, R.G.,  
44 2016. Investigating virtual reality navigation in amnesic mild cognitive impairment using fMRI. *Neuropsychol.*  
45 *Dev. Cogn. B Aging Neuropsychol. Cogn.* 23, 196-217.

46 Miller, T.D., Chong, T.T., Aimola Davies, A.M., Johnson, M.R., Irani, S.R., Husain, M., Ng, T.W., Jacob, S.,  
47 Maddison, P., Kennard, C., Gowland, P.A., Rosenthal, C.R., 2020. Human hippocampal CA3 damage disrupts  
48 both recent and remote episodic memories. *Elife* 9.

49 Milton, F., Muhlert, N., Butler, C.R., Smith, A., Benattayallah, A., Zeman, A.Z., 2011. An fMRI study of long-  
50 term everyday memory using SenseCam. *Memory* 19, 733-744.

51 Mitchell, A.S., Czajkowski, R., Zhang, N., Jeffery, K., Nelson, A.J.D., 2018. Retrosplenial cortex and its role in  
52 spatial cognition. *Brain and Neuroscience Advances* 2, 2398212818757098.

53 Modroño, C., Bermúdez, S., Cameirão, M., Pereira, F., Paulino, T., Marcano, F., Hernández-Martín, E., Plata-  
54 Bello, J., Palenzuela, N., Núñez-Pádrón, D., Pérez-González, J.M., González-Mora, J.L., 2019. Is it necessary to  
55 show virtual limbs in action observation neurorehabilitation systems? *J Rehabil Assist Technol Eng* 6,  
56 2055668319859140-2055668319859140.

57 Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Preferred reporting items for systematic reviews and  
58 meta-analyses: the PRISMA statement. *PLoS Med.* 6, e1000097.

1 Morgan, C.J.A., Dodds, C.M., Furby, H., Pepper, F., Fam, J., Freeman, T.P., Hughes, E., Doeller, C., King, J.,  
2 Howes, O., Stone, J.M., 2014. Long-term heavy ketamine use is associated with spatial memory impairment and  
3 altered hippocampal activation. *Frontiers in Psychiatry* 5.

4 Morina, N., Ijntema, H., Meyerbröcker, K., Emmelkamp, P.M., 2015. Can virtual reality exposure therapy gains  
5 be generalized to real-life? A meta-analysis of studies applying behavioral assessments. *Behav. Res. Ther.* 74,  
6 18-24.

7 Moscovitch, M., Cabeza, R., Winocur, G., Nadel, L., 2016. Episodic Memory and Beyond: The Hippocampus  
8 and Neocortex in Transformation. *Annu. Rev. Psychol.* 67, 105-134.

9 Moscovitch, M., Rosenbaum, R.S., Gilboa, A., Addis, D.R., Westmacott, R., Grady, C., McAndrews, M.P.,  
10 Levine, B., Black, S., Winocur, G., Nadel, L., 2005. Functional neuroanatomy of remote episodic, semantic and  
11 spatial memory: a unified account based on multiple trace theory. *J. Anat.* 207, 35-66.

12 Mueller, C., Luehrs, M., Baecke, S., Adolf, D., Luetzkendorf, R., Luchtman, M., Bernarding, J., 2012. Building  
13 virtual reality fMRI paradigms: a framework for presenting immersive virtual environments. *J. Neurosci.*  
14 *Methods* 209, 290-298.

15 Nau, M., Schroder, T.N., Frey, M., Doeller, C.F., 2020. Behavior-dependent directional tuning in the human  
16 visual-navigation network. *Nature Communications* 11.

17 Neğu, A., Matu, S.A., Sava, F.A., David, D., 2016. Virtual reality measures in neuropsychological assessment: a  
18 meta-analytic review. *Clin. Neuropsychol.* 30, 165-184.

19 Neisser, U., 1976. *Cognitive Psychology*. (Book Reviews: Cognition and Reality. Principles and Implications of  
20 *Cognitive Psychology*). Science.

21 Northoff, G., Heinzel, A., de Greck, M., Bermpohl, F., Dobrowolny, H., Panksepp, J., 2006. Self-referential  
22 processing in our brain--a meta-analysis of imaging studies on the self. *Neuroimage* 31, 440-457.

23 O'Keefe, J., Nadel, L., 1979. Précis of O'Keefe & Nadel's *The hippocampus as a cognitive map*. *Behav.*  
24 *Brain Sci.* 2, 487-494.

25 Oddo, S., Lux, S., Weiss, P.H., Schwab, A., Welzer, H., Markowitsch, H.J., Fink, G.R., 2010. Specific role of  
26 medial prefrontal cortex in retrieving recent autobiographical memories: an fMRI study of young female  
27 subjects. *Cortex* 46, 29-39.

28 Parslow, D.M., Rose, D., Brooks, B., Fleminger, S., Gray, J.A., Giampietro, V., Brammer, M.J., Williams, S.,  
29 Gasston, D., Andrew, C., Vythelingum, G.N., Loannou, G., Simmons, A., Morris, R.G., 2004. Allocentric spatial  
30 memory activation of the hippocampal formation measured with fMRI. *Neuropsychology* 18, 450-461.

31 Parsons, T., 2015. *Virtual Reality for Enhanced Ecological Validity and Experimental Control in the Clinical,*  
32 *Affective, and Social Neurosciences*. *Front. Hum. Neurosci.* 9.

33 Parsons, T., McMahan, T., Kane, R., 2017. Practice parameters facilitating adoption of advanced technologies  
34 for enhancing neuropsychological assessment paradigms. *The Clinical Neuropsychologist* 32, 1-26.

35 Peñate, W., Rivero, F., Viña, C., Herrero, M., Betancort, M., De la Fuente, J., Álvarez-Pérez, Y., Fumero, A.,  
36 2019. The Equivalence between Virtual and Real Feared Stimuli in a Phobic Adult Sample: A Neuroimaging  
37 Study. *Journal of clinical medicine* 8, 2139.

38 Picard, L., Abram, M., Orriols, E., Piolino, P., 2015. Virtual reality as an ecologically valid tool for assessing  
39 multifaceted episodic memory in children and adolescents. *International Journal of Behavioral Development*.

40 Piolino, P., Desgranges, B., Eustache, F., 2009. Episodic autobiographical memories over the course of time:  
41 cognitive, neuropsychological and neuroimaging findings. *Neuropsychologia* 47, 2314-2329.

42 Plancher, G., Gyselinck, V., Nicolas, S., Piolino, P., 2010. Age effect on components of episodic memory and  
43 feature binding: A virtual reality study. *Neuropsychology* 24, 379-390.

44 Plancher, G., Gyselinck, V., Piolino, P., 2018. The Integration of Realistic Episodic Memories Relies on  
45 Different Working Memory Processes: Evidence from Virtual Navigation. *Front. Psychol.* 9, 47.

46 Plancher, G., Piolino, P., 2017. *Virtual Reality for Assessment of Episodic Memory in Normal and Pathological*  
47 *Aging*.

48 Plancher, G., Tirard, A., Gyselinck, V., Nicolas, S., Piolino, P., 2012. Using virtual reality to characterize  
49 episodic memory profiles in amnesic mild cognitive impairment and Alzheimer's disease: influence of active  
50 and passive encoding. *Neuropsychologia* 50, 592-602.

51 Preston, A.R., Eichenbaum, H., 2013. Interplay of hippocampus and prefrontal cortex in memory. *Curr. Biol.* 23,  
52 R764-773.

53 Pu, Y., Cornwell, B.R., Cheyne, D., Johnson, B.W., 2017. The functional role of human right  
54 hippocampal/parahippocampal theta rhythm in environmental encoding during virtual spatial navigation. *Hum.*  
55 *Brain Mapp.* 38, 1347-1361.

56 Pu, Y., Cornwell, B.R., Cheyne, D., Johnson, B.W., 2018. High-gamma activity in the human hippocampus and  
57 parahippocampus during inter-trial rest periods of a virtual navigation task. *Neuroimage* 178, 92-103.

58 Putze, F., Herff, C., Tremmel, C., Schultz, T., Krusienski, D.J., 2019. Decoding Mental Workload in Virtual  
59 Environments: A fNIRS Study using an Immersive n-back Task. *Annu Int Conf IEEE Eng Med Biol Soc* 2019,  
60 3103-3106.

1 Regenbrecht, H.T., Schubert, T.W., Friedmann, F., 1998. Measuring the Sense of Presence and its Relations to  
2 Fear of Heights in Virtual Environments. *International Journal of Human-Computer Interaction* 10, 233-249.

3 Reggente, N., Essoe, J.K.-Y., Aghajan, Z.M., Tavakoli, A.V., McGuire, J.F., Suthana, N.A., Rissman, J., 2018.  
4 Enhancing the Ecological Validity of fMRI Memory Research Using Virtual Reality. *Front. Neurosci.* 12.

5 Reggente, N., Essoe, J.K.Y., Baek, H.Y., Rissman, J., 2020. The Method of Loci in Virtual Reality: Explicit  
6 Binding of Objects to Spatial Contexts Enhances Subsequent Memory Recall. *Journal of Cognitive Enhancement*  
7 4, 12-30.

8 Regian, J.W., Yadrick, R.M., 1994. Assessment of configurational knowledge of naturally- and artificially-  
9 acquired large-scale space. *J. Environ. Psychol.* 14, 211-223.

10 Renoult, L., Tanguay, A., Beaudry, M., Tavakoli, P., Rabipour, S., Campbell, K., Moscovitch, M., Levine, B.,  
11 Davidson, P.S.R., 2016. Personal semantics: Is it distinct from episodic and semantic memory? An  
12 electrophysiological study of memory for autobiographical facts and repeated events in honor of Shlomo Bentin.  
13 *Neuropsychologia* 83, 242-256.

14 Riccelli, R., Passamonti, L., Toschi, N., Nigro, S., Chiarella, G., Petrolo, C., Lacquaniti, F., Staab, J.P., Indovina,  
15 I., 2017. Altered Insular and Occipital Responses to Simulated Vertical Self-Motion in Patients with Persistent  
16 Postural-Perceptual Dizziness. *Front. Neurol.* 8, 529-529.

17 Rissman, J., Chow, T.E., Reggente, N., Wagner, A.D., 2016. Decoding fMRI Signatures of Real-world  
18 Autobiographical Memory Retrieval. *J. Cogn. Neurosci.* 28, 604-620.

19 Riva, G., 2005. Virtual Reality in Psychotherapy: Review. *CyberPsychology & Behavior* 8, 220-230.

20 Rizzo, A., Schultheis, M., Kerns, K., Mateer, C., 2004. Analysis of assets for virtual reality applications in  
21 neuropsychology. *Neuropsychological Rehabilitation - NEUROPSYCHOL REHABIL* 14, 207-239.

22 Roberts, G., Holmes, N., Alexander, N., Boto, E., Leggett, J., Hill, R.M., Shah, V., Rea, M., Vaughan, R.,  
23 Maguire, E.A., Kessler, K., Beebe, S., Fromhold, M., Barnes, G.R., Bowtell, R., Brookes, M.J., 2019. Towards  
24 OPM-MEG in a virtual reality environment. *Neuroimage* 199, 408-417.

25 Robin, J., 2018. Spatial scaffold effects in event memory and imagination. *Wiley Interdiscip. Rev. Cogn. Sci.* 9,  
26 e1462.

27 Rosenbaum, R.S., Köhler, S., Schacter, D.L., Moscovitch, M., Westmacott, R., Black, S.E., Gao, F., Tulving, E.,  
28 2005. The case of K.C.: contributions of a memory-impaired person to memory theory. *Neuropsychologia* 43,  
29 989-1021.

30 Rosenbaum, R.S., Priselac, S., Köhler, S., Black, S.E., Gao, F., Nadel, L., Moscovitch, M., 2000. Remote spatial  
31 memory in an amnesic person with extensive bilateral hippocampal lesions. *Nat. Neurosci.* 3, 1044-1048.

32 Rugg, M.D., King, D.R., 2018. Ventral lateral parietal cortex and episodic memory retrieval. *Cortex* 107, 238-  
33 250.

34 Saleh, S., Yarossi, M., Manuweera, T., Adamovich, S., Tunik, E., 2016. Network interactions underlying mirror  
35 feedback in stroke: A dynamic causal modeling study. *Neuroimage Clin* 13, 46-54.

36 Salgado-Pineda, P., Landin-Romero, R., Portillo, F., Bosque, C., Pomes, A., Spanlang, B., Franquelo, J.C.,  
37 Teixido, C., Sarró, S., Salvador, R., Slater, M., Pomarol-Clotet, E., McKenna, P.J., 2016. Examining  
38 hippocampal function in schizophrenia using a virtual reality spatial navigation task. *Schizophr. Res.* 172, 86-93.

39 Sanchez-Vives, M.V., Slater, M., 2005. From presence to consciousness through virtual reality. *Nature Reviews*  
40 *Neuroscience* 6, 332-339.

41 Scheunemann, J., Unni, A., Ihme, K., Jipp, M., Rieger, J.W., 2018. Demonstrating Brain-Level Interactions  
42 Between Visuospatial Attentional Demands and Working Memory Load While Driving Using Functional Near-  
43 Infrared Spectroscopy. *Front. Hum. Neurosci.* 12, 542.

44 Schinazi, V.R., Epstein, R.A., 2010. Neural correlates of real-world route learning. *Neuroimage* 53, 725-735.

45 Serino, S., Mestre, D., Mallet, P., Pergandi, J.-M., Cipresso, P., Riva, G., 2015. Do not get lost in translation:  
46 The role of egocentric heading in spatial orientation. *Neurosci. Lett.* 602.

47 Serino, S., Pedrolí, E., Tuena, C., De Leo, G., Stramba-Badiale, M., Goulene, K., Mariotti, N.G., Riva, G., 2017.  
48 A Novel Virtual Reality-Based Training Protocol for the Enhancement of the "Mental Frame Syncing" in  
49 Individuals with Alzheimer's Disease: A Development-of-Concept Trial. *Front. Aging Neurosci.* 9, 240-240.

50 Serino, S., Repetto, C., 2018. New Trends in Episodic Memory Assessment: Immersive 360° Ecological Videos.  
51 *Front. Psychol.* 9.

52 Shamay-Tsoory, S.G., Mendelsohn, A., 2019. Real-Life Neuroscience: An Ecological Approach to Brain and  
53 Behavior Research. *Perspect. Psychol. Sci.* 14, 841-859.

54 Sharples, S., Cobb, S., Moody, A., Wilson, J.R., 2008. Virtual reality induced symptoms and effects (VRISE):  
55 Comparison of head mounted display (HMD), desktop and projection display systems. *Displays* 29, 58-69.

56 Shine, J.M., Matar, E., Bolitho, S.J., Dilda, V., Morris, T.R., Naismith, S.L., Moore, S.T., Lewis, S.J.G., 2013a.  
57 Modeling freezing of gait in Parkinson's disease with a virtual reality paradigm. *Gait Posture* 38, 104-108.

58 Shine, J.M., Matar, E., Ward, P., Bolitho, S., Pearson, M., Naismith, S., Lewis, S., 2013b. Differential Neural  
59 Activation Patterns in Patients with Parkinson's Disease and Freezing of Gait in Response to Concurrent  
60 Cognitive and Motor Load. *PLoS One* 8, e52602.

1 Siemerikus, J., Irle, E., Schmidt-Samoa, C., Dechent, P., Weniger, G., 2012. Egocentric spatial learning in  
2 schizophrenia investigated with functional magnetic resonance imaging. *Neuroimage Clin* 1, 153-163.

3 Skouras, S., Torner, J., Andersson, P., Koush, Y., Falcon, C., Minguillon, C., Fauria, K., Alpiste, F., Blenow, K.,  
4 Zetterberg, H., Gisbert, J.D., Molinuevo, J.L., 2020. Earliest amyloid and tau deposition modulate the influence  
5 of limbic networks during closed-loop hippocampal downregulation. *Brain* 143, 976-992.

6 Slobounov, S., Ray, W., Johnson, B., Slobounov, E., Newell, K.M., 2015. Modulation of cortical activity in 2D  
7 versus 3D virtual reality environments: An EEG study. *Int. J. Psychophysiol.* 95, 254-260.

8 Slobounov, S., Wu, T., Hallett, M., Shibasaki, H., Slobounov, E., Newell, K., 2006. Neural underpinning of  
9 postural responses to visual field motion. *Biol. Psychol.* 72, 188-197.

10 Slobounov, S., Zhang, K., Pennell, D., Ray, W., Johnson, B., Sebastianelli, W., 2010. Functional abnormalities  
11 in normally appearing athletes following mild traumatic brain injury: A functional MRI study. *Exp. Brain Res.*  
12 202, 341-354.

13 Smith, D.M., Miller, A.M.P., Vedder, L.C., 2018. The retrosplenial cortical role in encoding behaviorally  
14 significant cues. *Behav. Neurosci.* 132, 356-365.

15 Smith, S.A., 2019. Virtual reality in episodic memory research: A review. *Psychonomic Bulletin & Review* 26,  
16 1213-1237.

17 Sonkusare, S., Breakspear, M., Guo, C., 2019. Naturalistic Stimuli in Neuroscience: Critically Acclaimed.  
18 *Trends Cogn. Sci.* 23, 699-714.

19 Steel, A., Robertson, C.E., Taube, J.S., 2020. Current Promises and Limitations of Combined Virtual Reality and  
20 Functional Magnetic Resonance Imaging Research in Humans: A Commentary on Huffman and Ekstrom (2019).  
21 *J. Cogn. Neurosci.*, 1-8.

22 Steemers, B., Vicente-Grabovetsky, A., Barry, C., Smulders, P., Schröder, T.N., Burgess, N., Doeller, C.F.,  
23 2016. Hippocampal Attractor Dynamics Predict Memory-Based Decision Making. *Curr. Biol.* 26, 1750-1757.

24 Steinisch, M., Tana, M., Comani, S., 2013. A Post-Stroke Rehabilitation System Integrating Robotics, VR and  
25 High-Resolution EEG Imaging. *IEEE transactions on neural systems and rehabilitation engineering* : a  
26 publication of the IEEE Engineering in Medicine and Biology Society 21.

27 Stojan, R., Voelcker-Rehage, C., 2020. Neurophysiological correlates of age differences in driving behavior  
28 during concurrent subtask performance. *Neuroimage* 225, 117492.

29 Sulpizio, V., Committeri, G., Lambrey, S., Berthoz, A., Galati, G., 2016. Role of the human retrosplenial  
30 cortex/parieto-occipital sulcus in perspective priming. *Neuroimage* 125, 108-119.

31 Summerfield, J.J., Hassabis, D., Maguire, E.A., 2009. Cortical midline involvement in autobiographical  
32 memory. *Neuroimage* 44, 1188-1200.

33 Suthana, N., Ekstrom, A., Moshirvaziri, S., Knowlton, B., Bookheimer, S., 2011. Dissociations within human  
34 hippocampal subregions during encoding and retrieval of spatial information. *Hippocampus* 21, 694-701.

35 Sutton, J.E., Joannisse, M.F., Newcombe, N.S., 2010. Spinning in the Scanner: Neural Correlates of Virtual  
36 Reorientation. *Journal of Experimental Psychology-Learning Memory and Cognition* 36, 1097-1107.

37 Szpunar, K.K., Spreng, R.N., Schacter, D.L., 2014. A taxonomy of prospection: Introducing an organizational  
38 framework for future-oriented cognition. *Proceedings of the National Academy of Sciences* 111, 18414.

39 Tarrant, J., Viczko, J., Cope, H., 2018. Virtual Reality for Anxiety Reduction Demonstrated by Quantitative  
40 EEG: A Pilot Study. *Front. Psychol.* 9.

41 Tau, G.Z., Marsh, R., Wang, Z., Torres-Sanchez, T., Graniello, B., Hao, X., Xu, D., Packard, M.G., Duan, Y.,  
42 Kangarlu, A., Martinez, D., Peterson, B.S., 2014. Neural Correlates of Reward-Based Spatial Learning in  
43 Persons with Cocaine Dependence. *Neuropsychopharmacology* 39, 545-555.

44 Taube, J.S., Valerio, S., Yoder, R.M., 2013. Is Navigation in Virtual Reality with fMRI Really Navigation? *J.*  
45 *Cogn. Neurosci.* 25, 1008-1019.

46 Tremmel, C., Herff, C., Sato, T., Rechowicz, K., Yamani, Y., Krusienski, D.J., 2019. Estimating Cognitive  
47 Workload in an Interactive Virtual Reality Environment Using EEG. *Front. Hum. Neurosci.* 13.

48 Tromp, J., Peeters, D., Meyer, A.S., Hagoort, P., 2018. The combined use of virtual reality and EEG to study  
49 language processing in naturalistic environments. *Behav. Res. Methods* 50, 862-869.

50 Tsakiris, M., 2010. My body in the brain: a neurocognitive model of body-ownership. *Neuropsychologia* 48,  
51 703-712.

52 Tuena, C., Malighetti, C., Chirico, A., Serino, S., Di Lernia, D., Muratore, M., Pedrolì, E., Cipresso, P., Setti, A.,  
53 Repetto, C., Riva, G., 2020. Exploring the impact of multisensory integration and episodic memory with  
54 machine learning: a proof-of-concept study in anorexia nervosa.

55 Tuena, C., Serino, S., Dutriaux, L., Riva, G., Piolino, P., 2019. Virtual Enactment Effect on Memory in Young  
56 and Aged Populations: A Systematic Review. *Journal of Clinical Medicine* 8.

57 Tuena, C., Serino, S., Gaston-Bellegarde, A., Orriols, E., Makowski, D., Riva, G., Piolino, P., 2017. How virtual  
58 embodiment affects episodic memory functioning: a proof-of-concept study. *Annu. Rev. Cyberther. Telemed* 15,  
59 98-103.

1 Tulving, E., 1972. Episodic and semantic memory, *Organization of memory*. Academic Press, Oxford, England,  
2 pp. xiii, 423-xiii, 423.

3 Tulving, E., 1985. Memory and consciousness. *Can. Psychol.* 26, 1-12.

4 Tulving, E., 2002. Episodic Memory: From Mind to Brain. *Annu. Rev. Psychol.* 53, 1-25.

5 Tulving, E., Markowitsch, H.J., 1998. Episodic and declarative memory: role of the hippocampus. *Hippocampus*  
6 8, 198-204.

7 Valladares-Rodríguez, S., Pérez-Rodríguez, R., Anido-Rifón, L., Fernández-Iglesias, M., 2016. Trends on the  
8 application of serious games to neuropsychological evaluation: A scoping review. *J. Biomed. Inform.* 64, 296-  
9 319.

10 Vourvopoulos, A., Jorge, C., Abreu, R., Figueiredo, P., Fernandes, J.-C., Bermúdez i Badia, S., 2019. Efficacy  
11 and Brain Imaging Correlates of an Immersive Motor Imagery BCI-Driven VR System for Upper Limb Motor  
12 Rehabilitation: A Clinical Case Report. *Front. Hum. Neurosci.* 13.

13 Weniger, G., Ruhleder, M., Lange, C., Wolf, S., Irle, E., 2011. Egocentric and allocentric memory as assessed by  
14 virtual reality in individuals with amnesic mild cognitive impairment. *Neuropsychologia* 49, 518-527.

15 Weniger, G., Siemerikus, J., Barke, A., Lange, C., Ruhleder, M., Sachsse, U., Schmidt-Samoa, C., Dechent, P.,  
16 Irle, E., 2013. Egocentric virtual maze learning in adult survivors of childhood abuse with dissociative disorders:  
17 Evidence from functional magnetic resonance imaging. *Psychiatry Research-Neuroimaging* 212, 116-124.

18 Weniger, G., Siemerikus, J., Schmidt-Samoa, C., Mehrlitz, M., Baudewig, J., Dechent, P., Irle, E., 2010. The  
19 human parahippocampal cortex subserves egocentric spatial learning during navigation in a virtual maze.  
20 *Neurobiol. Learn. Mem.* 93, 46-55.

21 Wiederhold, B., Wiederhold, M., 2008. Virtual reality with fMRI: A breakthrough cognitive treatment tool.  
22 *Virtual Reality* 12, 259-267.

23 Witmer, B.G., Bailey, J.H., Knerr, B., Parsons, K., 1996. Virtual spaces and real world places: transfer of route  
24 knowledge. *Int. J. Hum. Comput. Stud.* 45, 413-428.

25 Wolbers, T., Weiller, C., Buchel, C., 2004. Neural foundations of emerging route knowledge in complex spatial  
26 environments. *Cognitive Brain Research* 21, 401-411.

27 Xu, L., Wang, B., Xu, G., Wang, W., Liu, Z., Li, Z., 2017. Functional connectivity analysis using fNIRS in  
28 healthy subjects during prolonged simulated driving. *Neurosci. Lett.* 640, 21-28.

29 Yonelinas, A.P., Ranganath, C., Ekstrom, A.D., Wiltgen, B.J., 2019. A contextual binding theory of episodic  
30 memory: systems consolidation reconsidered. *Nat. Rev. Neurosci.* 20, 364-375.

31 Zilles, K., Eickhoff, S., Palomero-Gallagher, N., 2003. The human parietal cortex: a novel approach to its  
32 architectonic mapping. *Adv. Neurol.* 93, 1-21.

33

1 **TABLES & FIGURES**

2

	Natural setting	Laboratory setting	Virtual reality
Validity criteria			
Ecological validity	+++++	+	++++
Experimental control	+	++++	+++++
Transfer to daily life	+++++	+	++++
Other characteristics			
Diversity and richness of situations	+++++	++	++++
Ecological context	+++++	+	++++
Spatial & temporal context	+++++	++	++++
Multimodality	+++++	++	++++
Feeling of presence	+++++	+	++++
Interaction with the environment	+++++	+	++++
Self-reference	+++++	++	+++
Presence	+++++	+	++++

3 *Table 1: Validity criteria and main characteristics of different experimental settings: natural,*  
 4 *laboratory, virtual reality. Ranging from + (weak) to +++++ (very strong).*

5

STUDY	VR DISPLAY & HARDWARE	VR SOFTWARE	COGNITIVE FUNCTION	POPULATION	CONTROL / BASELINE
Burgess et al. (2001)	Screen and keyboard	Commercial PC video game	Retrieval of spatial context	Young, healthy, right-handed	Moving in the VE before and after the event
Ku et al. (2003)	Goggles, LCD projector, glove	WorldUp, Sense8 Inc.	Feasibility of tactile feedback	Young, healthy, right-handed	Rest periods
Hoffman et al. (2004)	VR helmet and track ball	SnowWorld	Thermal pain	Young, healthy	Black fixation cross, no sounds
Calhoun et al. (2005)	LCD projector, adapted controlled	Driving game (Need for Speed IITM, Electronic Arts 1998)	Effects of alcohol intoxication on navigation (driving)	Young, healthy, right-handed	Sober vs high or low doses of alcohol
Slobounov et al. (2006)	Mirror, response device and goniometer	Specially developed VR software	Visual field motion	Young, healthy, right-handed	Stationary virtual room
Adamovich et al. (2009)	Projector, glove	C++/OpenGI or Virtools (Dassault Systèmes, Virtools Dev 3.5, 2006)	Action observation / execution	Young, healthy, right-handed	Rest; between experimental conditions
Beck et al. (2010)	HMD, button, glove	ReactorMan software (VR toolkit ViSTA)	Spatial processing	Young, healthy, right-handed	Far vs near space, horizontal vs vertical tasks
Kalpouzos et al. (2010)	Goggles, joystick, button	Colosseum3D, Autodesk, Inc., 3ds Max	Prospective memory	Young, healthy, right-handed	Planning offset, roaming,



					animation, end
Suthana et al. (2011)	Goggles, headphones	Pyepl, Snapz Pro X, yellowcab2, edited with iMovie	Encoding and retrieval of spatial information	Young, healthy, right-handed	Control without objects of interest (city without stores)
Mueller et al. (2012)	Mirror, buttons	Autodesk, Inc., 3ds Max	Navigation	Young, healthy, right-handed	Rest (black screen)
Shine et al. (2013b)	Screen, foot pedals	Virtual Gait Laboratory	Freezing of gait in Parkinson's disease	Patients with Parkinson's disease	Rest blocks
Cyr et al. (2016)	Goggles, joystick	OpenGL	Spatial learning	Adolescents with bulimia nervosa, healthy controls	Control condition without possibility of learning
Lee et al. (2016)	Screen, button box	Unreal Development Kit, Epic Games	Spatial memory	Young, healthy, right-handed	Control trials with an object unseen during study phase
Migo et al. (2016)	Screen, goggles, trackerball	Superscape Virtual Reality software	Navigation	Patients with amnesic mild cognitive impairment, healthy controls	Resting baseline and different experimental conditions
Saleh et al. (2016)	Mirror, gloves	Virtools software	Mirror visual feedback	Patients with hemiparesis due to strokes	Rest trials, control feedback conditions
Salgado-Pineda et al. (2016)	Glasses, fibreoptic joystick	XVR framework	Schizophrenia	Schizophrenic patients and healthy controls	Control blocks (no coloured landmarks)
Sulpizio et al. (2016)	Screen and projector, buttons	3Dstudio MAX 9	Perception of perspective	Young, healthy, right-handed	Inter-trial intervals
Gilat et al. (2017)	Mirror, foot pedals	Virtual Gait Laboratory	Parkinson's disease	Patients with Parkinson's disease and healthy controls	Control "watch" (observation) block
Kirlic et al. (2017)	Screen, button pad, surface electrodes	Vizard Virtual Reality Software Toolkit	Reaction to threat	w/ first-degree mood disorder and others w/ no family history of mood disorders	Safe context, interstimulus interval
Limanowski and Blankenburg (2017)	Googles, specific design with foam pads	Blender	Evaluation of brief visual information	Young, healthy	Jittered interstimulus interval and null events
Limanowski et al. (2017)	Googles, glove	Blender	Manual tracking	Young, healthy, right-handed	Static hand vision; rest

Riccelli et al. (2017)	Googles	PsychoToolbox	Effect of simulated vertical self-motion	Patients with Persistent Postural-Perceptual Dizziness and healthy controls	First static frame
Brihmat et al. (2018)	Goggles, headphones	Presentation	Action observation, execution and imitation	Young, healthy, right-handed	Rest trials (fixation cross)
Ehgoetz Martens et al. (2018)	Mirror, foot pedals	Virtual Gait Laboratory	Freezing of gait in Parkinson's disease	Patients with Parkinson's disease	Normal walk (vs freezing)
Lorenzetti et al. (2018)	(rtfMRI) headphones	Unity	Emotion regulation	Young, healthy	Neutral condition
Forlim et al. (2019)	Screen via mirror / goggles with 3D stereoscopic stimulation / goggles with 2D monoscopic presentation	Unity	Effect of stereoscopic rendering in VR	Young, healthy	Contrasts between conditions (baseline 2D or screen)
Ju and Wallraven (2019)	Goggles, button box	Unity	Subjective gaming experience	Young, healthy, right-handed	Specific baseline driving condition; resting period
Manuweera et al. (2019)	Screen, gloves	Virtools software	Visuomotor network (hand function)	Young, healthy, right-handed	'Rest' cue
Matar et al. (2019)	Screen, foot pedals	Virtual Gait Laboratory	Freezing of gait in Parkinson's disease	Patients with Parkinson's disease	Rest blocks
Modroño et al. (2019)	Eyeglasses	Reh@Task	Action observation and virtual limbs	Young, healthy, right-handed	Fixation task (gray cross)
Andoh et al. (2020)	Goggles, glove, electromyographic activity	KISMET	Phantom limb pain	Middle-aged, healthy and amputees	Movement vs rest
Brand et al. (2020)	LCD monitor via a mirror, rigid plastic tubes of varying diameters, glove, oculography system	Unity	Action and observation of finger movements	Young, healthy, right-handed	Resting periods (fixation cross)
Faul et al. (2020)	Television via mirror, 3D glasses	Unity	Fear acquisition and extinction	Young, healthy, right-handed	Simple walk in the VE
Skouras et al. (2020)	(rtfMRI)	Unity	Early detection of Alzheimer's	Old, risk of Alzheimer's	First volumes for acquisition baseline

1 *Table 2: Sample of studies using concomitant VR and fMRI. Sorted by date of publication,*  
2 *including indications of the type of VR display, hardware and software.*  
3

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2  
3

Type of task	Group 1	Group 2	Group 3
Navigation	100	37	29
Episodic memory	37	100	48
Autobiographical memory	29	48	100

4 *Table 3: Correlation table for navigation, episodic memory and autobiographical memory*  
5 *activations. Group 1: presets for navigation; group 2: presets for EM; group 3: presets for*  
6 *autobiographical memory. Data obtained from linkRbrain (Mesmoudi et al., 2015).*  
7

Ref.	Sample(s)	Virtual software and hardware	Experimental conditions	Memory assessment	Main primary outcomes
Antonova et al. (2011)	20 (mean age: 28.1; age range: 23-35; all men)	Software: Superscape Virtual Reality software. Room with coloured walls. Hardware: joystick, projector, and screen.	Subcutaneous administration of scopolamine bromide vs saline (placebo). Block: moving towards a pole in the VE, blank screen to rehearse the position of the pole, and back to the VE with a different starting point. After recall, blank screen (rest) then static picture of abstract coloured pattern matching the arena's walls (visual control), then blank screen (rest).	(SM) Recall during the block. Performance accuracy (mean displacement error).	During activation, for both placebo and scopolamine, DLPFC, lateral and medial parietal cortex, thalamic and cerebellar areas. HPC and PHG activations disrupted by scopolamine, added activation of striatum during acquisition and recall, orbitofrontal cortex during acquisition.
Astur et al. (2005)	13 (mean age: 20.5; age range: 18-30)	Software: software written by the first author. Radial arm maze in a rectangular room with a variety of texture and landmarks throughout. Hardware: MR-compatible joystick, back projection screen and mirror.	Visible condition: rewards in each arm, 4 to be retrieved. Spatial condition: only 4 arms have rewards to be found.	(SM) Number of reference memory errors (entering an arm that doesn't contain a reward).	Bilateral HPC. Decreasing signal from visible to hidden condition.
Bellmund et al. (2016)	24 (mean age: 24.5; age range 18-29; all men)	Software: Donderstown by Doeller Lab. Hardware: /	After learning phase outside the scanner, direction imagination task between two buildings, followed by the confirmation of the imagined direction in a sparse VE.	(EM) Accuracy of the behavioural response with the angular distance between the correct direction and the response direction. Absolute direction in fMRI. Map test outside the fMRI.	PHG implicated in representing the directional aspect of imagined views (angular resolution of 30°). Grid-like entorhinal processing during imagined movement.
Burgess et al. (2001)	13 (mean age: 27.2; all men)	Software: Duke Nukem 3D, 3D Realms Entertainment, Apogee Software Ltd., USA Virtual town with Hardware: keypad, screen.	During practice, learning of associations of people, places, and objects. Scan while retrieval (paired forced choice recognition test), different types of questions: place, person, object, width (perceptual, non-memory condition).	(EM) Answers: debriefing for memory strategy. Answers for memory questions.	Memory for spatial context: as seen by contrasting place with width. Place condition: precuneus, PHG, HPC, bilateral posterior parietal cortex, anterior and mid cingulate, bilateral dorsolateral, ventrolateral and anterior PFC. Person condition: similar network of activation to the place contrast

					(without PHG and ventrolateral PFC, anterior cingulate and HPC). Almost same pattern of results for comparison of place and person with object. Object condition: weaker activation in the precuneus and parieto-occipital sulcus and additional activation in the right fusiform gyrus. Place versus person: bilateral posterior PHG and RSC, lateral posterior parietal area. Person versus place: mid cingulate, left superior temporal gyrus.
Cyr et al. (2016)	27 adolescents with bulimia nervosa (BM) (all women), 27 matched healthy controls (HC)	Software: C++ and OpenGL Virtual maze. Hardware: non-magnetic goggles, MRI-compatible joystick (CurrentDesigns Inc.).	Search for rewards in the environment without revisit of maze arms. Spatial configuration of extra-maze cues randomised. Control condition: without possibility of spatial learning, terminated after same number of arm visits as the previous learning condition.	(SM) Improvement across runs.	Spatial navigation: inferior frontal gyrus in HC while learning; for both groups, temporal and parietal regions (HPC, lingual and fusiform gyri, superior parietal lobule). Reward-processing: right anterior HPC, super frontal gyrus. Greater in HC. For BN, deactivation of right anterior HPC in the learning condition, activation in the control condition (i.e., when receiving unexpected rewards).
Demanele et al. (2015)	19 (mean age: 27; 10 men)	Software: OGRE 3D virtual reality environment. Park with landmarks, gold coins hidden in alleys. Hardware: fMRI-compatible 4-button diamond-shaped fiber optic response pad (Current Designs, USA)	Training, delay, test, and matched control phases. Visuomotor control phase: retrieval of marked coins, control delay period. Training phase: collection of accessible coins, control delay period. Test phase: find the gold coins in the previously blocked arms.	(SM) Number of correct choices.	Regions such as DLPFC, precuneus, somatosensory motor and primary visual areas distinguish task vs control stages (no relevance: Heschl gyrus, insula).

Doeller et al. (2010)	42 (mean age: 23.1; age range: 18-31; all men)	Software: UnrealEngine2 Runtime software (Epic Games). Grassy plane with a cliff and background of mountains, clouds, sun (Terragen, Planetside Software). Hardware: keys.	Collection and replacement of objects: first collection during initial trial. Then, prompt with an image of the object and the subject had to go to where they thought the object had been. Response by a button press, feedback. Phases without navigation.	(EM) Proximity of the replace response location to the correct object location.	Orientationally aligned grid-cell firing in the EC. Significant activation in the right EC for fast runs. Correlation between EC activation and memory performance.
Duarte et al. (2014)	15 (mean age: 25.2; age range 20-31; 8 women)	Software: Vizard (WorldViz, USA). Everyday scenes, interior (landmarks and targets). Hardware: stereoscopic glasses (Avotec Inc.), MRI-compatible joystick (Mag Design and Engineering, USA)	Blocks in two parts: memory encoding and (egocentric or allocentric) retrieval. Baseline condition between each pair encoding/retrieval. The subject needs to memorise the position of chairs along a path and to replace them with various starting positions.	(EM) Correct repositioning of missing objects.	The posterior third of the HPC activates for 3D visual spatial encoding, slightly less for retrieval. For 3D spatial navigation: superior parietal lobe, occipital cortex, cuneus, right RSC. Anterior-posterior asymmetrical activation (antagonistic BOLD coupling) for the HPC.
Gomez et al. (2014)	18 (mean age: 23.5; age range 17-30; 13 men)	Software: Virtual Reality Markup Language. Room with objects and different spatial layouts. Hardware: joystick, back-projection screen with a mirror attached to the head coil.	Three visual spatial encoding conditions: allocentric, egocentric-updating and egocentric with rotation only. Encoding phase: film with sequential presentation of objects in the VE. Retrieval: point to the direction of an object (cued retrieval). Control condition: mix of the others. Joystick picture for behavioural performance.	(EM) Trial performance (error angle).	Spatial encoding: occipito-parieto-temporal network. Self-related conditions: RSC for orientation changes, right HPC for self-location changes. The HPC supports spatial processing (egocentric-updating and allocentric, landmark-based, processing)
Hartley et al. (2003)	16 healthy right-handed (mean age: 28.9; age range: 23.0-40.3; all men)	Software: Qoole mal editor (Lithium Software). Towns with landmark locations. Hardware: keys to move in the VE.	Three variations of a cued navigation task, first-person perspective, without having to store a representation of the current target location: - "wayfinding": free navigation between pre-learned target locations towards one of them. - "route following": visit of landmarks in a fixed, pre-learned order.	(EM) Speed and accuracy of the path chosen by the subject (distance error between the ideal i.e., shortest path and the one chosen by the subject).	Activity in the right HPC is associated with accurate wayfinding within subjects. On the contrary to poorer navigators, better navigators activate their hippocampi in wayfinding and the head of the right caudate in route following (specificity). There are two different mechanisms for navigation: place learning, relying on the HPC and forming

			- following a visible trail to the goal location, no training. Rest period during each block.		flexible cognitive maps, and response learning, relying on the caudate nucleus for action-based representation (navigation via the same well-learned route).
Iglói et al. (2015)	19 (mean age: 24.3; age range: 19-38; all men)	Software: 3D StudioMax (Autodesk Fortune 1000, USA), Virtools (v3.5) (Dassault Systèmes, France). Maze, environmental cues. Hardware: keypad.	Finding a constant goal in the maze (feedback when found). Training trials (sequence-based strategy or memory of location), probe trials (end before feedback), control trials (displacement task, no landmark).	(SM) Accuracy of the path, interviews.	In place-based responses, implication of the left cerebellum, right HPC and medial parietal cortex. In sequence-based egocentric responses, implication of right cerebellum, left HPC and medial PFC. Both networks are simultaneously activated in training sequences.
Javadi et al. (2019)	22 (mean age: 21.8; age range: 19-27; 14 women)	Software: WorldViz. Island maze environment, walkable “sand” and unpassable “lava”. Hardware: buttons, ear plugs, foam padding, back screen with a mirror attached to the head coil.	Training: learning of goal locations. Test phase: finding the way to and arriving at a given goal object. Target objects nonvisible, position of lava changing with a screen freeze creating detours, shortcuts, false shortcuts, and a control condition of no change. Control “follow” trials (arrow indicating the direction to go).	(EM) Memory test during learning: blank grid with the lava marked where the participants have to place all the objects they remember. Prompts for missing objects. Assessment: accuracy (optimal path chosen or not).	HPC, bilateral PHG, RSC and medial frontal areas are more active with active navigation as with arrow following. Superior and lateral PFC and caudate activity was evoked by detours, rIPFC responds when false shortcuts need to be avoided. Activity in the caudate nucleus bilaterally, and not in the HPC, correlate with the change in path distance for all events (coding of a prediction error about future event?). No specific activity of HPC for total path distance in detours was found.
Lee et al. (2016)	16 (mean age: 22.1; age range: 19-25; 5 women)	Software: Unreal Development Kit, Epic Games, Cary, NY. Circular environment with a virtual maze in the centre, natural landmarks, buildings with objects. Hardware: projection on a screen using an LCD projector (Canon XEED SX60), mirrors on goggles, MRI-compatible button box.	Exploration of the buildings in the VE. In each, sampling of objects in different corners. After the learning period outside the scanner, three periods: object-cuing period, object-cued place recognition period, spatial memory period (navigation in the chosen building).	(EM) Memory test (object recognition) in the VE. Reaction time for each period (timestamps associated with button presses), cumulative amount of angular rotation in	Activity in the HPC shifts from left to right HPC as additional spatial components (place memory, spatial navigation) are required in the task (as seen also with the correlation of BOLD signals with efficiency of retrieval for object-place memory and spatial memory). Other areas: shift from early visual information processing areas (e.g., middle

			Control trials: same as regular trials, but the target building is marked by a light cue, and same object presentation in all trials during object-cuing period. Intertrial interval period.	the second period. Post-scan interview for individual strategies.	occipital gyrus) to higher information processing areas (superior and middle temporal gyri) as the task changes from object recognition to object-cued place recognition and spatial navigation. Areas associated with EM retrieval such as the HPC and angular gyrus were also active during the object-cuing period.
Migo et al. (2016)	8 patients (5 men) with amnesic mild cognitive impairment (aMCI), control group of 10 matching healthy volunteers (6 men). All participants aged between 61 and 80.	Software: Superscape Virtual Reality software (Superscape, UK) Hardware: via a projector onto a Perspex screen at the foot of the scanning table; trackerball. MR-compatible vision-correcting goggles when needed.	Going to each platform once with allocentric strategy (platforms = landmarks). Periods of rest and visual control image (passive viewing).	(SM) Platform performance, reaction time, time to realise the task.	Control group: posterior parietal cortex, precuneus, visual cortex. Left supramarginal gyrus more active with more platforms. Cluster in the right HPC. Patient group: similar network with less activation. Deactivation in the midline cuneus. No activation or deactivation in the HPC or PHG. In the control group, more navigation regions active (RSC, bilateral precuneus, left DLPFC, caudate nucleus, PHG and HPC). More activation in patients for right DLPFC, superior frontal gyrus and primary motor cortex.
Morgan et al. (2014)	11 ketamine users (8 men) 15 controls (10 men) Age range: 20-44	Software: UnrealEngine2 Runtime software (Epic Games). First-perspective view of a plain surrounded by visual landmarks. Hardware: keypad.	Cue phase, finding the previously learned location of the object (replace phase). Feedback. Then, fixation cross. Control trials: picture of the same object across every control trial. The object is visible for collection in a landmark-free environment.	(EM) Distance error.	Navigation from memory: in controls, HPC and PHG. Updating of spatial memory: greater activation for controls in the left caudate. Walking toward a visible object compared to rest: no group differences or main effect of task.
Nau et al. (2020)	20 (age range: 19-36; 11 women)	Software: UnrealEngine2 Runtime software (Epic Games). First-perspective view of a plain surrounded by visual landmarks. Hardware: /	After learning phase, navigation to the location of a cued object.	(EM) Memory error (Euclidian distance between true and remembered	Activity in RSC, HPC, PHG, EC and visual regions. Accuracy reflected by activation of RSC and pmEC. Tuning in strength in pmEC and PHG and tuning in width and



				location), virtual head direction.	topology in RSC depends on memory (but variability).
Parslow et al. (2004)	11 (mean age: 26.71; age range: 19-45; all men)	Software: Superscape Virtual Reality software (UK). Virtual arena with abstract patterns on the walls. Hardware: projector onto a Perspex screen. MR-compatible analogue joystick.	Tasks: encoding (reaching a pole), rest after image freeze, retrieval (moving to the location of the pole), rest after image freeze, visual (control static image), rest (additional resting control condition).	(SM) Displacement error distance.	Viewer-independent condition: medial frontal, anterior cingulate, inferior frontal, precentral, temporal (HPC and PHG), superior temporal, parietal, occipital, cerebellum and thalamus. Viewer-dependent: similar set of regions. HPC and PHG involved mainly in processing of allocentric processing, at the encoding phase.
Salgado-Pineda et al. (2016)	27 right-handed patients with schizophrenia 32 healthy controls (matched groups)	Software: XVR framework. Virtual city with coloured structures (navigation cues). Hardware: fMRI-safe VR glasses (VisuaStim Digital, Resonance Technology Inc., Los Angeles, USA), fiberoptic joystick (Current Designs Inc., Philadelphia, USA).	After the landmark-learning period, spatial navigation condition (reaching the objective before the end of the block). Inter-block intervals. Control blocks: same city without landmarks, following of arrows on the ground.	(SM) Efficiency of spatial navigation (how much time was spent, how close they got to the goal, total distance travelled).	In healthy controls: HPC, PHG bilaterally, neocortical regions (RSC, PFC) Schizophrenia patients: reduced activity in the left DLPFC and left occipital and temporal cortex. No difference in the HPC.
Siemerkus et al. (2012)	16 patients (5 women) with schizophrenia 16 matching healthy controls (6 women)	Software: Realimation VSG 4.4 and Microsoft C++. Maze with cul-de-sacs containing goals. Hardware: head-mounted display (Resonance Technology, USA), joystick (Current Designs, USA)	Trials to find goals. Distracting mental task to restrict navigationally relevant cognition to intersection.	(SM) Errors, time to find the goal, number of unsuccessful trials. Questionnaires (strategy of navigation).	During virtual learning: precuneus, cuneus, parietooccipital sulcus, PCRS, PHG. Stronger activation of task-relevant regions in the right hemisphere for controls (precuneus, inferior parietal lobule, caudate nucleus and middle frontal gyrus) + PCRS. In patients, not consistent decrease of activation in precuneus and PCRS across trials.
Slobounov et al. (2010)	15 neurologically normal student-athletes (mean age: 21.3; 30% women) 15 student-athletes with recent mild traumatic brain injury	Software: VTC Open GL developing kit (InnovativeVR, Inc, USA). Virtual corridor. Hardware: MRI-compatible joystick (magconcept), mirror mounted on the head coil.	Conditions: encoding of a navigation route to a target room in a corridor (training in free navigation), retrieval (the subject shows the route), free navigation, baseline (tracking of a white cross on black background via the joystick).	(SM) Accuracy of retrieval.	No behavioural effect of group. During encoding, activation in lateral extrastriate visual cortex extending into V2, bilateral parietal cortex, precuneus and right DLPFC. Bigger clusters and increased activation of right DLPFC and left parietal cortex during encoding for

	(mean age: 20.8; 30% women)				concussed subjects, additional activation of left DLPFC and cerebellum. During retrieval, increased activation for both groups in occipital area, precuneus, parietal cortex, premotor cortex. Bilateral activation of HPC during encoding for both groups.
Stemmers et al. (2016)	20 (mean age: 21.3; age range: 19-28; 14 women)	Software: UnrealEngine2 Runtime software, Matlab 7.9 and Terragen software package. Virtual arena with a circular grassy plane surrounded by walls and asymmetrical mountains. Hardware: button-box.	Learning of object locations in two environments. In the scanner, same task in four new environments (linear variations of the background).	(EM) Distance error in object replacement as a fraction of the arena's width.	The neural activity pattern in the HPC follows nonlinear dynamics that match the behavioural response pattern. The divergence of orthogonal representations in the HPC translates into mnemonic decisions (putative attractor dynamics).
Suthana et al. (2011)	18 (mean age: 24.89; age range: 20-31; 9 women)	Software: pyepl, Snapz Pro X (Ambrosia software), yellowcab2, iMovie. Town with buildings. Hardware: magnet-compatible 3D goggles and headphones (Resonance Technologies), keys.	Navigation (passive view of videos) through the VE using single starting points and multiple starting points. Learning of store locations. Retrieval: passive viewing of navigation to old (target) or new (lure) locations: determination by pressing a key. Direction-pressing control condition: pressing the corresponding button on the keypad every time the direction changes. Baseline task.	(EM) Performance and learning rate.	Single starting point: activation in dentate gyrus for encoding and right subiculum for retrieval. Importance of MTL for both. Multiple starting points: no significant difference in activation between encoding and retrieval. Increase activity in CA1.
Sutton et al. (2010)	16 (mean age: 23; age range: 18-31; 8 women)	Software: Half-Life 2 game engine and the Source Software Development Kit (Valve Software, WA) Hardware: mirror above the head coil; five-button directional keypad.	Encoding of the position of an object followed by a blank screen. During retrieval, subject replaced the object where they remembered it was. Three experimental conditions: geometry (room: rectangle shape with all walls light grey), feature + geometry (same as geometry with	(EM) Placement of the object (correct corner, near correct corner error, rotational error, far corner error).	Bilateral HPC and left PHG were more engaged when the feature wall present. Greater activation of left PHG trials with the feature. Activation of MTL during retrieval. During encoding, greater MTL activation on F trials relative to G trials.

			one red wall), feature (square with one red wall).		
Tau et al. (2014)	13 men with cocaine dependence (CD), 13 matched men for healthy controls (HC)	Software: VE (radial maze with extra-maze cues) built using C++, OpenGL Hardware: non-magnetic goggles, MRI-compatible joystick (Current Designs Inc.).	Active condition: all arms with awards. After each arm visit (trial), reappearance of the subject at the center of the maze with a randomised viewing perspective. Control condition: randomisation of the extra-maze cues to avoid spatial learning. rewards at the same frequency as in the active condition without regard of the performance.	(SM) Completion of the spatial learning task.	When searching the maze, the CD group activated frontal, striatal and MTL regions more in the control condition. MTL activations are reduced in CD compared to HC during spatial learning. In CD, DS activity was decreased in the active condition, and increased in the control condition. Inverse association of DS activation with abstinence. In HC, searching was associated with the cingulo-opercular network (goal-directed behaviour), ventral and dorsal visual streams (visual processing, attention). Activations in the CD group include lateral PFC, striatum. Increased activation of amygdala and VS especially for CD when reward-based learning (+ alteration of neural systems for reward-based learning: reduced activations of HC regions in CD).
Weniger et al. (2010)	19 (mean age: 25; age range: 20-38; 11 men)	Software: Kinetix 3D Studio Max R2. Maze without landmarks. Hardware: MRI compatible HMD (Resonance Technology, Northridge, USA), joystick (Current Designs, Inc., USA).	Finding an object in a maze. Baseline as calculated by the fMRI analyses software (BrainVoyager).	(SM) Learning performance assessed by the number of errors across trials. Strategies in post-experiment questionnaires.	While learning to navigate the maze, MTL activity only, in the PHG. Further areas: left postcentral gyrus, left anterior insula.
Weniger et al. (2013)	14 patients with childhood abuse (all women) 14 matching healthy controls (all women)	Software: Realimation VSG 4.4 and Microsoft C++. Maze with cul-de-sacs containing goals. Hardware: MRI-compatible HMD (Resonance Technology, USA), joystick (Current Designs, USA)	Trials to find goals.	(SM) Number or errors, questionnaire for navigation strategy.	Increased activity in controls within the parietal lobes (precuneus, parietooccipital sulcus, inferior parietal cortices), PHG, RSC and cingular cortex. Weaker activity changes of patients relying on

					egocentric learning within parietal cortices, insula, superior temporal gyrus, cingulate gyrus, caudate nucleus and posterior thalamus. Less activity for patients in cingulate, insular, inferior parietal cortex.
Wolbers et al. (2004)	14 (mean age: 29.3; age range: 23-35; all men)	Software: Milkshape 3D (Chumbalum Soft) and Blitz 3D. Town with specific buildings as landmarks. Hardware: liquid crystal display video-projector with a screen on top of the head coil, buttons.	Encoding (route through the town, memorising spatial relationships between landmarks), retrieval, encoding control, retrieval control. Retrieval: still images of landmarks. Assessment of the position of one compared to another. Control condition for encoding: single corridor with varying landmarks placed behind walls at both ends. Control condition for retrieval: null events, identical buildings.	(EM) Type of memory: spatial memory (1 temporo-spatial associations between consecutive landmarks) Assessment: performance at retrieval, maps drawn after fMRI scanning.	Route learning: left medial frontal gyrus, left RSC, bilateral posterior inferior parietal cortices. Only the activity of posterior inferior parietal regions increased across learning sessions. No activation in HPC or PHG.

Table 4: Summary of the studies included in the PRISMA analysis. Results for EM and spatial memory (SM). Classified with population (sample(s)), virtual software and hardware, experimental conditions, memory assessment and type of memory, main primary outcomes. See list of abbreviations.

	Immersion	Interaction	Cybersickness	Naturalistic complexity
No equipment	+	+	+	+
Keypad, buttons	++	++	++	++
Pedals	++++	++++	+++	++++
Trackball	++++	++	++	++
Gloves	++++	+++++	++	++++

Table 5: Main types of equipment used in VR-fMRI. Ratings from + (weak) to +++++ (very strong) in immersion, interaction, potential cybersickness, and naturalistic complexity.

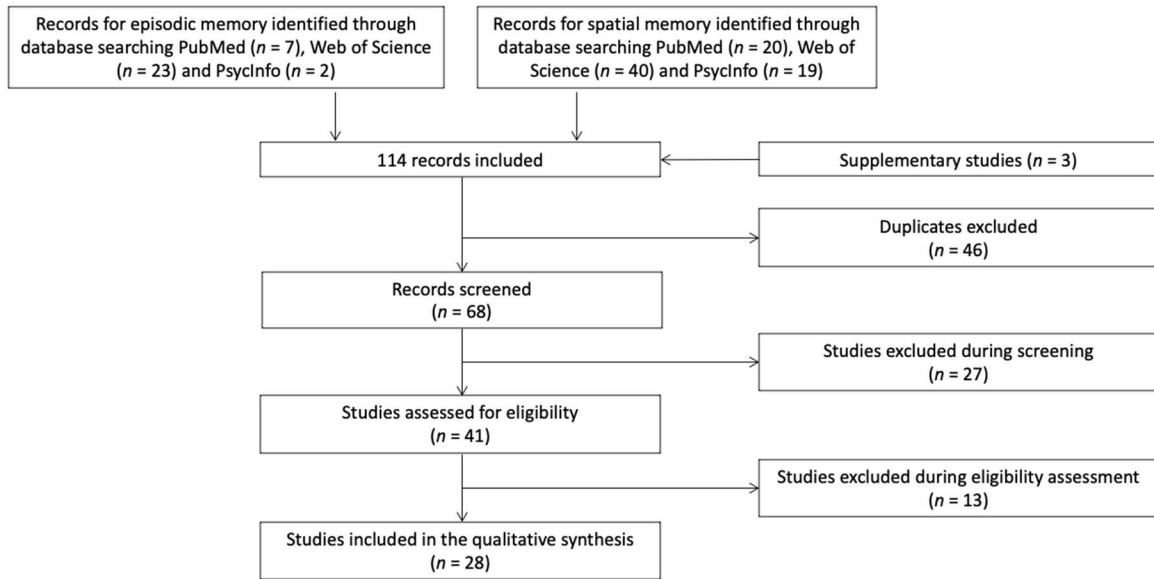


Figure 1: PRISMA flow chart

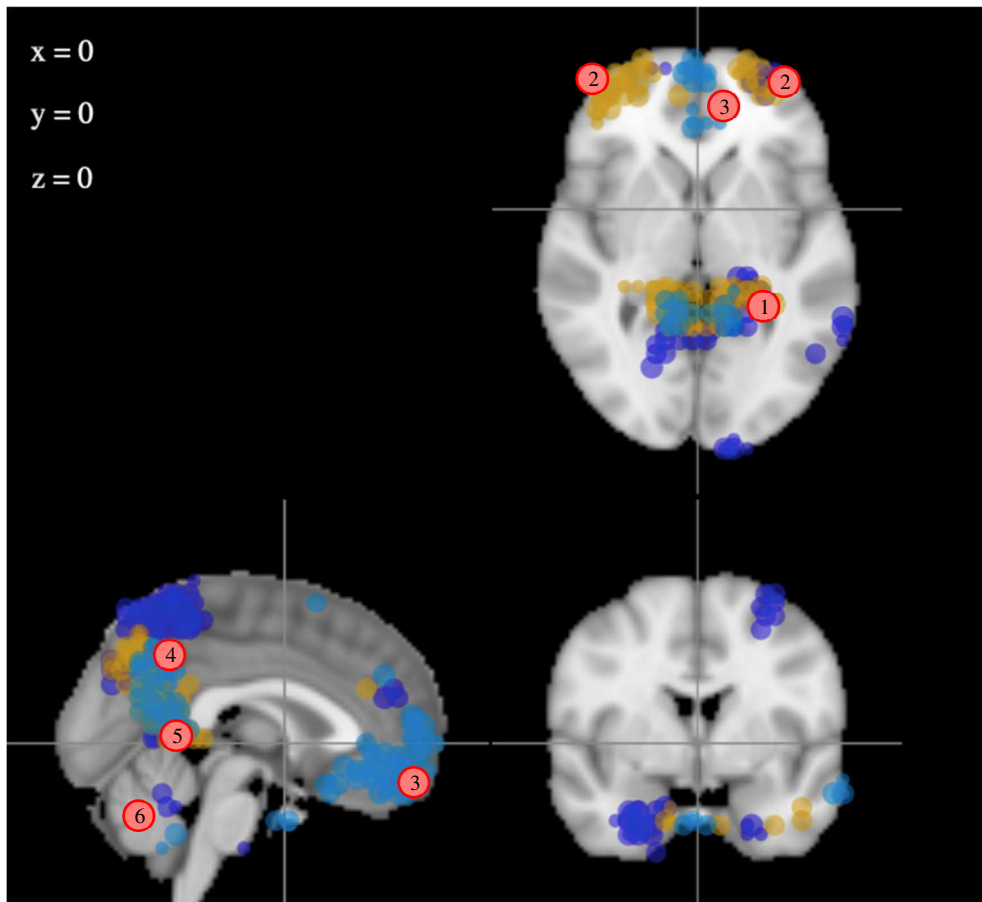
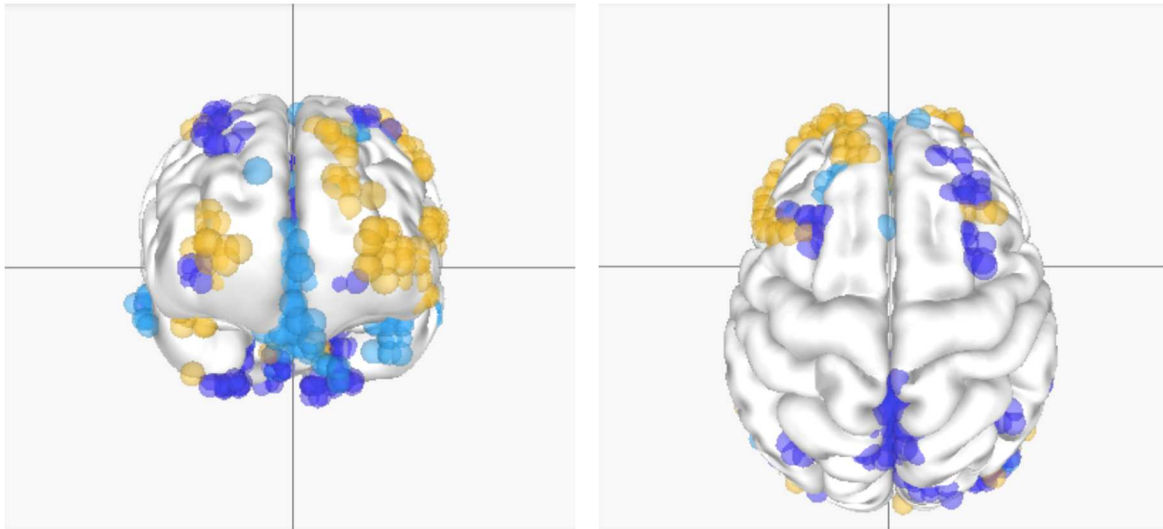
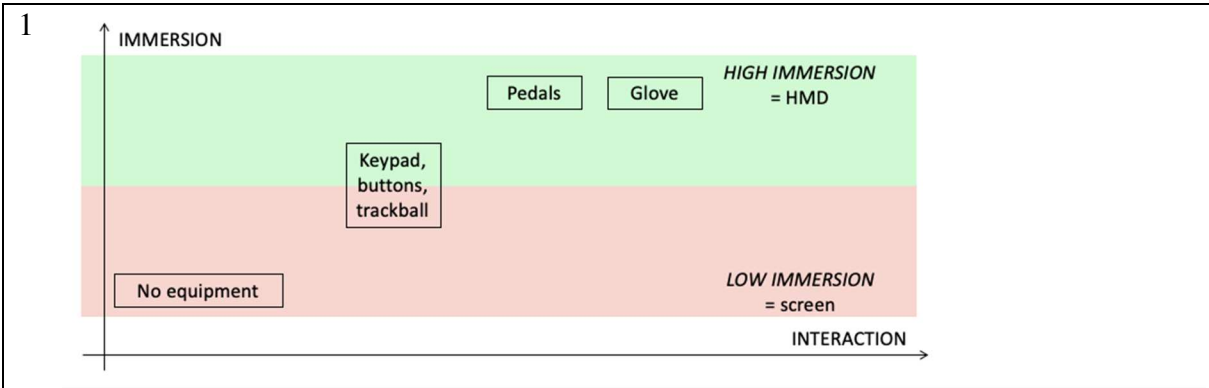


Figure 2: Brain mapping in 2D for navigation, episodic memory and autobiographical memory activity, as obtained with linkRbrain, based on the MNI-152 model (Mesmoudi et al., 2015). See Table 3. In purple: navigation. In yellow: episodic memory. In blue: autobiographical memory. From top to bottom and then left to right: horizontal, sagittal and coronal sections. Main regions of interest: 1: HPC and PHG area; 2: PFC; 3: medial PFC; 4: parietal lobe; 5: RSC; 6: cerebellum.



*Figure 3: Brain mapping in 3D (grey matter) for navigation, episodic memory and autobiographical memory, as obtained with linkRbrain, based on the MNI-152 model (Mesmoudi et al., 2015). See Table 3. In purple: navigation. In yellow: episodic memory. In blue: autobiographical memory. Left: rostral view. Right: dorsal (superior) view.*



2

A

What Where Who Width

C

B

D

3

A

B

C

*Figure 4: Description of the main paradigms found in concomitant VR-fMRI for episodic memory. 1: Classification of the main equipment found during concomitant VR-fMRI paradigms inside the MRI scanner. Main axes: immersion and interaction. 2: Description of the main tasks seen in the PRISMA review for EM (A, B) and spatial memory (C,D). A: based on Burgess et al. (2001). The subject encounters avatars who show them objects. During retrieval, avatars ask them about the objects (where, from who, what, how big they were). B: based on studies asking participants to encode the spatial location of objects and replacing them. Objects may be daily-life objects (chairs, other...) or landmarks (buildings). In the latter case, some studies asked for the physical relationships between two landmarks during retrieval. C: based on studies asking participants to look for rewards in mazes, without going back twice to the same location in the maze (arms for instance). D: based on studies asking for the specific encoding and retrieval of one location in the environment. 3: Examples of VE. A: Burgess et al. (2001); B: Kalpouzos et al. (2010); C: Weniger et al. (2010).*