Chapter 3 - Investigating the unconscious encoding of episodically associated visual stimuli: an fMRI study

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3.1 Abstract

According to the processing-based-memory model (Henke 2010), episodic memory is flexible, can form rapidly, and is supported by medial temporal lobe (MTL) structures - particularly the hippocampus. According to this model, a memory with these characteristics can exist at both conscious and unconscious levels. In this study, we tested the involvement of MTL structures in unconscious encoding and subsequent unconscious retrieval of complex visual stimuli to test the predictions of the processing-based-memory model. Healthy volunteers participated in an fMRI study where novel face-scene associations were masked from consciousness to allow only unconscious encoding. One of the associate scenes was subsequently presented as a cue to provoke unconscious retrieval of face-scene associations. Participants then freely viewed two faces. In experimental trials, these were the associated face (target) and a distractor face. In control trials, the two faces presented were not associated with the cue scene but were associated with other encoded scenes. Eye-tracking measures were also used as an index of unconscious retrieval. There was a higher activation in the right hippocampus during the experimental compared to the control free-viewing. Activation in the MTL during the unconscious encoding correlated with the number of fixations on the target face and also with the right hippocampal activation during the experimental free-viewing. Our findings suggest that MTL has a critical role in unconscious encoding and subsequent unconscious retrieval of complex visual associations. MTL activation during unconscious encoding can predict unconscious retrieval in a way that is consistent with the characteristics of episodic memory as defined by the processing-based-memory model.

3.2 Introduction

Episodic memory has historically been classified as a subcategory of explicit memory limited only to conscious encoding and retrieval of events (Tulving 2002). This definition was predominantly based on observations about the deficits of amnestic patients with hippocampal damage in forming explicit, but not implicit, memories of associations (Milner, Corkin et al. 1968, Knowlton, Ramus et al. 1992, Clark and Squire 1998, Levy, Stark et al. 2004). However, subsequent studies showed that such patients had a deficit during the retrieval at both conscious and unconscious levels if the associated items that they tried to encode were semantically distant, such as unrelated word pairs (Warrington and Weiskrantz 1982, Mayes, Holdstock et al. 2002, Mayes, Holdstock et al. 2004). Recent brain imaging studies have suggested a new role for the hippocampus in unconscious as well as conscious encoding and retrieval of novel associations (Degonda, Mondadori et al. 2005, Daselaar, Fleck et al. 2006, Hannula and Ranganath 2009, Reber, Luechinger et al. 2012, Duss, Reber et al. 2014, Zust, Colella et al. 2015). These observations led to the proposal of a processing-based-memory model (Henke 2010).

According to the processing-based-memory model, episodic memory is a rapidly formed, flexible memory of associations that can last over short or long retention times. This definition of episodic memory is not limited by consciousness and can also include unconscious encoding and retrieval of events. We used this definition of episodic memory to investigate unconscious encoding and subsequent unconscious retrieval of episodic memory.

Many studies have previously investigated the memory of novel associations at an unconscious level (Degonda, Mondadori et al. 2005, Daselaar, Fleck et al. 2006, Kirwan, Shrager et al. 2009, Reber, Luechinger et al. 2012, Duss, Reber et al. 2014, Zust, Colella et al. 2015), but these are largely limited to verbal associations. The few studies about the neural correlates of unconscious memory of visual associations focus on unconscious retrieval after conscious

encoding (Ryan, Althoff et al. 2000, Hannula, Ryan et al. 2007, Hannula and Ranganath 2009). To the best of my knowledge, no study so far has investigated the neural correlates of unconscious encoding of episodically associated visual stimuli. In previous chapter using eye tracking measures, I found supportive evidence for the possibility of unconscious encoding and subsequent unconscious retrieval of visual episodic memory. In this chapter, I investigated the neural correlates of unconscious encoding and subsequent unconscious retrieval of visual episodic memory. This way I was able to test the prediction of the processing-based-memory model that the same brain areas responsible for conscious episodic memory are also involved in unconscious form of visual episodic memory (Henke 2010).

In the current study, complex and novel visual associations (face-scene pairs) were masked from awareness and presented for a very short time during the encoding phase. After a distraction interval, one of the scenes was presented as a cue. Subsequently, participants freely viewed either a target face (previously presented with the cue scene) alongside a distractor face (previously presented with a scene other than the cue), or, in the control condition, two faces from un-cued scenes. If unconscious memory complies with the characteristics of episodic memory according to the processing-based-memory model, it should be compositional and flexible (Henke 2010). Compositionality means that each of the elements that make the whole memory and their associations are stored independently. Hence, the memory could be reactivated through many routes by viewing different elements of the memory as a cue (Henke 2010). Consequently, I predicted that presentation of a cue scene would facilitate or trigger the retrieval of the associated face (target) during the free-viewing in the experimental condition; such retrieval would not happen in the control condition, where the faces were not associated with the cue scene.

For decades, eye movements have been used to investigate memory of previous experiences (Hannula, Althoff et al. 2010, Meister and Buffalo 2016). It has been shown that eye

movements can be modulated as a result of memory retrieval without consciousness (chapter 2) (Ryan, Althoff et al. 2000, Ryan and Cohen 2004, Hannula, Ryan et al. 2007, Hannula and Ranganath 2009). The number of fixations that we make on an image has been considered the most important eye-tracking measure that can reflect recognition memory or episodic memory (Loftus 1972, Kafkas and Montaldi 2011, Molitor, Ko et al. 2014, Meister and Buffalo 2016, Liu, Shen et al. 2017). For example, it has been shown that participants fixate more on manipulated parts of consciously encoded images without conscious retrieval of the manipulation (Ryan, Althoff et al. 2000, Ryan and Cohen 2004). In chapter 2, I found that unconscious retrieval of face-scene associates after their unconscious encoding was accompanied by enhancement in the number of fixations on the target compared with the distractor in the left visual field. Hence in this experiment, I expected that increment in the number of fixations on the target in the left visual field reflected the success of retrieval.

In the processing-based-memory model, the medial temporal lobe (MTL), particularly the hippocampus, plays a critical role in both conscious and unconscious forms of episodic memory. I expected to see the MTL activation (particularly the hippocampus) during the unconscious encoding. It has been shown that MTL activation during encoding reflects the success of encoding and correlates with the success of its subsequent retrieval (Fernandez, Weyerts et al. 1998, Staresina and Davachi 2008). Thus, I expected that the participants who had a higher activation in MTL during the encoding phase to also have a higher number of fixations on the target during the free-viewing phase.

There is a large body of evidence indicating that right hemisphere is functionally specialized for face processing (Kapur, Friston et al. 1995, Kim, Andreasen et al. 1999, Nakamura, Kawashima et al. 2000, Schweinberger, Huddy et al. 2004, Kloth, Dobel et al. 2006, Yovel, Tambini et al. 2008). Brain imaging (Ranganath and D'Esposito 2001, Taylor, Mills et al. 2011, Von Der Heide, Skipper et al. 2013) and clinical studies (Crane and Milner 2002, Milner 2003)

also show that right MTL has a dominant role in retention of novel face. Hence, I expected to see a significant change in the activation of right MTL, particularly right hippocampus, during the experimental free-viewing compared with the control free-viewing due to the unconscious retrieval of the target.

Both subjective and objective awareness tests were used to make sure that encoding and retrieval of the masked stimuli were without conscious awareness (Hannula, Simons et al. 2005). The subjective test of awareness was based on the participants' verbal reports about conscious perception of the masked stimuli. The objective awareness test involved presentation of the masked stimuli using the same method as the main experiment. The participants who were able to recognize those masked stimuli above chance in a forced choice manner were excluded from the experiment. These conservative measures ensured that the masked stimuli cannot be perceived consciously and hence cannot be retrieved at conscious level.

3.3 Methods

3.3.1 Participants

Fourteen right-handed volunteers[1] (5 men) participated in this experiment (age range: 18-38 years, mean= 28.07, SD= 4.89). All the participants reported normal vision with no history of oculomotor problems or eye surgery. They also reported having no history of psychological or psychiatric diseases. They reported no current consumption of illegal or prescribed drugs. One participant was excluded due to anxiety during the scanning. Four participants were also excluded from the experiment due to the awareness criteria described in the awareness test section (see below and Chapter 2), leaving 9 participants for the unconscious episodic memory

[1] Each session of my fMRI experiment cost around 1000 AUD. Due to the funding limitations I was not able to test more than 14 participant. Low number of participants is an issue for most of the published fMRI studies due to the cost of scanning. The replicability of such findings should be tested by future meta-analysis. Further explanation about this issue is provided in the discussion section.

analysis. The participants gave informed consent. The study was approved by the Human Research Ethics Committee at Macquarie University (MQ; reference number: 5201200035).

3.3.2 Eye tracking data acquisition

Eye tracking data was recorded using an fMRI compatible eye tracker (EyeLink CL) at a sampling rate of 500 Hz during the main experiment. Calibration of the right eye position was performed using the built-in Eyelink 5-point calibration at the beginning of each run.

3.3.3 MRI data acquisition

MRI data was acquired using the Siemens Verio 3T scanner at Macquarie Medical Imaging centre, Macquarie University Hospital, Sydney, Australia, using a 32-channel head coil. Functional images were acquired with a multiband echoplanar imaging (EPI) sequence (repetition time, 2000 ms; echo time, 32 ms; field of view, 240 x240 mm^2; matrix, 128 × 128; slice thickness, 2 mm (no gap) resulting in a voxel size of 1.9 X 1.9 x 2 mm^3; multiband factor, 3; phase-encode direction, anterior/posterior; flip angle, 62°). Each volume consisted of 45 axial slices acquired in a descending, interleaved order. The field of view covered the temporal lobe to inferior parietal areas to ensure good coverage of MTL.

Structural images were also acquired in axial orientation before the main experiment (2D-MPRAGE sequence, voxel size, 1 mm^3; field of view, 256 x 256 mm^2; 176 slices; TR,1800 ms; TE, 3.03; flip angle, 9°).

3.3.4 Stimuli

I selected 195 full color scene images (97 indoor and 98 outdoor) and 255 full color face images (128 male and 127 female) from the FERET data base (Phillips, Wechsler et al. 1998, Phillips, Hyeonjoon et al. 2000) and the Face Database of the Bonn-Rhein-Sieg, University of Applied Sciences (http://isf.h-brs.de/en/skin-db/) (Steiner, Sporrer et al. 2016). Each face was resized to 225 x 225 pixels and each scene was also resized to 800 x 600 pixels. For each participant, 195 face images (98 male, 97 female) were randomly superimposed on the scenes to make novel face-scene pairs presented during the encoding of the main experiment and the practice session. 180 faces (90 male, 90 female) were used in the main experiment and 60 faces (30 male, 30 female) were used in the awareness test. Faces were randomly assigned to the main experiment or the awareness test for each participant.

3.3.5 Unconscious stimulus presentation

For the unconscious presentation of face-scene associations, I masked the faces while the scenes were visible during the encoding (as in Chapter 2). In this way the face-scene association was not consciously perceivable, but the scenes could be consciously encoded. I adopted the unconscious presentation parameters of Henke et al (Henke, Mondadori et al. 2003). To conceal the main purpose of the experiment and ensure attention to the display, participants performed an orientation task superimposed on the stimuli. During the attention task, participants responded to the direction (vertical or horizontal) of a small bar via a button press. The bars and the masked faces were both presented at the center of the screen. For each face-scene pair, the scene was presented for 6s while the masked face or the bars were briefly superimposed on it. The order and the timing of the presentation of the stimuli during the unconscious encoding was as follows: The presentation duration was 17 ms for the faces (F),

183 ms for the masks (M), and 233 ms for the bars (B). Each stimulus was presented in the following sequence: B–M–F–M–M–F–M–B–M–F–M–M–F–M–B–M–F–M–M–F–M–B–M–F–M–M–F–M–B–M–F–M–M–F–M–B–M–F–M–M–F–M (Figure 1. A).

3.3.6 Main experiment procedure

The participants had a practice session in which they performed a brief version of the main experiment with a different set of stimuli. The event-related fMRI experiment consisted of 5 runs and each run included 12 trials. At the start of each run, the position of the right eye was calibrated. The experimental paradigm is illustrated in Figure 1. Each trial consisted of different events or phases: encoding, distraction, cue and free-viewing. Between these events, we had fixation events during which participants were instructed to simply keep their gaze on a fixation cross on the centre of the screen. During the encoding in each trial, three novel face-scene pairs were displayed using the same method explained in the section of unconscious presentation of stimuli. The participants responded to the direction of the bar that was presented very briefly on the scene.

At the same time they were instructed to memorize the scenes. Then there was a fixation for 500ms. Subsequently, there was a delay during which the participants were distracted from the encoded items by solving three math problems. Each math problem consisted of three random digits presented on the screen for 3s. The participant responded, by button press, as to whether the biggest number was equal to the sum of the other two digits. After another fixation for 2s, the cue scene was presented, with a fixation cross was superimposed on its centre. Participants were instructed to remember the cue scene while maintaining fixation on the cross. The cue scene was chosen with equal probability from any of the three scenes presented during the encoding phase of the same trial. Immediately after that two faces appeared on the screen, the

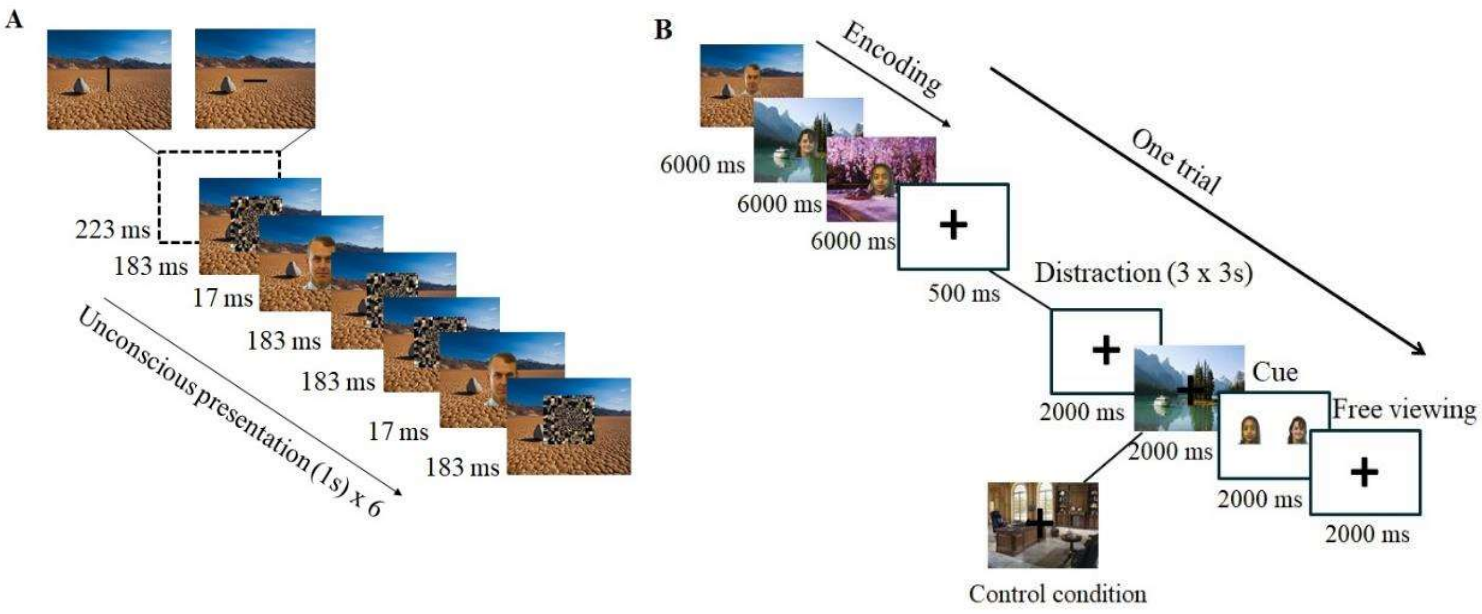

Figure 1. Experimental paradigm. **A)** Illustration of unconscious encoding of face-scene associations. The sequence depicted above was repeated six times during the unconscious encoding. In the beginning of each repetition, a fixation bar was presented and the participants responded to the direction of the bar (vertical or horizontal) via button press while they were encoding the background scene. **B)** Illustration of the main experiment. During the encoding, 3 novel face-scene associations were presented using the same method explained in part A. During the distraction, participants solved 3 math problems. One of the encoded scenes was then presented as a cue and the participants were instructed to retrieve the scene while keeping their gaze on a fixation cross on its centre. Subsequently, participants freely viewed two faces. In the experimental condition, one of the faces had been superimposed on the cue scene during the encoding phase of the trial. In the control condition, none of the faces were superimposed on the cue scene and those faces were superimposed on other scenes during the encoding.

participants were instructed to look at both of the faces freely. In experimental trials, one of the faces (target) was associated with the cue scene during the encoding phase. In the control trials,

the faces were not associated with the cue scenes but had been presented on the un-cued scenes in that trial.

It is well established that face recognition is better (faster and more accurate) when faces are presented in the left visual field compared with the right visual field (Rizzolatti, Umilta et al. 1971, Hilliard 1973, Leehey and Cahn 1979, Gainotti 2013). In my previous experiment (Chapter 2), I found a significant modulation in the eye-tracking measures as a result of unconscious retrieval only when the target was in the left but not the right visual field. In line with the literature and my previous findings in chapter 2, I decided to present the targets only in the left visual field. This would give me more trials in which I could expect to detect the unconscious episodic memory. As the participants had no awareness of which face was the target, and were not doing a conscious task on the faces, the potential confound of having a consistent target position seemed minimally problematic. But still there might be a potential risk of unconscious prediction of the position of the target. It is worth considering that unconscious prediction of the position of the target was not possible without a prior retrieval of the targe-cue association. At the same time, if I found a correlation between the MTL activation during the encoding and the number of fixation on the target during the free-viewing, such a correlation could not be simply induced by a mere prediction of the position of the target. The potential risk of having the target always in the left visual field regarding the results in this chapter is further explained in the discussion section. The experimental and the control trials were presented randomly interleaved using permuted randomization. I had a fixation event at the end of each trial for 2s. Eye movements were recorded during the whole fMRI experiment.

3.3.7 Awareness test

After the main experiment, the participants were informed of the presentation of the masked faces. They were asked whether they consciously perceived any face during the unconscious

encoding. The participants who confirmed seeing a face during the unconscious encoding were excluded from the study (N=2). After that, the participants took part in an objective awareness test inside the MRI scanner. The awareness test consisted of 30 trials. In each trial, one masked face was presented using the same method as during the unconscious encoding in the main experiment. The participants tried to see the faces that were briefly flashed between the masks as well as also respond to direction of the bar at the centre of the mask by button press. Immediately after the unconscious presentation of each face, there was a free-viewing phase. During the free-viewing phase, there was a test image with two faces presented on it. One of them was the masked face and the other was a novel distractor face. In a forced choice manner, the participants were asked to choose the face that was behind the mask by pressing a button. I used a binomial test to compare the participants' performance with chance. The participants who performed above chance level of 19 trials (binomial test $p<0.05$) were excluded from the rest of analysis.

3.3.8 Eye tracking analysis

EyeLink Data Viewer (SR Research, Ottawa, ON, Canada) was used to analyse the eye tracking data. The average number of fixations on the target and the control face in the left visual field was calculated during the free-viewing phase. During the presentation of the cue, participants were instructed to keep their gaze on the fixation cross on the centre of the screen. This provided an estimate of the actual centre of the screen to correct for any eye-tracker drift. I defined the interest areas (IA) for the faces in the left and the right visual fields with respect to the estimated centre of the screen. In a few trials the participants did not fixate on the centre of screen during the cue. These trials, for which I was not able to correctly define the IAs, were excluded from the rest of our analysis. Trials with more than 15% of the retrieval time in blinks

were also excluded from the analysis. On average, 0.1% trials were excluded for each participant in this experiment.

3.3.9 fMRI Analysis

The event related analysis of functional images was performed using SPM 12 software (https://www.fil.ion.ucl.ac.uk/spm/). The analysis consisted of pre-processing, single subject analysis and group level analysis. During the pre-processing, I performed a slice timing correction on the fMRI data of each subject using sinc interpolation with the slice containing the hippocampus as the reference. The slice timing corrected data then were realigned to correct for head motion. I co-registered the anatomical image to the realigned functional images. The anatomical image was then segmented to grey matter, white matter and cerebro-spinal fluid using the tissue probability maps embedded in SPM 12. The deformation field for the forward transformation of the segmented anatomical image to the Montreal Neurological Institute (MNI) template image was calculated. I then used this forward deformation field for the transformation of all the functional images to MNI space.

The experimental design was event related with a fixed order of events in each trial. The duration of each trial was 35.5 s which was not a multiple of the TR. This way I was able to estimate the hemodynamic response function (HRF) for small event durations.

The first level analysis was performed using a mass univariate approach based on the general linear model (GLM). The event related paradigm included the following events: Exp encoding, Ctrl encoding, fixation, distraction, Exp free-viewing, Ctrl free-viewing (Exp: experimental, Ctrl: control). The onset time of the events were entered to specify the model. A high pass filter of 128 s was also applied. Contrast images from the single subject analysis (main effect of encoding: (Exp encoding + Ctrl encoding) versus implicit baseline (zero) and Exp free-viewing

- Ctrl free-viewing) were calculated and then further analysed at group level using one sample t test in SPM.

The fixations event, (looking at a fixation cross) is not an appropriate baseline for medial temporal lobe activation particularly in memory tasks (Stark and Squire 2001). It has been shown that even during very short periods of fixation event, medial temporal lobe shows high levels of activation (Stark and Squire 2001). Hence, as discussed by Stark and Squire considering fixation events as baseline can "*reduce, eliminate or even reverse the sign of effects related to memory functions*". Regarding the subtlety of unconscious influences and to prevent a false negative, I did not use the fixations as baseline for calculating the main effect of encoding in my experiment. Instead I used implicit baseline (zero) as calculated by the GLM in the SMP software. Implicit baseline (zero) is used in event related fMRI studies when there is a hesitation about the fixation to be an appropriate baseline (Geukes, Huster et al. 2013, Cignetti, Chabeauti et al. 2017). (It is worth considering that, the main effect of encoding compared with implicit baseline (zero) was only used to define the functional ROI in MTL for further correlation analysis and no inference about the main hypothesis was based on it.)

Region of interest analysis

Based on my a *priori hypothesis* I created a structural mask of the MTL (i.e. hippocampus, parahippocampus, perirhinal and entorhinal cortices) using the WFU pickatlas implemented in SPM12 (Maldjian, Laurienti et al. 2003) . This mask was interrogated to create a functional MTL ROI. As this was for ROI definition, I used a lenient threshold of uncorrected $p<0.005$ at voxel level and 10 voxel extent (Lieberman and Cunningham 2009). Uncorrected threshold is used for defining functional ROI in some fMRI studies to create an inclusive functional ROI for the cognitive function of interest (Matsuda, Fujimura et al. 2013). I did not make any

inference about the main hypothesis based on the results of uncorrected analysis and I used it just to define the functional ROI for further analysis. The active cluster within the MTL representing the main effect of encoding (Exp encoding + Ctrl encoding relative to the implicit baseline (zero)) was saved as a functional ROI for further correlational analyses. Based on my *a priori* hypothesis, I expected that a higher activation in the MTL functional ROI during the experimental encoding would accompany a higher number of fixations on the target during the experimental free-viewing. The mean percentage signal change in the MTL functional ROI during the encoding in both the experimental and the control conditions was extracted using the MarsBar toolbox implemented within the SPM12 (Brett, Anton et al. 2002). The extracted data was then entered in to the SPSS, Statistical Package for the Social Sciences (SPSS), version 25.0 for correlational analysis. According to my *a priori* hypothesis, I expected that the participants who had a higher activation in the MTL functional ROI during the encoding also had a higher number of fixations on the target during the free-viewing. I performed a one tailed Pearson's correlational analysis to test my hypothesis.

I also interrogated the structural MTL ROI for the unconscious retrieval effect, during the free-viewing. The contrast (exp free-viewing – ctrl free-viewing) only resulted in small active clusters (< 10 voxels) at the uncorrected threshold $p<0.005$ (no cluster was larger than 10 voxels in extent) (Lieberman and Cunningham 2009). As the right hippocampus was the main focus of my hypothesis, I also defined an structural ROI of right hippocampus using the WFU pickatlas to further investigate the difference between the exp free-viewing and the ctrl free-viewing events (exp free-viewing – ctrl free-viewing) (Maldjian, Laurienti et al. 2003). The mean percentage signal change in the right hippocampal structural ROI for each event (the exp free-viewing and the ctrl free-viewing) were calculated using the MarsBar toolbox implemented within SPM12 (Brett, Anton et al. 2002). According to my *a priori* hypothesis, I expected to see a significant difference in the mean percentage signal change in the structural

ROI of the right hippocampus between the exp free-viewing and the ctrl free-viewing events. The SPSS, was then used to perform a paired t test on the extracted data to test my *a priori* hypothesis. Cohen's d was calculated by dividing the mean of paired differences by the standard deviation (SD) of paired differences. In addition, I performed an exploratory analysis on the left hippocampal structural ROI to investigate the difference in the left hippocampal activation between the exp free-viewing and the ctrl free-viewing events using the same approach explained above.

The graphs of the paired t tests, were made according to the Cousineau-Morey method (Cousineau 2005, Morey 2008). In line with this method and just for visualization purpose, the data was normalized and the error bars showed the within subject 95% confidence interval of the normalized data (Cousineau 2005, Morey 2008).

The result of the hippocampal ROI analysis confirmed that activation in the right hippocampus was significantly higher during the exp free-viewing compared with the ctrl free-viewing. According to my a priori hypothesis this modulation of activation in the right hippocampal structural ROI reflected involvement of the right hippocampus in unconscious retrieval of the target provoked by the cue. In a post hoc analysis, I tested whether a more successful encoding of the target would lead to a more successful retrieval of the target. My findings also showed a positive correlation between the activation in the MTL functional ROI during the experimental encoding and the number of fixations on the target during the experimental free-viewing. According to my *a priori* hypothesis this finding provided an evidence for the involvement of the MTL functional ROI in unconscious encoding of the face-scene associations. It has been shown that fMRI activity in MTL during encoding as well as retrieval reflects the success of encoding and retrieval of episodic memory (Fernandez, Weyerts et al. 1998, Staresina and Davachi 2008, Hannula and Ranganath 2009). This way I considered the activation in the MTL functional ROI to be a reflective of success of unconscious encoding. I also considered that

size of activation in the right hippocampal structural ROI during the free-viewing could reflect the success of unconscious retrieval. Hence I expected that the participants who had a higher activation in the MTL functional ROI during the experimental encoding would also have a higher activation in the right hippocampal structural ROI during the experimental free-viewing. If this correlation was driven by factors other than memory I expected to see such a correlation in the control condition too. The mean percentage signal changes in the MTL functional ROI (during the experimental and the control encoding) and the right hippocampal structural ROI (during the experimental and the control free-viewing) were entered in to the SPSS. I performed a one tailed Pearson's correlational analysis to test my hypothesis.

3.4 Results

3.4.1 Awareness test

4 participants were excluded from the experiment due to awareness criteria explained in the methods section. A group of 9 participants who according to the awareness test were considered unaware of the masked stimuli entered the next steps of analysis. The fMRI data of the participants who did not pass the awareness test was not used in the fMRI analysis.

3.4.2 fMRI results

During the encoding, I found an active cluster in the MTL using the uncorrected analysis. The peak of the cluster in the MTL was located in the right hippocampus (x = 20, y = -24, z = -12, t = 6.34). The activation in the cluster also extended to the right parahippocampal gyrus. I used this cluster as a functional ROI for further correlational analysis (Figure 2).

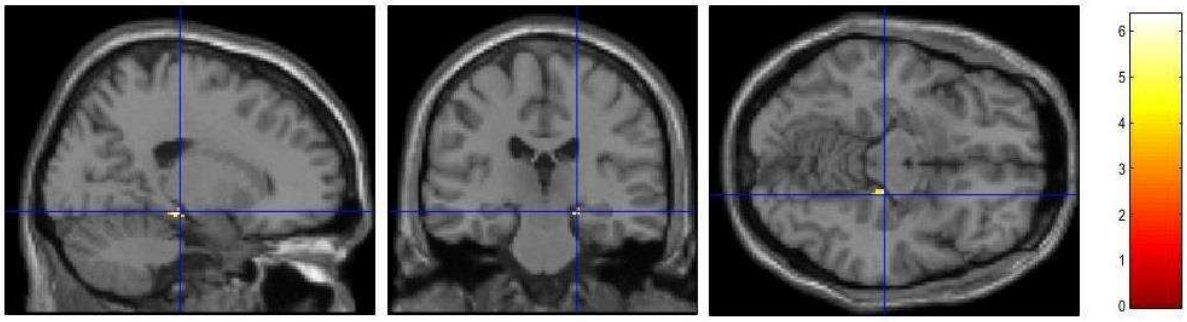

Figure 2. The active cluster that was used as a functional region of interest within the medial temporal lobe during the encoding: ([experimental encoding + control encoding) relative to the implicit baseline (zero). The peak of activation (crosshair) was in the right hippocampus and the activation also extended to the right parahippocampal gyrus. Activation is thresholded at uncorrected $p<0.005$ at voxel level and 10 voxel extent.

MTL activation during the encoding predicted the number of fixations on the target during the free-viewing

I found a significant correlation between the mean percentage signal change in the MTL functional ROI during the experimental encoding and the number of fixations on the target during the experimental free-viewing ($r = 0.802$, $p = 0.005$, Figure 3A).

There was no significant correlation between the mean percentage signal change in the MTL functional ROI during the control encoding and the number of fixations on the left face during the control free-viewing ($r = 0.081$, $p = 0.418$, Figure 3B).

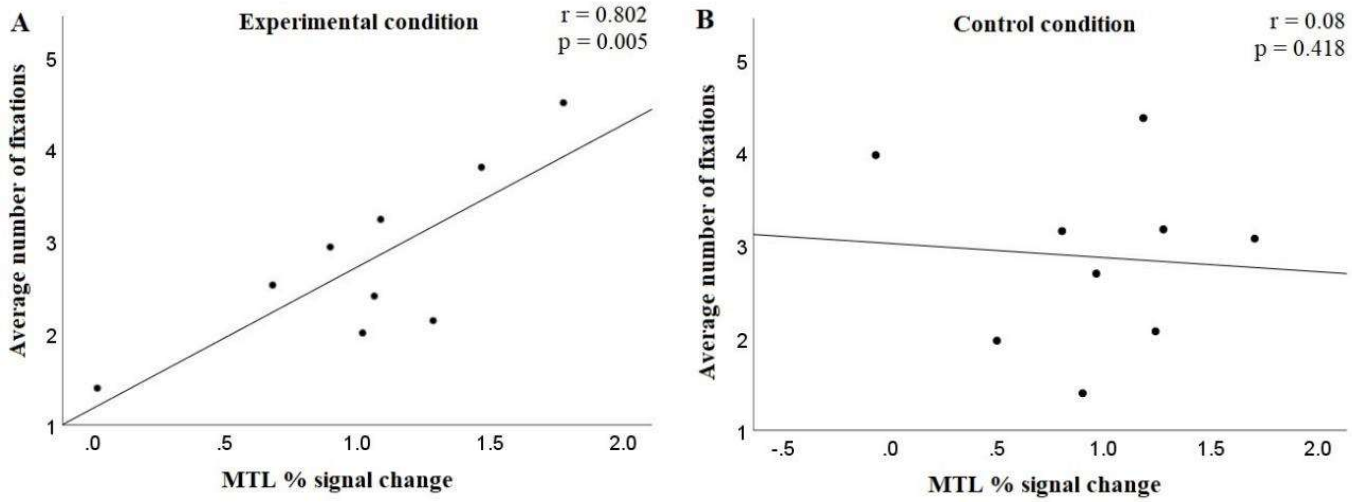

Figure 3. MTL activation during the encoding predicted the number of fixations on the target. A) The mean percentage signal change in the MTL functional ROI during the experimental encoding correlated with the number of fixations on the target during the experimental free-viewing. B) There was no significant correlation between the mean percentage signal change in the MTL functional ROI activation during the control encoding and the number of fixations on the left face during the control free-viewing.

The experimental free-viewing was accompanied by a higher activation in right hippocampus compared with the control free-viewing

The mean percentage signal change in the structural ROI of the right hippocampus was significantly higher during the exp free-viewing compared with the ctrl free-viewing, paired samples t-test (*mean of paired differences=0.107; SD of paired differences=0.128;* t(8)=2.51, p=0.036, Cohen's d = 0.836, Figure 4.A). I did not find a significant change in the mean percentage signal change in the structural ROI of the left hippocampus during the exp free-

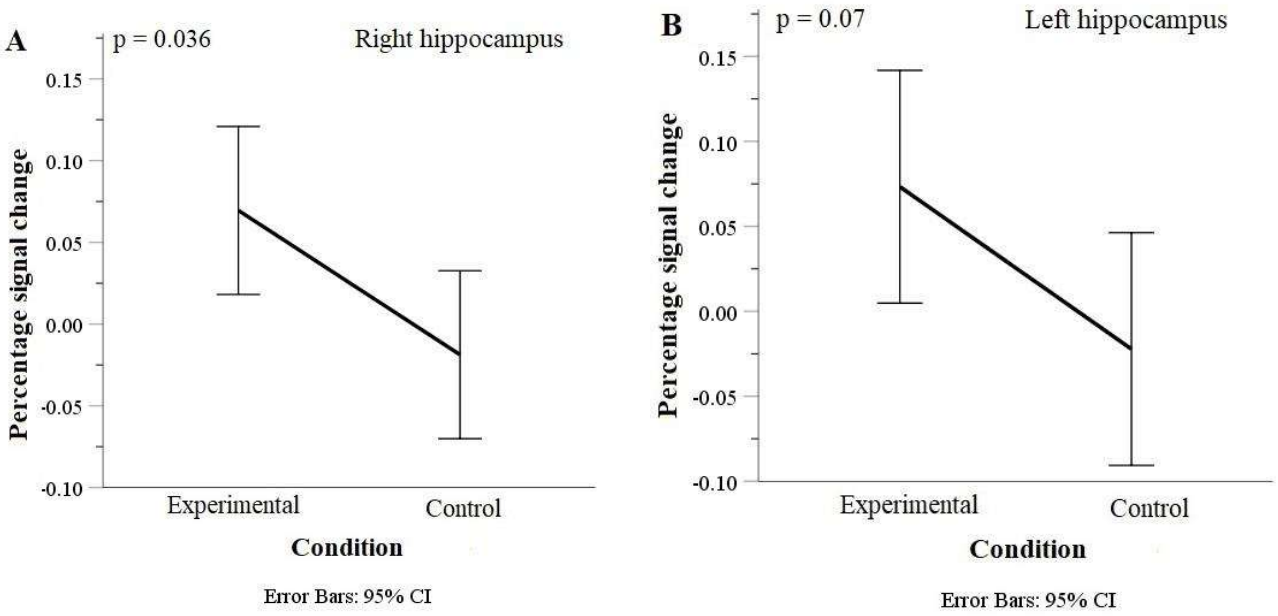

Figure 4. Enhancement of hippocampal activation between the experimental free-viewing and the control free-viewing. There was a significant enhancement in the mean percentage signal change in the structural ROI of right hippocampus during the experimental free-viewing compared with the control free-viewing. **B)** There was no significant change in the mean percentage signal change in the structural ROI of the left hippocampus during the experimental free-viewing compared with the control free-viewing. The error bars show 95% confidence interval.

viewing compared with the ctrl free-viewing, paired samples t-test (*mean of paired differences=0.113; SD of paired differences=0.162;* t(8)= 2.091, p= 0.07, Figure 4B).

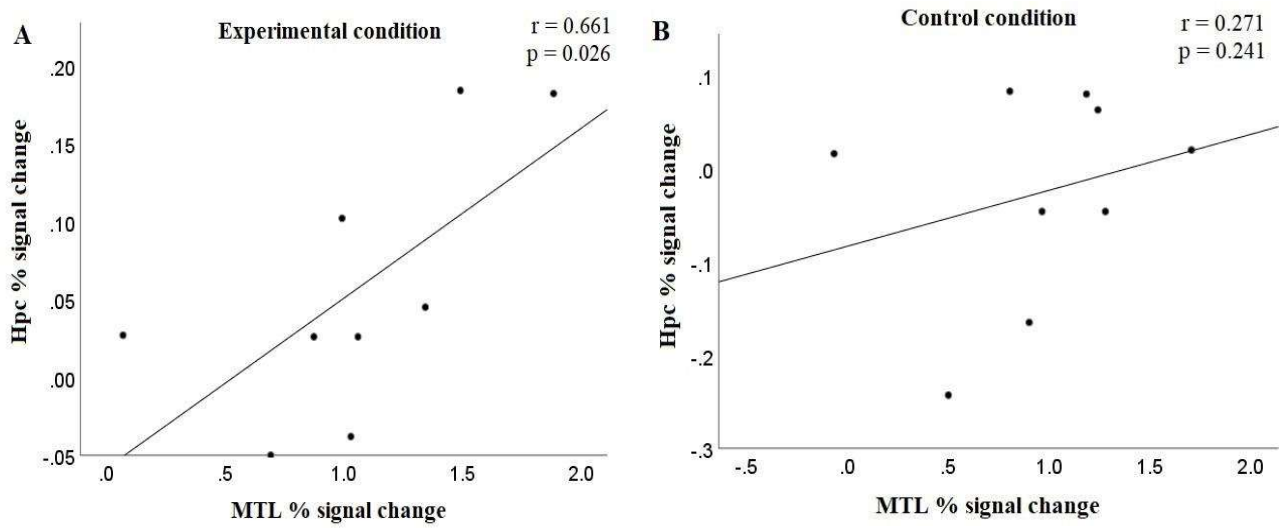

Figure 5. MTL activation during the encoding predicted right hippocampal activation during the free-viewing. **A)** The mean percentage signal change in the MTL functional ROI during the experimental encoding correlated with the mean percentage signal change in the right hippocampal structural ROI during the experimental free-viewing. **B)** There was no significant correlation between the mean percentage signal change in the MTL functional ROI during the control encoding and the mean percentage signal change in the right hippocampal functional ROI during the control free-viewing. Hippocampus (Hpc).

MTL activation during the encoding predicted right hippocampal activation during the free-viewing

I found a significant correlation between the mean percentage signal change in the MTL functional ROI during the experimental encoding and the mean percentage signal change in the right hippocampal structural ROI during the experimental free-viewing ($r = 0.661$, $p = 0.026$, Figure 5. A). There was no significant correlation between the mean percentage signal change in the MTL functional ROI during the control encoding and the mean percentage signal change

in the right hippocampal structural ROI during the control free-viewing ($r = 0.271$, $p = 0.241$, Figure 5B).

3.5 Discussion

In this study, I investigated the involvement of the MTL in unconscious encoding of complex visual associations and their subsequent unconscious retrieval predicted by the characteristics of episodic memory according to the processing-based-memory model (Henke 2010). During the encoding phase, the faces in the novel face-scene associations were masked to prevent awareness of these stimuli. Using a liberal threshold, I found an active cluster in the MTL with a peak in the right hippocampus during the encoding phase that was used as a functional ROI for the rest of analysis (uncorrected, $p<0.005$). I investigated whether the activation in this MTL cluster (functional ROI) could predict the unconscious memory retrieval, using the number of fixations on the target as a measure of unconscious memory retrieval provoked by the cue (Ryan, Althoff et al. 2000, Ryan and Cohen 2004, Meister and Buffalo 2016). The activation in the MTL functional ROI during the encoding predicted the number of fixations on the target during the free-viewing. The unconscious retrieval of face-scene associations provoked by the cue also led to an increase in the right hippocampal activation during the free-viewing phase (identified by comparing the experimental free-viewing with the control free-viewing). I also found a significant correlation between the activation in the MTL functional ROI during the encoding and the right hippocampal activation during the free-viewing phase in the experimental condition. Together these results suggest that the MTL, especially the hippocampus, plays a critical role in the unconscious encoding and subsequent retrieval of complex visual associations consistent with the episodic memory as specified by the processing-based-memory model.

One possible concern with this study can be whether retrieval of the faces is truly unconscious. Here, I used a number of methods to reduce the likelihood of conscious retrieval. First, the participants were unaware of the fact that there was a face behind the mask during the encoding and that the memory of that face would influence their eye movements during the free-viewing phase. This slight deception reduced the likelihood that they would see the face behind the mask. If the participants were making a conscious effort to retrieve a face, this could interfere with the effect of unconscious retrieval on viewing behaviour. After the main experiment the participants who reported seeing any face behind the mask were excluded from the experiment. There was also an objective awareness test and the participants who performed above chance in deciphering a face behind the mask were excluded. These steps made it very unlikely that the participants consciously retrieved a face that they never saw consciously. Hence even though I did not ask the participants to report the conscious retrieval of a face during the free-viewing phase in each trial the awareness tests I used made it very unlikely for them to consciously retrieve a face.

The MTL activation could also be modulated by the level of familiarity of the stimuli (Eichenbaum, Yonelinas et al. 2007, Kafkas and Migo 2009). In our experiment, all the faces displayed during the free-viewing in both the experimental and the control conditions were chosen from the encoded faces and were therefore equally familiar, ruling out this alternative explanation. The only difference between these conditions was that during the experimental condition the target face was superimposed on the cue scene during the encoding. Hence any difference between the experimental condition and the control condition should have arisen from the unconscious retrieval of face-scene associations after viewing the cue.

Besides memory processing, hippocampal activation in each individual could vary for different reasons such as the level of emotional arousal (e.g. stress inside the scanner), vigilance and age (Khalili-Mahani, Dedovic et al. 2010, Madan, Fujiwara et al. 2017, Archer, Lee et al. 2018).

However, it seems unlikely that such factors could drive the observed correlation between the activations in the MTL ROI during the encoding and the hippocampal activation during the free-viewing phase in the experimental condition. If the observed correlation was driven by factors other than memory, I should see a similar correlation during the control condition, which was not the case.

It is worth considering that the right hippocampal activation during the experimental free-viewing can be also driven by unconscious retrieval of the distractor (both the target and the distractor were seen before during the encoding phase). To the contrary the number of fixations on the target does not reflect the memory of the distractor. Hence, the right hippocampal activation during the experimental free-viewing is a less reliable measure of the unconscious retrieval of the target compared with the number of fixations on the target.

The MTL functional ROI also extended to the right parahippocampal gyrus. The parahippocampal gyrus also contributes to episodic memory, especially when place-related stimuli and contextual information are involved (Aminoff, Gronau et al. 2006, Bar, Aminoff et al. 2008). It has been proposed that parahippocampal gyus is involved in forming contextual associations (Bar 2004). During encoding in our study, novel faces were presented in the context of novel scenes. Hence our findings were also in line with the role of the parahippocampal gyrus in the encoding of contextual associations at the unconscious level.

Unfortunately, due to funding restrictions, I was only able to scan 14 participants, only 9 of whom passed the awareness test. Due to the cost of fMRI experiments, low sample size in most of the fMRI studies has reduced the replicability of these studies (Turner, Paul et al. 2018). It has been shown that even very large samples (N=100, that are very rare), are still far from perfect replicability (Turner, Paul et al. 2018). In this regard the replicability of low powered

fMRI studies, should be tested by future meta-analysis. Apart from the replicability the other concern about low sample size is that it increases the possibility of the false negative: the type II error (Cremers, Wager et al. 2017). One solution to increase the power of studies with small sample size is to decrease the number of statistical tests by using a region of interest analysis based on previous hypothesis (Cremers, Wager et al. 2017). Hence in this study I only concentrated on the mean percentage signal change whithin the areas primarily involved in episodic memory and tested specific *a priori* predictions. Due to my focus on the MTL, I did not acquire whole brain data. This means that I could only explore within my specific predicted ROIs, rather than potentially looking at other areas of the brain. This was necessary to ensure sufficient signal from the hippocampus and to reflect the focus of the literature (Henke 2010).

The length of my scanning session also precluded having the target face appear on both sides equally, which would have allowed replication of the eye tracking findings from my previous study. As in that study (Chapter 2), only targets on the left showed effects of unconscious encoding, I had to make the decision to only present targets on the left in the fMRI study to optimise my data. But it increases the potential risk of predicting the location of the target at unconscious level. It has been shown that episodic encoding and retrieval of overlapping word pairs (winter-red, red-computer) induces higher activation in the hippocampus compared with the unconscious encoding of non-overlapping words (spring-red, yellow-ball) (Reber, Luechinger et al. 2012). Hence the hippocampal activation can be modulated by unconscious inference making. Thus, it could be possible that the participants were able to make an inference about the position of the target during the free-viewing at unconscious level. But making an inference about the position of the targets could not be possible without a prior unconscious retrieval of the target-cue associations. Hence even if the hippocampal activation during the free-viewing of the target was influenced by making inference about the position

of the target at unconscious level the observed change in the hippocampal activation between the experimental and the control free-viewing is still a reflective of the unconscious retrieval of the target-cue associations. At the same time the observed correlations between the MTL activation during the encoding and the number of fixation (or the hippocampal activation) during the free-viewing can not be simply induced by a mere prediction of the position of the target. Future studies with the target in both visual field can be beneficial in testing the extent of the infulence of this inference making on the hippocampal activation or the viewing behaviour during the free-viewing at unconscious level .

In the current experiment, I found that activation in MTL during the unconscious encoding predicted the number of fixations on the target and also predicted the activation of right hippocampus during the free-viewing. I also found an enhancement in right hippocampal activation during the experimental free-viewing compared with the control free-viewing. These findings emphasise the role of MTL structures, particularly the hippocampus, in unconscious encoding and subsequent unconscious retrieval of episodic memory in line with the processing-based-memory model. The mechanism by which the unconsious retreival modulates the number of fixations on the target is not yet clearly understood (Meister and Buffalo 2016). In the next chapter using a functional connectivity approach I will investigate the underlying neural mechanism for comdulation of viewing behaviour by unconscious episodic memory retrieval.

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Chapter 4 - How does functional connectivity related to unconscious episodic memory of visual associations modulate viewing behaviour?

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How does functional connectivity related to unconscious episodic memory of visual associations modulate viewing behavior?

4.1 Abstract

Viewing behavior is the most important behavioral measure to investigate unconscious episodic memory. Despite its importance, the underlying neural mechanism for modulation of viewing behavior by unconscious episodic memory is not yet known. According to the attention-to-memory model proposed by Cabeza et al (Cabeza, Ciaramelli et al. 2008), I hypothesized that interaction between episodic memory and the bottom-up attention system plays a dominant role in modulation of viewing behavior by unconscious episodic memory. I tested this hypothesis by performing a functional connectivity analysis on the fMRI data from chapter 3. It has been shown that ventral frontoparietal network mediates the bottom-up attention. This network extends from supramarginal gyrus (SMG) to ventral frontal areas. Right hippocampus (HPC) also has a dominant role in episodic memory of novel faces. I investigated connectivity of right HPC and ventral frontoparietal network between the experimental and the control free-viewing. According to the attention-to-memory model, involuntary episodic memory signals are sent from HPC to ventral parietal areas (including the SMG) to control visual attention. I also tested whether right HPC- right SMG connectivity modulates the number of fixations on the target. I found that during the free-viewing, right HPC connectivity with a ventral frontoparietal network in the right hemisphere was greater in the experimental compared with the control free-viewing. This network included the right supramarginal gyrus (SMG), right angular gyrus, right precentral gyrus and right inferior frontal gyrus. Right HPC-right SMG connectivity also predicted the number of fixations on the target during the free-

viewing. The right HPC- right SMG connectivity also predicted the number of fixations on the left face during the control free-viewing. My findings support the hypothesis that interaction between unconscious episodic memory and bottom-up attention plays a dominant role in modulation of viewing behavior provoked by unconscious episodic retrieval. The last finding suggests that interaction between the right dominant memory of faces and right dominant bottom-up attention could increase leftward attentional bias during the control free-viewing.

4.2 Introduction

Viewing behaviour has been the most important measure to investigate unconscious visual episodic memory. To the best of my knowledge all of the studies in this field have relied on viewing behaviour as being indicative of unconscious retrieval (Ryan, Althoff et al. 2000, Ryan and Cohen 2004, Hannula and Ranganath 2009) (and chapter 2). To my knowledge no study so far has investigated the neural mechanisms underlying the modulation of viewing behaviour by unconscious retrieval of visual episodic memory. Gaining knowledge about the relationship between eye movements and unconscious memory could be beneficial in designing and optimizing clinical tools to investigate unconscious retrieval of memory in disorders like post-traumatic stress disorder. In the current study I investigated the interaction between brain areas involved in episodic memory and brain areas involved in controlling viewing behaviour.

In Chapter 2, I investigated unconscious encoding and subsequent unconscious retrieval of episodically associated visual stimuli using fMRI and eye tracking. During the encoding phase, novel face-scene associations were masked from consciousness. After a distraction interval, one of the encoded scenes was presented as a cue to provoke retrieval of the associate face (target). Subsequently, participants were instructed to freely view two faces, one of which was the target face (previously presented masked on the cued scene) alongside a distractor face in

the experimental condition. In the control condition, neither of the faces presented was associated with the cue scene but had been presented on other scenes. I had two types of objective and subjective awareness tests to make sure that the participants did not have conscious access to the retrieved memory of the target (Hannula, Simons et al. 2005). In this chapter I performed functional connectivity analysis on the data from Chapter 3, to investigate the underlying neural mechanism through which unconscious episodic memory modulates viewing behavior[2].

According to models of oculomotor guidance, selection of saccades depend on both visual characteristics of stimuli (colour, luminance etc.) and also previous experience and expectations about the stimuli (Findlay and Walker 1999, Itti and Koch 2000, Hamker 2006). In 2019, Ryan et al. reviewed the literature on oculomotor control by hippocampal memory and concluded that there are many candidate brain areas for receiving signals from the hippocampus for oculomotor control (Ryan, Shen et al. 2019). The key question for this chapter is which brain area is *functionally relevant* for controlling viewing behaviour when unconscious retrieval of a memory is influencing free viewing.

To determine the best candidate regions for modulation of eye movements by unconscious retrieval, we need to consider a number of factors. First, modulation of viewing behaviour by unconscious memory should be driven by cognitive control of saccades by memory rather than visual characteristics of the stimuli. Second, free viewing of stimuli means that participants have no goal or expectation for unconscious retrieval. This ensures that goal-driven executive control of saccades cannot be the dominant mechanism for oculomotor control in this condition. These ideas exclude many of the brain areas known to be involved in oculomotor control based on visual saliency of the stimuli or the goal of the task from being candidates for

[2] Despite the low sample size (due to funding limitations), because of the importance of the question to be answered in this chapter and according to my initial plan, I decided to have this chapter based on the connectivity analysis of the fMRI data.

oculomotor control by unconscious retrieval during the free-viewing phase. This narrows the potential areas for this analysis.

In their review, Cabeza et al. suggested an "attention-to-memory" model and explained how involuntary hippocampus-mediated memory modulates visual attention. According to this model, involuntary memory retrieval, as an incoming signal, captures attention through interaction with ventral parietal cortex (VPC) (VPC is an important part of bottom-up attention network) (Cabeza, Ciaramelli et al. 2008, Ciaramelli, Grady et al. 2010). This model may be a little confusing since the bottom-up attention network is known to be involved in stimulus-driven guidance of attention (Katsuki and Constantinidis 2014). But as explained in the model *"if one defines bottom-up attention as attention driven by incoming information, regardless of its source"* then role of bottom-up attention in modulation of viewing behaviour by unconscious episodic memory becomes clear (Cabeza, Ciaramelli et al. 2008). In contrast, the top-down attention network is involved goal driven control of saccades based on expectations of task (Cabeza, Ciaramelli et al. 2008). I therefore focused on interaction between the hippocampus and the regions involved in the bottom-up attention network, particularly in the VPC to investigate modulation of viewing behavior by unconscious episodic memory.

Bottom-up attention is mediated by a ventral frontoparietal network that extends from supramarginal gyrus (SMG is part of VPC) to inferior frontal areas (Corbetta, Patel et al. 2008). VPC is known to have a dominant role in the integration of incoming inputs (e.g. sensory or mnemonic) to modulate oculomotor responses. VPC has a strong functional connection with the hippocampus during resting state and this connectivity is modulated during the recollection of encoded information (Vincent, Snyder et al. 2006). Functional coupling between VPC and hippocampus has been reported during detection of encoded items in a bottom-up manner when sudden retrieval grabs attention (Cabeza, Mazuz et al. 2011). These findings make the VPC,

particularly the SMG, a good candidate for the modulation of visual attention by interaction with hippocampus during unconscious memory retrieval.

According to the literature, episodic memory is mediated by medial temporal lobe structures particularly the hippocampus (Tulving 2002, Henke 2010). There is accumulating evidence that right MTL has a dominant role in memory of novel faces (Ranganath and D'Esposito 2001, Crane and Milner 2002, Milner 2003, Taylor, Mills et al. 2011, Von Der Heide, Skipper et al. 2013). In Chapter 3, I also found that the right hippocampal activation increased during the experimental free-viewing compared with the control free-viewing. This enhancement in the right hippocampal activation was related to the unconscious retrieval of the target face provoked by the cue. Hence I investigated the functional connectivity between the right hippocampus and the ventral frontoparietal network during the free-viewing of faces. In the current study, I tested whether unconscious retrieval of the target led to a higher functional connectivity between right hippocampus and the ventral frontoparietal network during the experimental free-viewing compared with the control free-viewing.

The number of fixations is an important eye-tracking measure that reflects recognition memory or episodic memory (Loftus 1972, Kafkas and Montaldi 2011, Molitor, Ko et al. 2014, Meister and Buffalo 2016, Liu, Shen et al. 2017). Unconscious retrieval of manipulated parts of scenes is accompanied by more fixations on manipulated parts compared with the same part in original images (Ryan, Althoff et al. 2000, Ryan and Cohen 2004). In chapter 2, I found that unconscious retrieval of the target provoked by the cue during the free-viewing led to an enhancement in the number of fixations on the target compared with the distractor in the left visual field. Hence, in this chapter, I expected that unconscious retrieval of the target would be accompanied by an increment in visual attention toward the target that would increase the number of fixations on the target. As discussed before, SMG is a good candidate for modulation of visual attention through interaction with hippocampus during unconscious episodic memory

retrieval. Thus, right hippocampal activation during the experimental free-viewing (provoked by unconscious retrieval of the target) could interact with SMG in a way that increased visual attention toward the target.

In Chapter 2, I did not see any modulation in the number of fixations on the target in the right visual field. I hypothesized that leftward attentional bias and attention toward the target on the right could weaken or cancel each other out. In contrast, when the target was in the left visual field, attention toward the target and leftward attentional bias both guided visual attention to the left. This could explain why I only saw a significant modulation of viewing behaviour in the left visual field.

As mentioned above, during the experimental free-viewing, the interaction between the right hippocampus (HPC) and SMG induced by unconscious retrieval of the target, can lead to a memory-guided attention (i.e. guidance of attention by memory) toward the target. (Cabeza, Ciaramelli et al. 2008). But this interaction can also influence the leftward attentional bias. The leftward attentional bias has been related to the right hemisphere dominance in ventral frontoparietal network that extends from SMG to ventral frontal areas (de Schotten, Dell'Acqua et al. 2011). There is accumulating evidence that experimental variables that change this right hemisphere dominance can also changes the size of this leftward attentional bias (Cattaneo, Silvanto et al. 2009, Ricci, Salatino et al. 2012, Petitet, Noonan et al. 2015). For example, engagement in tasks that increase right hemisphere dominance in attentional processing like using left hand (Sampaio and Chokron 1992, McCourt, Freeman et al. 2001) or left eye (McCourt, Garlinghouse et al. 2001) increase leftward attentional bias. In addition, it has been shown that trans-cranial magnetic stimulation of ventral parietal areas, including angular gyrus or SMG in the right hemisphere, reduces or inverts leftward attentional bias (Cattaneo, Silvanto et al. 2009, Ricci, Salatino et al. 2012, Petitet, Noonan et al. 2015). Hence it is possible that performing a task that increases activation in right SMG also increases leftward attentional

bias. Right hemisphere is the dominant hemisphere for both memory of novel faces (Ranganath and D'Esposito 2001, Crane and Milner 2002, Milner 2003, Taylor, Mills et al. 2011, Von Der Heide, Skipper et al. 2013) and visuospatial attention (de Schotten, Dell'Acqua et al. 2011). Hence, the enhancement of functional connectivity between right HPC and right SMG induced by the unconscious retrieval of the target can increase leftward attentional bias. When the target is in the left this enhancement of the right HPC – right SMG connectivity increases both the memory-guided attention toward the target in the left and the leftward attentional bias that would increase the overall visual attention toward left. The enhancement of visual attention toward left increases number of fixations on the target in the left. Hence the enhancement of the right HPC- right SMG functional connectivity induced by unconscious retrieval would lead to an enhancement of number of fixations on the target in the left visual field.

In chapter 3, I found that right hippocampal activation during the experimental free-viewing could reflect the unconscious retrieval of the target. It has also been shown that hippocampal activation during retrieval correlates with success of retrieval (Heckers, Weiss et al. 2002). Hence more successful retrieval of the target could induce a higher activation in the right HPC during the free-viewing that could lead to a bigger interaction with the right SMG. As mentioned before the enhancement in right HPC-Right SMG connectivity would increase the number of fixations toward the target in the left visual field. Hence I hypothesized that more successful unconscious retrieval could accompany a higher functional connectivity between the right HPC and the right SMG during the free viewing of the target that should accompany a higher number of fixations on the target in the left visual field. In this way a positive correlation between the right HPC - right SMG connectivity and the number of fixations on the target in the left during the free-viewing would be consistent with the literature and my previous findings.

4.3 Methods

In this chapter I performed further analysis on the fMRI and the eye-tracking data from Chapter 3 to test my hypothesis about the underlying neural mechanism for modulation of viewing behaviour by unconscious visual episodic memory.

4.3.1 fMRI Analysis

Single level analysis was performed on the preprocessed fMRI images from chapter 3, using the general linear model (GLM) as implemented in SPM 12. The event related paradigm included the following events: Encoding, fixation, Math, Exp retrieval, Ctrl retrieval (Exp: experimental, Ctrl: control). The onset time of the events were entered to specify the model. The hemodynamic response to each event was modelled by convolution of a delta (stick) function (representing neural activity at the onset of stimulus presentation) with the canonical hemodynamic response function. A high pass filter of 128 s was applied. For each participant, the t-contrast images were made (exp free-viewing - ctrl free-viewing). The contrast images from single subject analysis were further analysed at the group level using a one sample t-test in which the mean value of each voxel across all participants was tested against zero. All the activations were thresholded at $p<0.001$ uncorrected at voxel level with a minimum 10 voxel extent. This uncorrected threshold was not used to test my main hypothesis but since it involved an activation in the right SMG it was presented to facilitate future meta analysis about this area (Lieberman and Cunningham 2009).

4.3.2 Functional connectivity analysis

The conn toolbox (http://www.nitrc.org/projects/conn) (Whitfield-Gabrieli and Ford 2012) was used for functional connectivity analysis. I performed a functional connectivity analysis on the pre-processed images from chapter 3. Functional outlier detection was performed using

Artefact Detection Tools (ART)-based scrubbing (www.nitrc.org/projects/artifact_detect/). This method created a first level covariate named 'scrubbing' which was used to scrub outlier scans for each subject/session during the de-noising step. Physiological noise and other sources of noise (i.e., white matter and CSF effects, scrubbing, main task effects and movement-related covariates) were removed using a component-based noise correction method (CompCor) implemented in the software (Behzadi, Restom et al. 2007). The default band pass filter of ($0.008 < f < 0.09$) was used for each brain voxel to reduce noise. This filter was also suitable for the event of interest in this analysis (i.e. the free-viewing event with the period of 35.5 s was passed through this filter). I performed a seed-to-voxel analysis using the weighted general linear model (GLM) to compare the connectivity of the right hippocampus and the other brain voxels between the experimental and the control free-viewing events. To generate the temporal connectivity map of each event and each subject, Pearson's correlation coefficient between the mean signal of the seed ROI and all the other brain voxels was calculated. The hemodynamic response function (HRF) was convolved with the impulse time series associated with each event to calculate weighted correlations between the voxels or the ROIs for that event. To perform a second level analysis the correlation coefficients were then transformed to normally distributed z-scores by Fisher transformation. The first level connectivity maps for each subject and each event were then entered into a group level analysis. The areas that had higher functional connectivity with the right hippocampal seed ROI at the group level during the experimental free-viewing compared with the control free-viewing were detected using paired t test. The group level functional connectivity results were thresholded according to the default setting of the CONN toolbox for the seed-to-voxel analysis. In this way, the group level functional connectivity results were initially thresholded at $p < 0.001$ (uncorrected, voxel level). This was the threshold to define a cluster. Among the resulted clusters, only the FDR-corrected clusters ($p<0.05$) were reported (Friston, Worsley et al. 1994).

The seed-to-voxel analysis revealed that the right hippocampus (HPC) had a higher connectivity with a network including the right supra-marginal gyrus (SMG) during the experimental free-viewing event compared with the control free-viewing event. Based on my *a priori* hypothesis, I performed a correlational analysis between the right HPC- right SMG connectivity and the number of fixations on the target and also the left control face during the experimental and the control free-viewing events respectively. Since the target was always presented in the left visual field, the left face during the control free viewing was used as a control. The SMG cluster resulted from the seed-to-voxel analysis was imported as a target ROI in the ROI to ROI analysis. I then extracted the connectivity values (Fisher z score) between the right HPC ROI and the SMG ROI during the experimental and the control free-viewing events to conduct correlational analysis using the SPSS, Statistical Package for the Social Sciences (SPSS), version 25.0.

The ROI-ROI connectivity values between the right HPC and the right SMG during the experimental free-viewing were not normally distributed - it contained a possible outlier. The test of normality was done using the Shapiro-Wilk test ($p<0.05$). As I only had a small sample size in this study, I treated the outlier with caution since it was possible that with a larger sample size, this outlier could fall within the normal distribution. Removing the outlier made a huge difference in the result of correlational analyses during the experimental free-viewing event. As a result, for the experimental free-viewing, I did the correlational analysis twice: once with the outlier and once without the outlier. In the first approach I assumed that the data had a normal distribution and the outlier was actually part of a normal distribution that just looked like an outlier due to the low sample size. In this analysis, I did not remove the outlier and I performed a Pearson correlation analysis on the data. In the second approach, I assumed that the data were not normally distributed and had extreme values. The Pearson correlation is not a proper tool for data sets with outliers and Spearman correlation is recommended for such data

sets (Rousselet and Pernet 2012, de Winter, Gosling et al. 2016). Hence, according to the skipped correlation approach recommended by Rousselet and Pernet, I excluded the outlier first and then performed a Spearman correlational analysis suitable for non-normally distributed datasets (Rousselet and Pernet 2012).

Based on my *a priori* hypothesis, I tested whether there was a positive correlation between the right HPC- right SMG connectivity and the number of fixations on the target during the free-viewing. One-tailed Pearson's correlational analysis was used to test this hypothesis when I assumed the normal distribution of the dataset. One-tailed Spearman's correlational analysis was used to test this hypothesis when I assumed that distribution of dataset had an outlier and was not normal.

4.4 Results

4.4.1 fMRI results

I assessed the brain areas that showed higher activation during the experimental free-viewing condition compared with the control free-viewing (uncorrected, $p<0.001$). The observed activation in the SMG and other brain areas could facilitate future meta-analysis in this field. I found activations with the peaks in the right SMG (part of the PVC), right inferior temporal gyrus and other temporal and occipital areas (table 1, figure 1). No supra-threshold cluster showed higher activation during the free-viewing phase in the control condition compared with the experimental condition. No inference about my main hypothesis was based on these uncorrected results.

Table 1. Local maxima of the clusters that showed higher activation during the experimental free-viewing compared with the control free-viewing.

Anatomical regions	MNI coordinate			t-value	Cluster size
	x	y	z		(voxels)
Right supramarginal gyrus	56	-32	22	7.31	17
Right inferior temporal gyrus	44	-60	-8	7.29	27
Right middle temporal gyrus	46	-50	16	6.92	13
Left middle occipital gyrus	-46	-76	-2	6.75	18
	-58	-64	0	6.45	19
Right cerebellum	16	-50	-12	6.44	19
Left cuneus	-8	-82	18	6.44	17
Left calcarine	-6	-80	10	5.98	17

All the activations were thresholded at uncorrected $p<0.001$ at voxel level and 10 voxel extent.

4.4.2 Results of the functional connectivity analysis

Hippocampal connectivity with a ventral frontoparietal network increased in the experimental compared with the control free-viewing

The brain areas that showed a higher functional connectivity with the right hippocampus seed during the experimental free-viewing compared with the control free-viewing were assessed using the seed-to-voxel analysis. The right hippocampus seed showed a higher functional

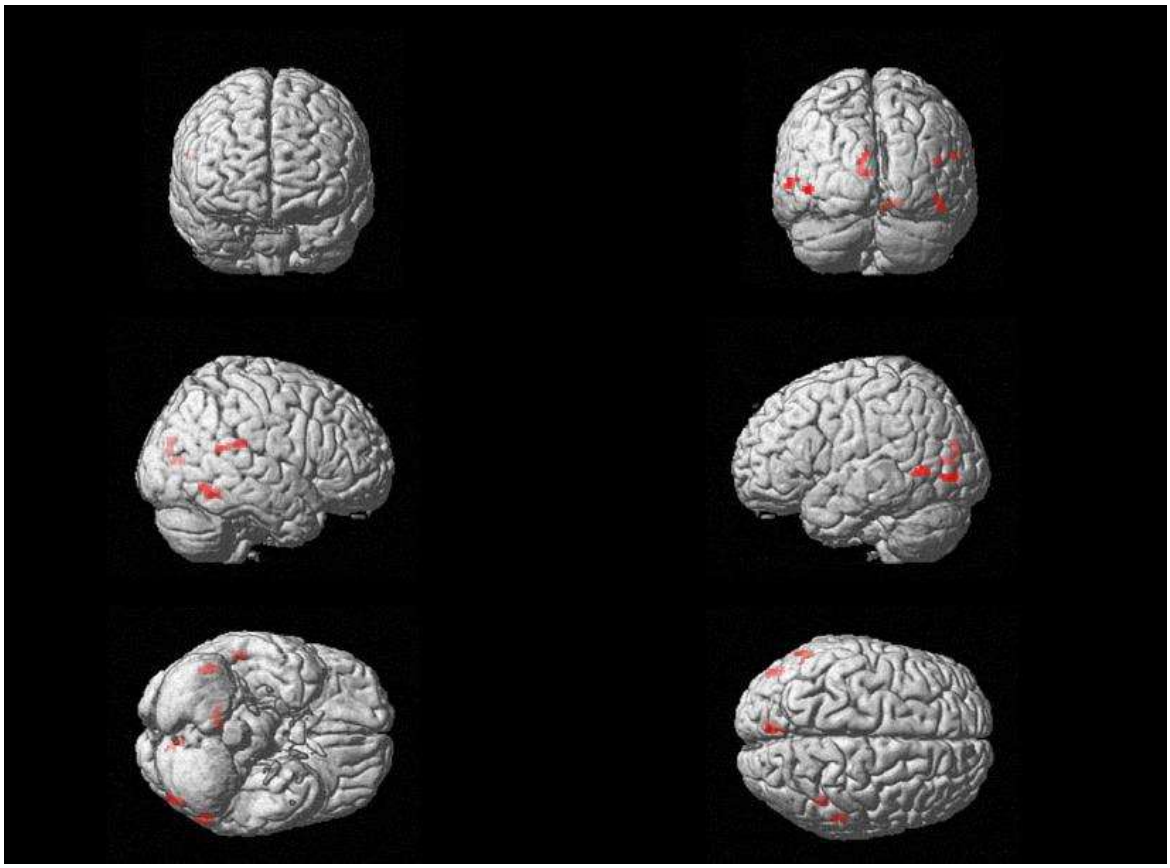

Figure 1. Brain activation resulted from the comparision of the experimental free-viewing and the control free-viewing (exp free-viewing > ctrl free-viewing). Activations are thresholded at uncorrected $p<0.001$ at voxel level and 10 voxel extent.

connectivity with a frontoparietal network in the right hemisphere and precuneus in the left hemisphere. The right frontoparietal network included active clusters in right SMG, right angular gyrus, right precentral gyrus, and right inferior frontal gyrus. (Figure 2, Table 2). I did not find any suprathreshold cluster that showed higher connectivity with the right hippocampus seed during the control free-viewing compared with the experimental free-viewing.

Table 2. The clusters that showed higher functional connectivity with the right hippocampal seed during the experimental free-viewing compared with the control free-viewing.

Seed	Anatomical regions	MNI coordinate			t-value	Cluster size
		x	y	z		(voxels)
R hippocampus	Right inferior frontal gyrus	56	29	10	13.10	9
	Right supramarginal gyrus	62	-22	32	12	12
	Right angular gyrus	50	-56	16	10.70	11
	Right precentral gyrus	58	8	28	9.99	13
	Left precuneus	-12	-62	24	8.22	11

Clusters that passed cluster-extent, FDR-correction ($p<0.05$) are reported (Friston, Worsley et al. 1994).

Right HPC – right SMG connectivity predicted the number of fixations on the face in the left visual field during the free-viewing

I explored the correlation between the number of fixations on the target and the right HPC - right SMG connectivity during the free-viewing. There was a significant correlation between the number of fixations on the target and the right HPC- right SMG connectivity during the experimental free-viewing (including the outlier) ($r=0.753$, $p= 0.01$, Figure 5A). There was also a significant correlation between the number of fixations on the target and the right HPC – right SMG connectivity during the experimental free-viewing (without the outlier)

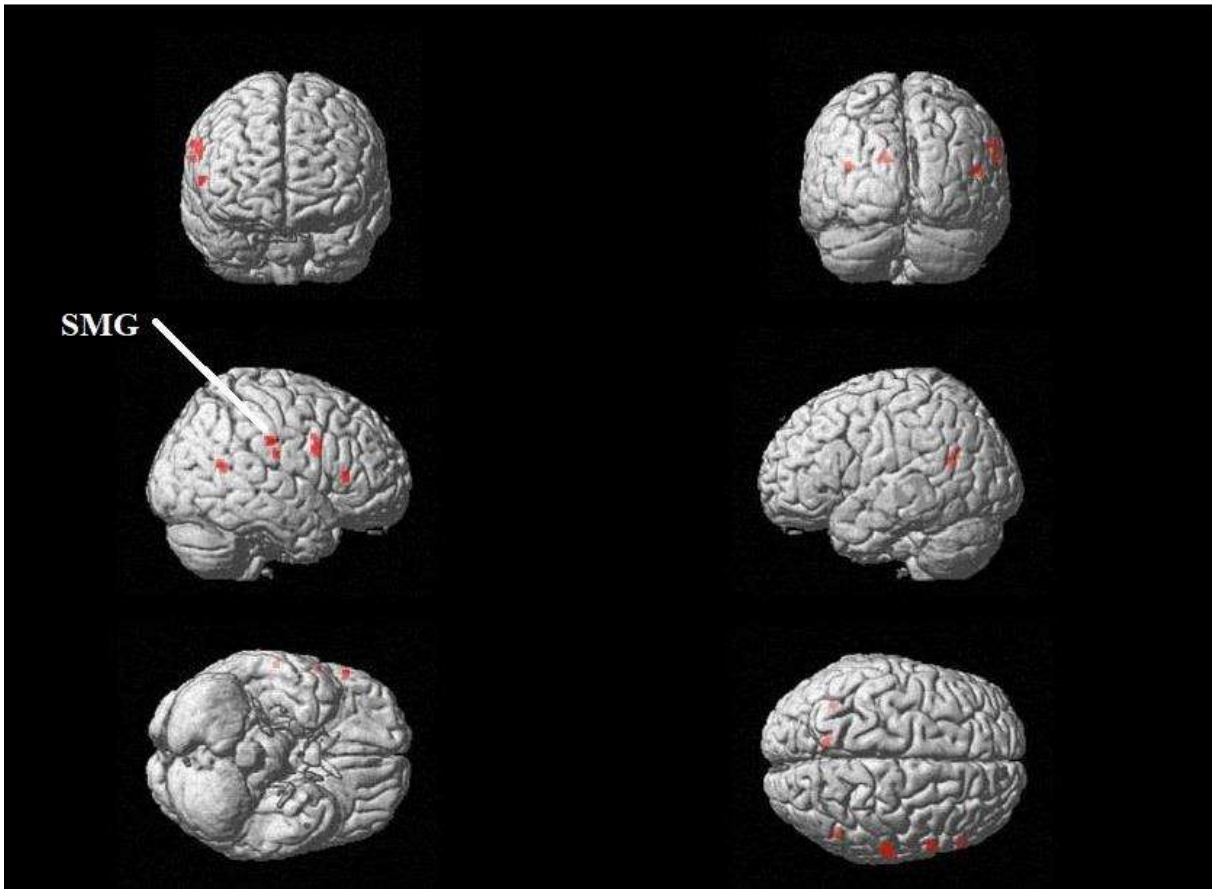

Figure 3. Right hippocampal seed had a higher functional connectivity with a frontoparietal network in the right hemisphere and the precuneus in left hemisphere during the experimental free-viewing compared with the control free-viewing. Clusters that passed cluster-extent, FDR-correction ($p<0.05$) are reported (Friston, Worsley et al. 1994). Supramarginal gyrus (SMG).

($r=0.667$, $p= 0.035$, Figure 5A). I also found a significant correlation between the number of fixations on the control face in the left visual field and the right HPC – right SMG connectivity during the control free-viewing ($r= =0.787$, $p=0.006$, figure 5 B).

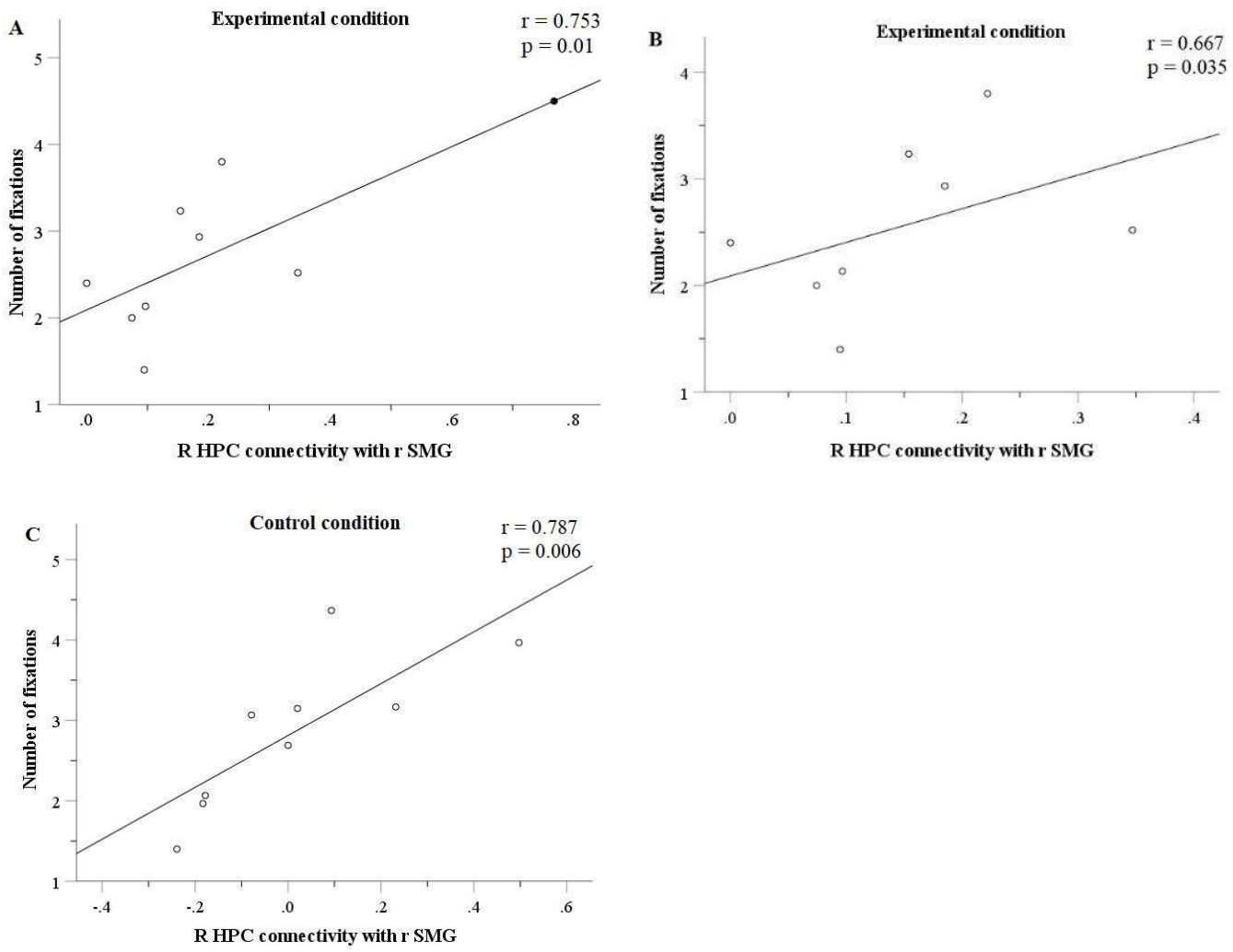

Figure 4. Correlation between average number of fixations on the left face and connectivity between right hippocampus (HPC) and right (SMG) during the free-viewing. A) The right HPC- right SMG connectivity including the outlier (filled dot) during the experimental free-viewing phase was significantly correlated with the average number of fixations on the target. B) The right HPC- right SMG connectivity (without the outlier) during the experimental free-viewing was still significantly correlated with the average number of fixations on the target. C) The right HPC- right SMG connectivity during the control free-viewing phase was significantly correlated with the average number of fixations on the left face.

4.5 Discussion

In the current study, I investigated the neural mechanism through which viewing behavior was modulated by unconscious retrieval of episodically associated visual stimuli after their unconscious encoding. I found that the functional connectivity between the right hippocampus (HPC) and a frontoparietal network in right hemisphere increased in the experimental compared with the control free-viewing. This network included active clusters in right SMG, right angular gyrus, right precentral gyrus and right inferior frontal gyrus. These findings provided evidence for an interaction between hippocampus and a ventral frontoparietal network that extends from ventral parietal cortex to inferior frontal regions during the free-viewing phase. This supported the hypothesis about the interaction between episodic memory and bottom up attention during unconscious retrieval of episodic memory.

All the faces presented during the free-viewing in both the experimental and the control conditions were presented during the encoding part of the same trial and were equally familiar. The only difference between the experimental and the control free-viewing phases was that the target was episodically related to the cue scene. Hence the difference in the hippocampal connectivity between the experimental and the control free-viewing could not be related to the familiarity of the faces and could have only been provoked by unconscious retrieval of the target faces provoked by the cue.

In addition, I found that the participants who had a higher right HPC- right SMG connectivity, also had a higher number of fixations on the target in the left visual field during the experimental free-viewing. This provided support for the hypothesis that the right HPC – right SMG connectivity increased the memory-guided attention toward the target as well as the

leftward attentional bias and both of these factors increased the number of fixations on the target in the left.

I also found that the participants who had a higher right HPC- right SMG connectivity, also had a higher number of fixations on the left face during the control free-viewing. Both of the faces presented during the control free-viewing were presented during the encoding part of the same trial. Hence it was probable that unconscious retrieval of the control faces was accompanied by an enhancement of the right HPC- right SMG connectivity. The enhancement of the right HPC- right SMG connectivity due to the unconscious retrieval of the control faces could increase the right hemisphere dominance in the ventral frontoparietal network and increase leftward attentional bias during the control free-viewing phase.

The correlation between the number of fixations on the left control face and the right HPC-right SMG connectivity could not reflect the preferential unconscious retrieval of the left face. During the control free-viewing, both of the faces in the left and the right visual fields were presented during the encoding part of the same trial. Hence, both of the faces were equally likely to provoke unconscious retrieval. Thus, unconscious retrieval of the left face could not explain the modulation of viewing behaviour on the left face by the right HPC – right SMG connectivity during the control free-viewing.

These findings provided support for the hypothesis that interaction between the right dominant episodic memory areas and the right dominant bottom-up attention areas could increase leftward attentional bias that is evident in eye movements. This could explain why, in Chapter 2, I did not see a modulation in viewing behaviour by unconscious retrieval in the right visual field. If unconscious retrieval increased the right HPC - right SMG connectivity during the free-viewing phase, then I expect an increment in the leftward attentional bias that could weaken or negate the memory-guided attention toward the target in the right.

The evidence for the enhancement of leftward attentional bias by unconscious retrieval during the free-viewing can explain some of previous results in the literature in this field. In a study in 2018, Wuethrich et al. also failed to see modulation of viewing behaviour provoked by unconscious retrieval of position of a target during free-viewing (Wuethrich, Hannula et al. 2018). In their experiment, simple objects in grids in scenes were masked from consciousness during the encoding. During the retrieval phase the object was presented as a subliminal cue. Then unconscious retrieval of the position of the object was then tested using eye tracking, while participant were freely viewing an empty grid in the associate scene. Clinical literature has provided evidence for the dominant role of right MTL in spatial memory (Abrahams, Pickering et al. 1997, Nunn, Graydon et al. 1999). Hence unconscious retrieval of spatial memory of the object in the grid could increase right hemisphere dominance during the free-viewing and increase leftward attentional bias in their experiment. Hence, if due to the attentional bias the unconscious memory effect was left lateralized, collapsing the right and the left visual fields together could eliminate the effect of unconscious retrieval on the viewing behaviour.

In current study, the ROI-ROI connectivity values between the right SMG and the right hippocampus were not normally distributed and had an extreme value. As I had a low number of participants, I treated this extreme value with caution and presented the results both with and without the potential outlier. In both analyses, there was a significant correlation between the right HPC-Right SMG connectivity and the number of fixations on the target. Future meta-analysis of similar experiment will be beneficial in testing the replicability of my findings.

In this study, I found that interaction between the main brain regions involved in episodic memory and bottom-up attention had a dominant role in modulation of viewing behavior on visual stimuli by unconscious episodic memory. These analyses focused on the functional connectivity between brain areas, but cannot elucidate the causal influence of the areas on each

other. Investigating the effective connectivity between the memory and the ventral attention networks would be a useful next step for research in this area.

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Chapter 5– General discussion

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General discussion

5.1 Overview of thesis

The main focus of this thesis was investigating the possibility of unconscious encoding and subsequent unconscious retrieval of visual episodic memory and investigating its neural correlates using different fMRI measures. In Chapter 2, I tested the possibility of unconscious encoding and retrieval of complex visual associations in a way that complied with the characteristics of episodic memory according to the processing-based-memory model (Henke 2010) using eye tracking measures. Using fMRI, in Chapter 3, I investigated whether the main brain areas thought to be involved in conscious episodic memory are also involved in unconscious visual episodic memory. In Chapter 4, I explored the functional connectivity between brain areas to investigate the underlying neural mechanism for the modulation of viewing behaviour by unconscious episodic memory. In this chapter, I will initially discuss the main findings and their contribution to the literature[3] in the field of unconscious episodic memory. I will then discuss challenges for, and limitations of, my experiments and pose questions for future research in this field. Lastly, I will present a discussion about episodic memory based on the processing-based-memory model compared to other models.

[3] Due to the publication-based format of this thesis, repeating the main findings of the experimental chapters and their implications caused a degree of repetition in the general discussion. That was because I wanted the general discussion to be an independent chapter without the need to refer to the experimental chapters too often.

5.2 Implications and limitations of findings in chapter 2

What can eye tracking tell us about unconscious memory of episodically associated visual stimuli?

5.2.1 Overview and implication of findings

In Chapter 2, I tested the possibility of unconscious encoding and subsequent unconscious retrieval of complex visual associations with the characteristics of episodic memory according to the processing-based-memory model. The experiment in chapter 2 was designed to see whether such memories exist and can be behaviourally measured, this formed the foundation for my fMRI experiment looking at the neural correlates of unconscious visual episodic memory. For this purpose, face-scene associations were masked from conscious awareness. After a distraction period, one of the encoded scenes was presented as a cue to instigate the recall of the associate face (target). After the cue, the participants freely viewed the target face alongside a distractor face that was associated with other scenes during the encoding. The participants' eye tracking measures were considered to be reflective of unconscious episodic memory retrieval. Participants made more fixations and had larger pupils while looking at the target compared with the distractor in the left visual field. There were no such effects in the right visual field. These findings provided evidence for encoding and subsequent retrieval of face-scene associations at unconscious level.

An important alternative explanation for the unconscious episodic retrieval is that the eye tracking measures, were merely influenced by familiarity. In this case, changes in the eye tracking measures between the target and the distractor could not be simply explained by familiarity of the target because both the target and the distractor were seen during the encoding

phase of the same trial. Hence all were equally familiar. The only difference between them was that only the target was superimposed on the cue scene during the encoding phase. Hence, the modulation of the eye tracking measures on the target compared with the distractor can only be related to the unconscious retrieval of the face-scene associations. This provides support for the existence of unconscious encoding, and unconscious and flexible retrieval of complex visual associations.

The asymmetry in effects between the visual fields also requires some additional explanation. The eye tracking measures in the right hemifield were not different between the target and the distractor. This could be explained by leftward attentional bias. Viewing behaviour can also be modulated by a leftward attentional bias during the free-viewing (Sampaio and Chokron 1992, McCourt, Garlinghouse et al. 2001). Hence the attentional bias toward left could negate or weaken the overall visual attention toward the target in the right visual field. This is in line with the literature about attentional bias indicating that engagement in tasks that increase right hemisphere dominance also increase the leftward attentional bias (Sampaio and Chokron 1992, McCourt, Garlinghouse et al. 2001). Many studies show that right hemisphere has a dominant role in memory of novel faces (Ranganath and D'Esposito 2001, Crane and Milner 2002, Milner 2003, Taylor, Mills et al. 2011, Von Der Heide, Skipper et al. 2013). Hence, retrieval of the target face in the right could at the same time increase the attention toward the target and also increase the leftward attentional bias.

I did not see any significant change in the total viewing time spent on the target compared with the distractor during the free-viewing. Several studies have shown that modulation of total viewing time during unconscious retrieval emerges only in a time window of 500-750 ms from the beginning of the free-viewing and fades away after that (Hannula, Ryan et al. 2007, Hannula and Ranganath 2009, Wuethrich, Hannula et al. 2018). In a review of eye movement-based memory studies, Hannula et al. indicated that modulation of total viewing time, always happens

within the above-mentioned time window and is impervious to task instructions (Hannula, Althoff et al. 2010). The average of total viewing time in my experiment was around 600 ms on each face. In the time window of 500-750 ms, in many trials of my experiment, the participants had not even started to look at the second face. Hence it was not possible to compare the total viewing time between the two faces within this time window in my experiment. Two of the above mentioned studies were about modulation of total viewing time by unconscious retrieval of face-scene associations after conscious encoding (Hannula, Ryan et al. 2007, Hannula and Ranganath 2009). All the faces presented during the retrieval phase in their experiment were consciously memorised before. Hence, all the faces presented during the retrieval phase were familiar. In my experiment, due to unconscious encoding of the faces, they were still novel at conscious level during the free-viewing. It has been shown that participants fixate less and also spend less time viewing the repeated images compared with new images (Smith and Squire 2008, Crutcher, Calhoun-Haney et al. 2009). Hence, it seems plausible that, in my experiment, viewing the faces took more time compared with Hannula's experiments. This could explain why in many trials, my participants did not start to look at the second face within the time window of 500-750 ms from the beginning of the free-viewing. It is therefore not surprising that I see no effects on total viewing time.

Some previous studies have reported null effects in their tasks about unconscious retrieval. In a series of studies, Smith et al. did not see any difference in viewing behaviour between manipulated parts of a scene and the same parts in original scenes (Smith, Hopkins et al. 2006, Smith and Squire 2008). This was contradictory to Ryan et al. 2000, whose findings indicate significant modulation of viewing behaviour on manipulated parts of scenes without conscious retrieval of the manipulations (Ryan, Althoff et al. 2000). There might be several reasons for the failure to replicate the modulation of viewing behaviour by unconscious retrieval in the studies by smith et al (Smith, Hopkins et al. 2006, Smith and Squire 2008). The most important

reason that comes to mind is that very low number of trials were used to investigate scene manipulation at unconscious level in the study by Smith et al. They then divided this low number of trials into conscious and unconscious trials based on subjective reports of awareness. In my experiment I had much higher number of trials compared with their experiment. I also used objective and subjective awareness tests after the experiment to exclude participants who were likely to have retrieved the masked faces at a conscious level. Hence, it was not necessary to remove some trials according to subjective reports of awareness. Hence as my experiment suggests, having high number of trials and using awareness tests after the experiment (when applicable), can be helpful in detecting subtle unconscious memory effect.

In chapter 2, I compared the eye tracking measures between the target and the distractor in each visual field separately (the left target compared with the left distractor and the right target compared with the right detractors). None of the studies in the field of unconscious episodic memory had this approach and despite this fact some studies have seen significant effects of unconscious episodic memory. For example in the studies by Hannula et al (Hannula, Ryan et al. 2007, Hannula and Ranganath 2009) despite collapsing across right and left visual fields, they observed a significant change in viewing behaviour between the target and the distractor provoked by unconscious retrieval. This may be because their experiment involved conscious encoding, which may have greater effects than the unconscious encoding in my experiment. Masked priming studies have shown that conscious representations compared to unconscious representations have stronger influence on behaviour and brain activity (Haynes, Driver et al. 2005, Van den Bussche, Vermeiren et al. 2013). It is possible that conscious encoding in their experiments compared with unconscious encoding in my experiment led to bigger unconscious retrieval activations and hence bigger memory-guided visual attention. Hence, after conscious encoding, the effect of attentional bias could be smaller in comparison with a larger memory-

guided visual attention effect. This could be a reasons why they were able to see a significant effect of unconscious retrieval despite collapsing the data of the right and the left visual fields.

Unconscious retrieval after unconscious encoding has also been reported without separating the viewing behaviour in right and left visual fields. In 2018, Wuethrich et al investigated the unconscious encoding of "easily recognizable objects" in grids inside scenes (Wuethrich, Hannula et al. 2018). In this experiment, simple objects in grids inside scenes were masked from consciousness during the encoding phase. After a delay, there were two types of retrieval phases. In the first type of retrieval phase, participants were presented with an empty grid inside the encoded scene and the associate object was placed outside the grid. Two locations inside the grid were highlighted. One of the highlighted locations was the position of the target during the encoding. The participants were instructed to put the object in one of the highlighted locations using button press responses. They saw a modulation of viewing behaviour on the empty position of the target compared with the other highlighted location despite that the participants' performance was at chance level. In the second type of the retrieval phase, there was a masked presentation of the encoded object as an unconscious cue. After that participants freely viewed the empty grid with the two highlighted locations inside the associate scene. In this second type of the retrieval phase, they did not see any modulation of viewing behaviour on the empty location of the object compared with the other highlighted location (Wuethrich, Hannula et al. 2018). One reason for their failure could be that contrary to my experiment they collapsed the eye tracking data of the left and the right visual fields together. Clinical studies suggest that right MTL has a dominant role in spatial memory (Abrahams, Pickering et al. 1997, Nunn, Graydon et al. 1999). Hence retrieval of spatial memory in their experiment could increase leftward attentional bias. This could lead to a left lateralized effect of unconscious retrieval that could negate the overall effect of unconscious retrieval while collapsing the data

of both of the visual fields. But this raises a question why they saw an unconscious memory effect during the first type of the retrieval phase. In the first type of the retrieval phase the participants made a conscious decision about the position of the target that involves a top-down control that recruits dorsal frontoparietal network (de Schotten, Dell'Acqua et al. 2011). It has been shown that dorsal frontoparietal network is bilaterally distributed. Hence it is also possible that studies with task instructions that recruit the top-down control system during the retrieval phase could be less prone to attentional bias. In the studies by Hannula et al, they also asked the participants to choose the target that was associated with the cue scene by pressing buttons (Hannula, Ryan et al. 2007, Hannula and Ranganath 2009). Hence the attentional bias could be less of a problem for their experiment too. Overall, compared with my experiment, using a task that recruits top down attention during the retrieval phase can recruit the bilateral top down attention system and be less prone to leftward attentional bias. This can provide one possible explanation why contrary to my experiment the above mentioned studies were able to see the modulation of viewing behaviour in both visual fields. To the contrary in my experiment, using a free-viewing paradigm recruits the bottom up attentional system and is prone to leftward attentional bias (As explained further in the implications of chapter 4). But at the same time free-viewing paradigms provide an ecologically valid condition similar to the condition when people unconsciously retrieve a memory by freely viewing a scene without any prior goal. This makes the free-viewing paradigm a worthy candidate for investigating unconscious retrieval despite the inherent attentional bias.

In chapter 2, modulation of the eye tracking measures during free-viewing was considered indicative of unconscious retrieval after unconscious encoding. But can we conclude anything about encoding from the modulation of viewing behaviour only? The most important novel aspects of the experiments in this thesis compared with other studies in the literature was the unconscious encoding of complex visual associations. In my experiments, the eye tracking

measures during the free-viewing phase were considered indicative of both unconscious retrieval and prior unconscious encoding. The rationale behind this interpretation was that unconscious retrieval of episodic associations would be impossible without their prior unconscious encoding. Hence if the eye tracking measures during the free-viewing phase provide evidence for unconscious retrieval, they should be indicative of the unconscious encoding of the retrieved stimuli during the encoding phase. This reasoning is in line with other studies in this field. In many of the other studies of unconscious encoding, behavioural measures during retrieval are considered as indicative of the prior unconscious encoding of retrieved stimuli (Reber, Luechinger et al. 2012, Zust, Colella et al. 2015, Wuethrich, Hannula et al. 2018). In chapter 3, I found a correlation between hippocampal activation during the encoding phase and the number of fixations on the target during the free-viewing phase (where the unconscious retrieval happens). In addition, in chapter 3, hippocampal activation during the encoding phase correlated with hippocampal activation during the free-viewing phase. It has been shown that size of MTL activation during encoding as well as retrieval reflects the success of encoding and retrieval of episodic memory (Fernandez, Weyerts et al. 1998, Staresina and Davachi 2008, Hannula and Ranganath 2009). Hence these findings also provided further evidence for the idea that unconscious retrieval correlates with and is an indicative of unconscious encoding. Hence, in this thesis, the evidence for the unconscious retrieval can be also considered as evidence for the prior unconscious encoding of the retrieved stimuli.

The number of fixations has been considered the most important eye tracking measure that reflects episodic memory (Hannula, Althoff et al. 2010, Meister and Buffalo 2016). In the current experiment, the size of the change in the average number of fixations between the target and distractor was very small compared with the mean. But since this small change in number of fixations was very consistent among participants, the effect was significant. This made the number of fixations on the left target a good candidate for a behavioural index of unconscious

retrieval of episodic memory after unconscious encoding. I also found a correlation between this measure and the MTL activation during unconscious encoding in Chapter 3, which supports the interpretation that the number of fixations is reflective of unconscious episodic memory. In chapter 4, I also found a correlation between the hippocampus-supramarginal gyrus connectivity in the right hemisphere and the number of fixations on the target in the left visual field. Overall, these findings emphasize the importance of *number of fixations* as an index of unconscious retrieval of episodic associations after their unconscious encoding.

5.2.2 Limitations and questions for future research

In experiments about unconscious retrieval after conscious encoding, participants are aware of memory test within the experiment. Hence, at the end of each trial, it is possible to ask the participants to report their awareness of retrieval (Smith, Hopkins et al. 2006, Smith and Squire 2008). In contrast, in experiments with unconscious encoding, participants are kept oblivious to the memory test within the experiment (Degonda, Mondadori et al. 2005, Reber, Luechinger et al. 2012, Zust, Colella et al. 2015). Asking participants about masked stimuli after each trial increases the chance of conscious perception of the stimuli. As a result, these experiments use objective and subjective tests of awareness at the end of the experiment to test for the possibility of conscious encoding and retrieval of the stimuli. The trial by trial awareness test can be a more sensitive method to the possibility of conscious retrieval in each trial compared with the awareness tests at the end of experiment. But at the same time, the difference among participants' criteria for reporting awareness of the stimuli can confound the results. For example, while some participants may be very conservative in reporting conscious retrieval, only doing so when they clearly see the stimulus, other participants may claim conscious retrieval on the basis of partial information about the stimulus. In contrast in objective tests of

awareness, the likelihood of conscious perception of the masked stimuli is tested after the experiment. In this way masked stimuli are presented to the participants and the participants are asked which of the masked face was afterwards in a forced choice manner. Participants who are able to recognize the masked faces above chance would be considered to be able to consciously perceive the masked stimuli. In my experiment in addition to the objective awareness test, I also had a subjective test of awareness, after the experiment, in which participants were asked whether they saw the relevant stimuli. Hence in my experiment, due to the unconscious nature of encoding I used both subjective and objective measures at the end of the experiment to exclude participants, resulting in a conservative criteria for exclusion based on either measure.

One of the key challenges in studying unconscious processes is the difficulty in maintaining ecological validity while still having tight control of the stimuli. In particular, for masking, it is important that the stimuli are not visible, and yet are still processed. In my experiments, I managed this by presenting everyday, coloured faces with hair (Figure 1). But at the same time, I manually equalized the faces in terms of brightness and contrast. The display devices and luminance of the room were different in the eye tracking lab and inside the MRI scanner. Hence, different sets of faces in terms of brightness and contrast were needed for efficient masking in each condition (Figure 1). Using these ecologically valid faces has its own limitations. For example, there is always a possibility that unconscious encoding of lower level visual characteristics of the masked faces (e.g. colour, shape, etc.) is inducing the unconscious memory retrieval. Investigating unconscious encoding of faces in gray scale or faces without different hair shapes in association with scenes will shed more light on the capacity of the unconscious encoding.

Figure 1. 255 coloured faces were prepared for efficient masking in the eye tracking experiment (Chapter 2) and the fMRI experiment (Chapter 3). The white background of each face was removed to allow effective masking of contours. The faces were manually equalized in terms of brightness and contrast. I mostly used faces without any accessories. Other than that I removed the accessories from the faces manually. The faces then were sandwiched between forward and backward masks (scrambled squares in the picture) during the encoding phase.

Investigating the unconscious episodic memory of complex visual associations in this thesis was an important step in understanding unconscious episodic encoding of real events in everyday life. The other important step in this regard could be investigating the unconscious episodic memory of the temporal ordering of visual associations. It has been shown that making an inference about association between words presented in different orders is possible at unconscious level (Reber, Luechinger et al. 2012) (e.g. if we present two associations, A-B and

B-C, then the inference about the order of stimuli would be that A and C are episodically related). Investigating the unconscious encoding of temporal ordering of visual stimuli and also making inference about order of visual stimuli is another interesting topic for research in the field of unconscious episodic memory. It will be a key step in testing the possibility of perceiving a complete event rather than just association between stimuli at unconscious level. To the best of my knowledge no study so far has investigated this possibility. My results indicating that number of fixations can be a reliable measure of unconscious episodic encoding and also the laterality of this effect may also be beneficial in conducting future research about unconscious episodic encoding. These findings may also be beneficial in designing clinical tool for disorders of unconscious episodic retrieval like post-traumatic stress disorder or intra-operative memory formation in future studies (Lubke, Kerssens et al. 2000, Kuriyama, Honma et al. 2013).

There is a possibility that increasing the number of participants in my experiment could increase the likelihood of seeing an unconscious memory effect in the right visual field. In the experiment by Wuethrich et al, they tested the eye tracking data of 32 participants (Wuethrich, Hannula et al. 2018). To the best of my knowledge their study (apart from my experiments) is the only study about episodic encoding of visual associations at unconscious level. Even though the number of participants in their study was higher than my experiment they still did not see any significant effect of unconscious encoding during the free-viewing (collapsing the data of the right and the left visual fields). This increases the possibility that increasing the number of participants might not lead to a significant effect of unconscious memory in the right visual field due to attentional bias. But still testing a much higher number of participants might be beneficial to test the unconscious memory effect in the right visual field in future studies.

Pupil size can show large changes with variables other than memory including level of alertness or fatigue, colour and contrast of visual stimuli (Morad, Lemberg et al. 2000, Lobato-Rincón,

Cabanillas-Campos et al. 2014). Pupil size also shows large variation in exposure to light between different individuals (Higuchi, Ishibashi et al. 2008). These variables can confound the detection of unconscious retrieval based on pupil size. Hence, pupil size may not be the optimal measure of episodic memory. Thus, regarding the literature and the findings of Chapter 2, I focused on the number of fixations as a reliable measure to reflect episodic memory in my fMRI experiment in Chapter 3.

5.3 Implications and limitations of findings in chapter 3

Investigating the unconscious encoding of episodically associated visual stimuli: an fMRI study.

5.3.1 Overview and implication of findings

In Chapter 3, I investigated whether the main brain areas involved in conscious episodic memory are also involved in unconscious encoding and subsequent unconscious retrieval of episodic memory. During the encoding phase, I found a cluster of activity that peaked in the right hippocampus and also included the right parahippocampal gyrus (uncorrected, $p<0.005$). I used this cluster as a MTL functional ROI for further correlational analysis. In this chapter, I found that activation in the MTL functional ROI significantly correlated with the number of fixations on the target but not the distractor during the free-viewing. As in the previous experiment, I used the number of fixations on the target as a measure of unconscious memory retrieval (Ryan, Althoff et al. 2000, Ryan and Cohen 2004, Meister and Buffalo 2016). This finding provided supportive evidence for the hypothesis that the unconscious form of episodic memory, similarly to conscious form of episodic memory, involves MTL structures.

The free-viewing in the experimental condition was accompanied with higher activation in the right hippocampus compared to the control condition. MTL activation can also be modulated by level of familiarity of the stimuli (Eichenbaum, Yonelinas et al. 2007, Kafkas and Migo 2009), but in this case, there was no difference in the stimulus presentation between the target and the distractor stimuli, ruling out this explanation. Similar to the experiment in chapter 2, in each trial, all the faces presented during the free-viewing in both the control and the experimental conditions were presented during the encoding part of the same trial. The only difference was that during the experimental free-viewing, the target face was episodically associated with the cue scene. This ensured that any difference between the experimental and control free-viewing was related to the unconscious retrieval of the target face provoked by the cue scene. This finding provides supportive evidence that unconscious encoding of complex visual associations can lead to a flexible unconscious retrieval mediated by the MTL, particularly the hippocampus. In other words, unconscious retrieval of episodic associations after unconscious encoding is mediated by the main brain area traditionally known to be involved in episodic memory (i.e. hippocampus) (Mishkin, Suzuki et al. 1997, Tulving 2002).

I also found a positive correlation between MTL activation during the encoding phase and the right hippocampal activation during the free-viewing in the experimental condition. Hippocampal activation can also vary under the influence of variables other than memory, like the level of emotional arousal (e.g. stress inside the scanner), vigilance and age (Khalili-Mahani, Dedovic et al. 2010, Madan, Fujiwara et al. 2017, Archer, Lee et al. 2018). In this case, however, it is unlikely that the observed correlation was the result of between individual differences in these variables, because they should cause a general effect in both the experimental and the control conditions. As the correlation was specific to the experimental condition, and did not appear in the control condition, the effect seems consistent with a memory interpretation.

During the encoding phase, the MTL cluster (functional ROI) had a peak in the right hippocampus and the activation also extended to the right parahippocampal gyrus. The parahippocampal gyrus is known to be involved in episodic memory particularly when the memory includes contextual information and place-related stimuli (Aminoff, Gronau et al. 2006, Bar, Aminoff et al. 2008). A dominant role for the parahippocampal gyrus in making contextual associations has been proposed (Bar 2004). In my experiment, during encoding, faces were presented in the context of scenes. Hence the activation found in the parahippocampal gyrus during the encoding phase is also in line with the role of this area in forming contextual associations. At the same time activation in the MTL functional ROI (including the parahippocampal gyrus) correlated with the number of fixations on the target. This suggests that parahippocampal gyrus can be involved in encoding of contextual information at unconscious level.

There might be other possible factors that could increase the number of fixations on the target in the left visual field without any regard to memory. For example conscious retrieval of the cue could bias viewing behaviour without any regard to unconscious retrieval of the face. It has been shown that engagement in tasks that increase right hemisphere dominance in attentional processing increase a bias of attention to the left side of space (Sampaio and Chokron 1992, McCourt, Freeman et al. 2001). In Chapter 4, I showed that participants who had higher connectivity between the areas involved in memory and attention in right hemisphere showed higher attentional bias towards the left. It has been shown that parahippocampal gyrus is involved in contextual mnemonic processing (Baumann and Mattingley 2016). There are mixed reports about laterality of parahippocampal activation during retrieval of scenes (Hayes, Nadel et al. 2007, Baumann and Mattingley 2016). Hence, it is possible that there is right lateralized activation of the parahippocampal gyrus during scene recognition produced by mere conscious retrieval of the cue scene without any unconscious

retrieval of the face-scene association. Participants who had better conscious encoding of the scenes should also have better conscious retrieval of the cue scene. Thus, the parahippocampal activation provoked by the conscious retrieval of the cue scene could emphasize the right hemisphere activation and increase a leftward attentional bias during the free-viewing. This way the modulation of viewing behaviour on the target during the free-viewing could happen without the involvement of unconscious retrieval. However, conscious encoding and conscious retrieval of the scenes was performed during both the experimental and the control conditions. If conscious scene retrieval was driving the modulation of viewing behaviour on the left face, I should have seen a similar effect during the control free-viewing. But there was no such correlation between the MTL activation during the encoding and the number of fixations on the left face during the control free-viewing. This provides evidence against the modulation of viewing behaviour by attentional bias provoked by the conscious retrieval of the cue.

MTL activation during the encoding could also reflect the conscious encoding of the scene. During the encoding, the scenes were presented at a conscious level while the faces were masked from conscious awareness. In this way the face-scene association was hidden from conscious awareness. Participants were instructed to memorize the scenes while they were performing an attention task. Hence, the MTL activation during the encoding represented both conscious encoding of the scene and unconscious encoding of the face-scene association. But at the same time, task instructions during the encoding reduced the role of conscious encoding of the scenes in the whole encoding effect. During the encoding, participants' gaze was kept at the centre of the scene where the masked faces were being presented by the orientation attention task. As a result, participants were not able to directly fixate on different parts of the scene and were only using peripheral vision to encode the scene. Previous studies in this field have shown that successful encoding drops considerably when the fixations are more than two visual degrees distant from the position of the critical details of a picture that should be retrieved later

(Nelson and Loftus 1980). Preventing the participants from directly looking at important parts of the scenes could have decreased MTL activation related to conscious scene encoding in comparison with studies in which participants are allowed to freely look at scenes. Hence the task instructions during the encoding in my experiment could reduce the size of activation associated with the conscious encoding of the scene. In addition as mentioned earlier, I saw a correlation between the activation in the MTL functional ROI during the encoding and the number of fixations on the target. This correlation also provides supportive evidence that unconscious encoding of the face-scene associations has a dominant role in the observed MTL activation during the encoding phase rather than mere encoding of the scenes at conscious level.

5.3.2 Limitations and questions for future research

The fMRI experiment that was the basis for Chapters 3 and 4 had some limitations. Each session of this experiment was very long (around 1.5 hours). Due to the high cost of each fMRI session ($1000 AUD per session) and funding limitations, I was able to test only 14 participants from which only 9 participants passed the awareness test. As the overall focus of this thesis was on using fMRI to investigate the underlying brain areas involved in unconscious episodic memory, I had also planned to perform a connectivity analysis on the fMRI data in Chapter 4. It has been shown that in fMRI studies, even very large sample sizes (N=100, that are rare) are far from perfect replicability (Turner, Paul et al. 2018), and obviously it would be ideal to have a much greater sample size for the basic fMRI findings, the correlational analyses, and the connectivity analyses. Hence (as it is also suggested for most of the published fMRI studies) replicability of my preliminary findings in Chapters 3 and 4 should be tested by future meta-analysis of similar studies (Turner, Paul et al. 2018).

The other important problem with small sample size is a higher probability of missing small effects: type II error (Cremers, Wager et al. 2017). One solution to increase the power of studies with small sample size is to use a region of interest analysis based on previous hypothesis to decrease the number of statistical tests (Cremers, Wager et al. 2017) . In my fMRI experiment, I focused primarily on the mean percentage signal change in the main regions of interest involved in episodic memory to optimise my approach given my constraints.

It has been shown that using stringent thresholds to decrease the type I error also increases the probability of type II error (Lieberman and Cunningham 2009, Cremers, Wager et al. 2017). This way small effects produced by complex cognitive processes are more likely to be missed. It leads to a deficient meta-analysis of fMRI data due to missed small effects (Lieberman and Cunningham 2009). As mentioned in an article by Cremers et al in 2012, *"Conventional wisdom holds that the increase in Type II error is a necessary evil, because it is a bigger sin to say an effect is real when it's not than to say it's not real when it is (i.e., we are willing to incur multiple Type II errors to avoid a single Type I error)"* (Cremers, Wager et al. 2017). The authors indicated that the rate of type II error to type I error using the conventional multiple comparison criteria is much higher than the *"gold standard 4:1 (ie. 80% power, 5% false positives)"*. They concluded that true balancing between type I error and type II error could lead to much less stringent thresholds (Cremers, Wager et al. 2017). To avoid missing an effect of unconscious episodic memory, in Chapter 3, I used uncorrected analysis to define functional ROIs. In Chapter 4, I also presented uncorrected fMRI results for the contrast (experimental free-viewing – control free-viewing) to facilitate future meta-analyses. But, as I am aware that doing this could inflate the chance of a type I error, I have not based any major inference on these analyses. My main inferences were based on the significant results of the correlational analyses or the t tests. Conducting meta-analysis of similar experiments with more participants will be very beneficial to test the replicability of my findings.

My fMRI experiment had an event related design with fixed order of events. It has been shown that in event related designs, randomizing interstimulus intervals between trials helps to estimate the shape of the hemodynamic response function (HRF) (Dale 1999, Liu, Frank et al. 2001). Having the power to estimate the shape of HRF is known as the estimation power (Liu, Frank et al. 2001). Regarding the nature of the memory test, I was not able to change the order of events in each trial in my experiment (e.g. encoding always comes before retrieval and a distraction (math problem) comes in between). Randomization can also be induced by changing the duration of each trial by adding null events of random lengths between trials (jittering). But increasing the estimation power has some disadvantages too. Event related paradigms have lower detection power compared with block designed paradigms. Detection power is defined as the ability of a design to detect an activation (Liu, Frank et al. 2001). Maximizing the estimation power with these methods comes in the cost of decreasing the detection power and vice versa (Liu, Frank et al. 2001). Hence it was possible that randomizing the inter-stimulus intervals from trial to trial that could increase the estimation power, would decrease the detection power (Liu, Frank et al. 2001). For example participants could be surprised by sooner or later beginning of each trail compared with previous trials and this change in their vigilance (because of surprise) could impact the hippocampal activation and increase the variance of the hippocampal activation. As unconscious episodic memory effects were already likely to be subtle, I did not want to reduce the detection power by adding to the estimation power through jittering. Hence, I did not use jittering in my experimental design. To be able to estimate different points of HRF during the events of interest, I ensured the trial duration was not a multiple of repetition time (TR). This way I was able to estimate the shape of HRF in the free-viewing events of 2s (4 points of the HRF during this event). But still regarding the above considerations, deconvolution of the HRF of the cue event (2s) from the free-viewing event (2s) might not be optimally efficient in my experiment.

In the fMRI experiment, I always presented the target in the left visual field to increase the number of trials in each condition. This was because my first experiment in chapter 2 suggested that modulation of viewing behaviour would only be evident for the targets in the left. In the fMRI experiment, I was looking for a correlation between viewing behaviour and MTL activation. Hence by having the target in the left I was able to investigate this correlation. But, without having a target in the right visual field I was not able to test whether the null effect in the right visual field in Chapter 2 could be replicated. It is possible that, similar to the condition with the target in the left, an fMRI experiment with a target in the right may lead to higher hippocampal activation during the experimental free-viewing compared with the control free-viewing due to unconscious retrieval of the target provoked by the cue. However, in Chapter 2, I did not find any modulation of the eye tracking measures by unconscious retrieval in the right visual field. As mentioned before this could be due to an increment in attentional bias toward the left during retrieval that negates attention toward the target in the right. If this is the case, I would not expect to see a correlation between MTL activation during the encoding and viewing behaviour on the target in the right visual field. These predictions can be tested with future experiments.

Presentation of the target only in the left visual field could induce some bias in hippocampal activation and viewing behaviour during the free-viewing, predicting the spatial position of the target at the unconscious level. There has been evidence supporting the possibility of making inference at unconscious level (using verbal stimuli) (Reber, Luechinger et al. 2012). It has also been shown that making inference about the encoded stimuli can modulate hippocampal activation during encoding (Reber, Luechinger et al. 2012). This opens a window of possibility for making inference about the position of the target at unconscious level that could bias hippocampal activation during unconscious retrieval in the free-viewing. But at the same time making inference about the position of the target will be impossible without initial unconscious

retrieval of the target-cue associations. Hence even though it is possible that unconscious prediction of the position of the target can bias the hippocampal activation or viewing behaviour during the free-viewing, but modulation of right hippocampal activation during the experimental free-viewing compared with the control free-viewing will still indicate the unconscious retrieval of the target-scene associations. At the same time the correlation between the MTL activation during the encoding and the number of fixations on the target (or the right hippocampal activation) during the free-viewing can not only be the result of predicting the position of the target. In chapter 3, I also showed that the MTL activation during the unconscious encoding correlated with the number of fixations on the target. This finding also provided evidence for the important role of unconscious episodic memory in the modulation of viewing behaviour on the target, rather than mere modulation of viewing behaviour by predicting the position of the target. Overall, even though presenting the target always in the left visual field can cause some confounding effects during the free-viewing, but my findings in this chapter still provide supportive evidence for the involvement of MTL in unconscious encoding and retrieval of visual episodic memory.

My analysis approach in this study had some differences with similar studies by Hannula et al (Hannula, Ryan et al. 2007, Hannula and Ranganath 2009). In the series of studies by Hannula et al (Hannula, Ryan et al. 2007, Hannula and Ranganath 2009) they investigated unconscious retreival of face-scene associations after conscious encoding. The experimental design in their experiment was very similar to my experiment. They found that hippocampal activation during the cue phase predicted the modulation of viewing behaviour on the target. In their eperiment both of the face and the scene in each association were encoded at conscious level. Hence retreival of the cue could be an index of the retreival of the associate face. To the contrary in my experiment the scenes were presented consciously while the faces were masked from conscious awareness. Hence it was possible that the participants successfully could encode the

secnes at conscious level while failing to encode the masked faces (for example due to inter-individual differences in perception of the masked stimuli). Hence retreival of the cue scene was not necessarily an index of the retreival of the associate face in my experiment. As a result contrary to their experiment, I did not use the hippocampal activation during the cue phase as an index of unconscious retreival of the target, in chpater 3.

An important question can be the capacity of unconscious episodic encoding (Hannula, Simons et al. 2005). It is not clear to what extent the masked faces-scene associations in my experiment could be perceived and episodically encoded without conscious awareness. There is always a possibility that encoding and retrieval of lower level visual characteristics of faces (e.g. colour, shape etc.) derived the modulation of viewing behaviour during the retrieval phase. Investigating the possible correlation between unconscious face perception and unconscious episodic memory can be helpful in understanding whether higher level characteristics of faces are episodically encode. The fusiform face area (FFA) is a brain area that has a key role in processing faces (Kanwisher, McDermott et al. 1997, Kanwisher and Yovel 2006). It has been shown that detection of a stimulus as a face increases activation in the FFA compared with faces that are not detected (Grill-Spector, Knouf et al. 2004). Activation in the MTL during encoding also reflects success of encoding and correlates with success of retrieval (Fernandez, Weyerts et al. 1998, Staresina and Davachi 2008). Hence, I would expect to see a correlation between the MTL activation and the FFA activation during the encoding phase that could predict the success of retrieval by modulating the number of fixations on the target during the free-viewing. For future research, it would be interesting to use a localizer to find the FFA in each participant (Berman, Park et al. 2010) and then test whether successful perception of the faces during the encoding phase leads to successful encoding and subsequent successful retrieval of the face-scene associations at unconscious level.

5.4 Implications and limitations of findings in chapter 4

How does unconscious memory of episodically associated visual stimuli modulate viewing behaviour?

5.4.1 Overview and implication of findings

In Chapter 4, the underlying neural network involved in modulation of viewing behaviour by unconscious visual episodic memory was investigated using functional connectivity analyses. According to an attention-to-memory model proposed by Cabeza and his colleagues in 2008, involuntary memory as an incoming signal interacts with bottom-up attention system. Contrary to the top-down attention system that is involved in goal driven guidance of attention, the bottom-up attention system is involved in stimulus-driven guidance of attention (Corbetta, Patel et al. 2008). Bottom-up attention is mostly involved when a salient stimulus (e.g. involuntary retrieval of a memory) suddenly grabs attention without a prior goal of the task for doing so (Corbetta, Patel et al. 2008). It has been shown that a ventral frontoparietal network mostly mediates the bottom-up attention (Corbetta, Patel et al. 2008). According to the attention-to-memory model, memory signals from hippocampus (HPC) interact with ventral parietal areas (part of ventral frontoparietal network) to guide attention toward involuntary memory. In Chapter 4, I found that right hippocampus had a higher connectivity with a frontoparietal network in the right hemisphere during the experimental free-viewing compared with the control free-viewing. This network included active clusters in right supramarginal gyrus (SMG), right angular gyrus, right precentral gyrus and right inferior frontal gyrus. Hence, functional connectivity between the right hippocampus and the ventral frontparietal network that extended from ventral parietal areas to the inferior frontal regions increased during the

free-viewing by unconscious retrieval of the target provoked by the cue. This finding provides support for the important role of the interaction between episodic memory and bottom-up attention in modulation of viewing behaviour by unconscious visual episodic memory.

In this chapter, I also found a significant correlation between the right HPC- right SMG connectivity and the number of fixations on the target during the experimental free-viewing. According to the attention-to-memory model, I expected that interaction between the HPC and the SMG would increase the memory-guided attention toward the target (Cabeza, Ciaramelli et al. 2008). According to my hypothesis, the right HPC- right SMG connectivity could increase dominance of right hemisphere in attentional processing and thereby increase leftward attentional bias. Based on my hypothesis, both of these forces could guide visual attention toward the left face during the free-viewing and increase visual attention to, and the number of fixations on, the target in the left. Hence, I expected a positive correlation between the right HPC-right SMG connectivity and the number of fixations on the target. In this way, my finding regarding the correlation between the right HPC-right SMG connectivity and the number of fixations on the target was in line with my hypothesis.

The other important finding of chapter 4 was that the right HPC– right SMG connectivity during the free-viewing correlated with the number of fixations on the left face in the control condition. This finding could suggest that interaction between right dominant facial memory and right dominant attention would increase leftward attentional bias. The interpretation of this finding requires more explanation. There might be several reasons other than attentional bias behind the observed correlation that should be explained. For example the modulation of attention toward the left face during the control free-viewing cannot be the result of preferential retrieval of the left face after its unconscious encoding. Both of the faces presented during the control free-viewing were previously presented during the encoding part of the same trial. Hence, both of faces during the control free-viewing were equally likely to provoke

unconscious retrieval. The other factor that can affect memory performance is the recency effect, manifesting in better memory performance for recently viewed items compared with less recent items (Buchsbaum, Lemire-Rodger et al. 2015). To control for the recency effect, the two faces during the free-viewing were chosen with equal probability from any of the faces presented during the encoding part of the same trial. As a result, during the control free-viewing, the observed correlation between the viewing behaviour on the left face and the right HPC- right SMG connectivity cannot be due to the preferential retrieval of the left face or its recency and can only be explained by an inherent leftward attentional bias.

Findings of this chapter provided support for the hypothesis of enhancement of leftward attentional bias by unconscious retrieval of the faces during the free-viewing. This also provides support for the hypothesis that unconscious retrieval of the target in the right visual field increases both the leftward attentional bias and memory guided attention toward the target and these two forces can negate each other. This can explain why in chapter 2, I only saw a significant effect of unconscious retrieval in the left visual field. As extensively explained in the implications of chapter 2, this leftward bias can also explain the null effect of unconscious retrieval reported by Wuethrich et al during the free-viewing while collapsing the data of both right and left visual fields (Wuethrich, Hannula et al. 2018).

The observed correlation between the right HPC–right SMG connectivity and the number of fixations on the left face during the control free-viewing could be related to anatomical reasons. The between-individual differences in right HPC–right SMG connectivity during the free-viewing could be related to the variance in the laterality of anatomical connection between the HPC and the parietal areas among the participants. Some studies have shown that anatomical connectivity correlates with functional connectivity between brain areas (Wang, Chen et al. 2013). Other studies indicate that functional connectivity can also exist between areas that only have indirect anatomical connections and are not directly connected (Honey, Sporns et al.

2009). Connections between HPC and parietal areas are not lateralized (Song, Mitchell et al. 2015). Anatomical connectivity in limbic pathways like fornix or cingulum bundle does not show any laterality among individuals (Song, Mitchell et al. 2015). These tracts connect different parts of limbic system like hippocampus to frontal and parietal areas (Lovblad, Schaller et al. 2014, Bubb, Metzler-Baddeley et al. 2018). Leftward attentional bias has been related to right hemisphere dominance in attentional processing (de Schotten, Dell'Acqua et al. 2011). Hence, it is not likely that inter-individual differences in the right hemisphere dominance of the tracts between the hippocampus and the parietal areas modulates the leftward attentional bias seen in Chapter 4.

In chapter 4, the seed-to-voxel connectivity results in left hemisphere showed a higher connectivity between right hippocampus and posterior parts of precuneus during the experimental free-viewing compared with the control free-viewing. Precuneus is part of medial parietal cortex and posterior precuneus is known to be involved in episodic memory tasks (Cavanna and Trimble 2006). The enhancement of the left precuneus connectivity with right HPC could further emphasize the role of episodic memory retrieval during the experimental free-viewing compare with the control free-viewing.

5.4.2 Limitations and questions for future research

The ROI-ROI connectivity values between the right SMG and the right HPC during the experimental free-viewing was not normally distributed and had an outlier. As mentioned before due to funding limitations, the number of participants in the fMRI experiment was low. This means that the existence of an outlier could largely influence the significance of statistical tests. Outliers can occur for a variety of reasons like technical errors, mistake in data transcription, participants not following task instructions, etc. But deciding whether a value is an outlier or not is not easy in small sample sizes when the normal sample distribution is not

known. It is possible that data that looks like an outlier actually represents the tail end of normal distribution (Jones 2019). As a result, by excluding these values, real and important information is not reported. It is suggested that in these situations, we should not use heuristic and automatic outlier detection techniques without caution. Instead, Jones (Jones 2019) recommends that we report the outlier data in the results and declare the criteria for our decision . Even though the ROI-ROI connectivity values between the SMG and the HPC had an outlier during the experimental free-viewing but the other parts of the fMRI, connectivity and eye tracking data of that participants (i.e. the participants with the outlier value) were normally distributed. The normal distribution of the other parts of this participant's data lowered the possibility that she was an abnormal participant in general, and increased the possibility that her data is part of the normal distribution. Hence, I treated the outlier with caution and reported the results of the analysis twice: once with the outlier included in the data and once without the outlier. I found a significant correlation between the right HPC- right SMG connectivity and the number of fixations on the left face during the experimental free-viewing both with and without the outlier. Meta-analysis of similar experiments will be beneficial in testing the replicability of my findings.

Apart from functional connectivity, inter-individual variance in anatomical connectivity can also change the leftward attentional bias and hence the number of fixations on the target. Right hemisphere dominance of anatomical connectivity has been reported in the ventral superior longitudinal fasciculus (SLF) that connects SMG to ventral frontal areas (de Schotten, Dell'Acqua et al. 2011). Apart from memory, inter-individual difference in the right dominance of the ventral SLF can change the size of leftward attentional bias and hence the number of fixations on the left face during the free-viewing (de Schotten, Dell'Acqua et al. 2011). This could confound the role of memory in modulation of viewing behaviour. As the SLF does not connect hippocampus to SMG, the observed correlation between the right HPC- right SMG

connectivity and the fixation number does not seem likely to be due to inter-individual difference in SLF laterality. Instead SLF laterality is a separate factor that may modulate the viewing behaviour on the left face without any regard to memory. Using tractography techniques in future studies can be helpful in differentiating between memory and anatomical factors in modulation of viewing behaviour during the unconscious retrieval.

In my fMRI experiment, the field of view did not cover the whole brain. This field of view covered an area from the bottom of the temporal lobe to the ventral parietal areas. The ventral frontoparietal network involved in bottom-up attention extends from ventral parietal areas, particularly SMG, to ventral prefrontal areas (Makris, Kennedy et al. 2005). Hence, my field of view covered the ventral frontoparietal network. Diffusion tensor MRI (DTI) shows that the dorsal frontoparietal network mainly involved in top-down attention extends from superior parietal areas to superior frontal, dorsal premotor and dorsolateral prefrontal regions (Makris, Kennedy et al. 2005). Since the partial volumes in my experiment did not cover dorsal parietal and dorsal frontal areas, I was not able to test the connectivity of dorsal frontoparietal network with hippocampus. According to the attention-to-memory model, bottom-up attention network interacts with dorsal attention network after receiving memory signal from the hippocampus to modulate viewing behaviour (Cabeza, Ciaramelli et al. 2008). Future studies with whole brain field of view can shed light on the possibility of interaction between the ventral and the dorsal attention networks for modulation of viewing behaviour during unconscious retrieval of episodic associations.

One of the most important confounding factors in functional connectivity analysis is non-neuronal noise that may lead to spurious connectivity between brain areas. The important sources of physiological noise are in cerebral metabolism, blood flow and cardiac or respiratory pulsations (Birn, Diamond et al. 2006, Rogers, Morgan et al. 2007). In addition, head movement can have an important confounding effect on functional connectivity measures

(Satterthwaite, Wolf et al. 2012). The spurious connectivity results are most evident in resting state functional connectivity experiments during which there is no task but still there is functional connectivity between different brain areas. It took many years for the early researchers in this field to show that the temporal correlations at resting state are not mere noise and indeed include important networks of neural activity (Birn 2012). In my experiment the mere temporal connectivity between different voxels is not enough to produce task-based functional connectivity maps and it should be weighted and analysed based on the timing of the task events. But still, noise correction is a very important step in both the task-based as well as the resting state functional connectivity analysis. For this reason, I used the component-based noise correction method (CompCor) that is efficient for reduction of noises with cardiac and respiratory origin as well as noise of head motion and noise related to other possible task related covariates (Behzadi, Restom et al. 2007, Whitfield-Gabrieli and Ford 2012). I also used a window of frequency of the BOLD signal to filter the none-neuronal sources of noise with very high or very low frequencies (Whitfield-Gabrieli and Ford 2012). Overall, being aware of the confounding effect of noise in functional connectivity analysis I used different noise correction approaches as implemented in the CONN software (Whitfield-Gabrieli and Ford 2012). More elaborate discussion about different noise reduction techniques goes beyond the scope of this thesis. Despite the different noise reduction methods used in my analysis, the interpretation of my functional connectivity results like other functional connectivity studies can still be done with caution about a possibility of contamination with noise.

5.5 Episodic memory models

There are different memory characteristics that traditionally have been used to distinguish between different memory types. These characteristics are consciousness of memory, retention period (short or long), capacity of memory (limited or un-limited), number of repetitions

required for encoding (single exposure or many repetitions), flexibility of memory representations (flexible or rigid), complexity of memory representations and also brain areas involved in memory. According to the literature, different types of memory have been defined with different characteristics (Camina and Güell 2017). The earliest definition of episodic memory goes back to the 1970s when episodic memory was defined as encoding and retrieval of personally experienced events, differentiated from semantic memory as being about general concepts and knowledge (Tulving 1972). This definition is still a well-accepted definition for episodic memory (Dickerson and Eichenbaum 2010, Camina and Güell 2017). According to this definition of episodic memory, we are able to form a permanent memory from a single exposure to complex events and we can retrieve it later in a flexible way with details. Flexibility means exposure to partial information about the event as a cue can help us to retrieve the whole memory of that event. The memory I have tested in this thesis was rapidly formed (200-400 ms exposure time), complex (face-scene associations) and flexible (retrieval of the cue helped retrieval of the associate face). In this thesis by investigating viewing behaviour as a reflective of episodic memory, I have found supportive evidence for the encoding and subsequent retrieval of a memory with the characteristics of visual episodic memory at unconscious level.

It is also well accepted that episodic memory is mediated by MTL structures particularly the hippocampus (Dickerson and Eichenbaum 2010, Camina and Güell 2017). Early clinical observations on patients with MTL damage suggested that episodic memory is only involved in conscious encoding and retrieval of events (Milner, Corkin et al. 1968, Knowlton, Ramus et al. 1992, Clark and Squire 1998, Levy, Stark et al. 2004). This view was challenged by later clinical and brain imaging findings which suggested that hippocampus (i.e. the main structure involved in episodic memory) is involved in forming new associations that may not be limited only to conscious events (Warrington and Weiskrantz 1982, Mayes, Holdstock et al. 2002, Mayes, Holdstock et al. 2004, Hannula and Ranganath 2009). In 2010, Henke proposed a

processing-based-memory model according to which a memory with the characteristics of episodic memory can form at both conscious and unconscious levels (Henke 2010). So far her proposed model has been supported by many brain imaging, behavioural and clinical studies (Degonda, Mondadori et al. 2005, Hannula, Ryan et al. 2007, Hannula and Ranganath 2009, Reber, Luechinger et al. 2012, Zust, Colella et al. 2015). The brain imaging findings in this thesis provide further supportive evidence for the involvement of MTL structures, particularly the hippocampus, in unconscious encoding and unconscious retrieval of episodic association between complex visual stimuli consistent with the processing-based-memory model.

Another major classification of memory is based on the period of time that mnemonic information is stored, including short-term memory and long-term memory. Traditionally, episodic memory is known as a subcategory of long-term memory. Short-term memory, in contrast, involves information processing over a short period of time and working memory mediates this processing (Camina and Güell 2017). The most influential memory model in this regard is the model proposed by Atkinson and Shiffrin (Atkinson and Shiffrin 1968). According to this model, when a stimulus is presented, it is primarily registered to sensory memory that decays in a few milliseconds. This information is then transferred to a short term store that can keep information for a short time (a few seconds for visual information). But a limited amount of information can be retained by working memory through rehearsal process. The final stage in the model is transfer of the information to a long-term memory store (Atkinson and Shiffrin 1968). It is well accepted that working memory is limited in capacity (Camina and Güell 2017). On the other hand, it has been shown that when memory load is high, short-term memory mostly depends on brain areas involved in episodic memory (e.g. hippocampus) (Cabeza, Dolcos et al. 2002, Nichols, Kao et al. 2006, Rissman, Gazzaley et al. 2008, Jeneson, Mauldin et al. 2011). High load conditions include retention of complex or novel associations for periods of over 7 seconds or retention in the presence of distractors. In

the processing-based-memory model, Henke also proposed that episodic memory is involved in short-term or long-term retention of information according to the characteristics of episodic memory (i.e. rapidity, complexity, flexibility) (Henke 2010). The hippocampus, as the main structure involved in episodic memory, is dominantly involved in forming flexible memories of novel associations over both short and long retention times (Henke 2010). Hence, classifying memory merely based on the period of time memory is held is not the best practice. In this thesis I investigated the unconscious and rapid encoding of complex and novel visual associations. I also investigated the unconscious and flexible retrieval of those information after retention times of over 7s in the presence of distractors. I found the involvement of MTL in unconscious encoding and unconscious retrieval of such a memory. Hence my findings support the hypothesis that episodic memory can have a dominant role in short-term retention of information according to the characteristics of episodic memory, especially when the memory load is high.

My findings in this thesis support the idea that instead of initial classification of memory based on consciousness or retention period it is better to classify memory based on other characteristics of memory. In this way, a memory with the characteristics of episodic memory can exist at both conscious and unconscious levels and can retain information for short or long periods.

5.6 Summary and conclusions

All in all, this research provides support for the possibility of unconscious encoding and unconscious retrieval of complex visual associations in a way that complies with the characteristics of episodic memory according to the processing-based-memory model (Henke 2010). The eye tracking results provide behavioural evidence for the abovementioned

hypothesis. The fMRI results also provide support for the prediction of the model that unconscious encoding and unconscious retrieval of visual episodic memory is mediated by the MTL structures thought to be involved in conscious episodic memory. The functional connectivity results support the hypothesis that interaction between episodic memory and bottom-up attention is involved in modulation of viewing behaviour by unconscious episodic retrieval. It also suggests that interaction between the right dominant facial memory and the right dominant visual attention could increase leftward attentional bias.

These findings confirm previous findings about the existence of unconscious episodic memory and its behavioural and neural attributes. In addition, these findings emphasise the possibility of unconscious episodic encoding and subsequent unconscious retrieval of complex visual associations. This is an important step towards understanding unconscious episodic memory in everyday life which includes complex visual events. The findings in this thesis in addition to literature suggest that investigating viewing behaviour, MTL activation and MTL connectivity are viable approaches to explore other aspects of unconscious episodic memory in future studies.

5.7 References

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Appendix 1

MACQUARIE University

HALEH KHOSHKHOUY DELSHAD <haleh.khoshkhouy-delshad@students.mq.edu.au>

Ethics Clearance (Student)

Shiree Heath <shiree.heath@mq.edu.au> Tue, Sep 20, 2016 at 9:24 AM
To: "haleh.khoshkhouy-delshad@students.mq.edu.au" <haleh.khoshkhouy-delshad@students.mq.edu.au>
Cc: Anina Rich <anina.rich@mq.edu.au>

Hi Haleh,

We have now been notified by the Ethics Secretariat that the amendment request to add you as personnel has been approved. You are now able to begin testing under this clearance.

Some additional information:

1. A requirement of this ethics approval is that an annual progress report is submitted each February. To complete this report, some information may be required from you regarding the studies that have been conducted under this clearance, including copies of any consent forms used.
2. I have **attached** a pdf copy of the original ethics application, with updated personnel details. Please ensure you are familiar with the details of this application. Note that in place of the contact details section, a list of named researchers is included – you have now been added to this list. These people are authorised to conduct research under this clearance.
3. I have also **attached** a word file of the approved information and consent form – the relevant sections marked in bold/italics must be completed before use. Please send me a copy of the final form before you commence testing.
4. The approval date of the original ethics clearance was 27 February 2012 and the approval number for this application is 5201200035 (Student).

If you have any questions, please contact me.

Regards,
--

Shiree Heath PhD
Acting Research Coordinator

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