THE EFFECT OF EARLY LIFE STRESS ON NEURAL ACTIVITY DURING AUTOBIOGRAPHICAL MEMORY RECALL

Abstract

Introduction: Retrieval of past events guides our behaviour in the future and affects our well-being. Sometimes this system is hyperactive, resulting in an extreme retention of traumatic memories and possibly a higher risk of developing PTSD or other psychopathologies. There are treatments for PTSD that do reduce the symptoms, including drug administration of Hydrocortisone for example, but there is still a high remission rate. One risk-factor is the experience of trauma early in life (ELS). These events can influence neurodevelopment and memory processes. It is important to gain a better understanding of memory systems and the development after ELS to possibly discover better and more personalized ways to help people with PTSD and ELS.

Research Question: The main objective is to verify if the Autobiographical Memory Task paradigm is effective in both participants with and without ELS. We expect that the mPFC, the hippocampal complex, the Precuneus, the cerebellum, the TPJ, the insula, amygdala and ACC will be activated during the Autobiographical Memory Recall Task (AMRT) in a group including both ELS and non-ELS subjects.

Methods: A placebo-controlled double-blind cross-over design will be used where both ELS and non-ELS participants perform two sessions of an AMRT in the MRI scanner. They will receive 20 mg of Hydrocortisone in one session and a placebo in the other.

Results: We found signification activation in some of the hypothesized areas and even some extra regions that could certainly be relevant to the AMRT. The most prominent regions that were predicted and show up in several contrasts during the analysis are the PCC/Midcingulate cortex, mPFC and the Precuneus.

Discussion: Significant activation was found in the hypothesized areas which suggests that the AMR task was verified. The group effect was rather small, because the study had not finished data acquisition yet, so there was a small sample size and we were unable to take the ELS status or drug effect into account. Nonetheless we found a trend in activation that is promising for the main study.

Frédérique Maas

Supervisors: Dr. E.J. Hermans and H. Wang

Department of Cognitive Neuroscience

Introduction

Our brain seems to have evolved into a perfectly functioning system designed to aid our survival. However, some 'functions' have stopped evolving just a bit too soon in some individuals. Certain traits that were beneficial in our past or only in some rare cases, are more likely to cause problems in our current society. Our ability to emotionally enhance memories and create strong and vivid recollection of significant events is such a trait that is malfunctioning in some of us. This is a highly adaptive mechanism which is fundamental to our survival when it functions accordingly (Atsak et al., 2015). Our memories enable us to bring past experiences to the present to relive and reimagine consequences. This retrieval of past events guides our behaviour and decision making in the future and affects our well-being. Most importantly, it prevents us from repeating mistakes or helps us avoid certain situations when memories are associated with negative emotions or consequences (Kensinger & Ford, 2020). However, this memory system is hyperactive in some cases, which could cause an individual to retain the memory of a traumatic experience too vividly. So when an individual with such a hyper-reactive system faces a traumatic experience during their lifetime, there is an increased risk of developing Post-Traumatic Stress Disorder (PTSD). But this is not the only factor influencing the possible development of PTSD. Another factor that increases the risk of developing these kinds of psychopathologies is the experience of trauma early in life (ELS) (Garrett et al., 2019; Villain, Benkahoul, Birmes, Ferry, & Roullet, 2018). These events so early in life can influence neurodevelopment and other memory processes, for example it could result in such a hyperactive memory system. It is therefore important to gain a better understanding of how these processes involved in memory and stress work and develop after these traumatic experiences early in life to increase our knowledge, possibly discover more and better ways to help people with a history of ELS and understand how this influences the risk of PTSD and the reduced effect of current treatments.

The first step to understanding the memory systems better is to further explore the subject of emotional memory, which is a component of the core of our personal history. Memories can either have a high or low level of arousal and either a positive or negative valence (LaBar & Cabeza, 2006). This spectrum of emotional aspects can alter the way memory is stored and retrieved, which sometimes elicits different effects on memory functions. In general, the effects of emotion are beneficial, but long-lasting detrimental consequences can occur sometimes (Kensinger & Ford, 2020; LaBar & Cabeza, 2006). In the case of ELS, these memories include high arousal levels and a negative valence, presenting through emotions like fear or sadness. There is evidence that

during the encoding of emotional stimuli there is activity in the amygdala and medial temporal lobe (MTL), which also correlates with individual differences in later memory for these emotional events (Hamann, 2001). These frontotemporal brain regions act together to promote the retention of emotionally arousing events and retrieve them from long-term storage for declarative emotional memory. This enhancing effect of emotional arousal involves the interactions between sub-cortical and cortical regions and engagement of central peripheral neurohormonal systems that are coordinated by the amygdala (LaBar & Cabeza, 2006). The interaction among the amygdala, hippocampus and sensory regions is very important for the retrieval of emotional events as well (Kensinger & Ford, 2020). Thus, the amygdala, PFC and MTL contribute to both the retrieval and consolidation of emotional memories from the personal past (LaBar & Cabeza, 2006). One paradigm that is particularly useful in exploring these brain regions and further examining emotional memory functioning involves the use of autobiographical memory recall (Kensinger & Ford, 2020).

Autobiographical memory recollection (AMR) has been studied quite a lot in fMRI research. It involves a core neural Autobiographical Memory (AM) network in healthy individuals, which includes the retro splenial cortex (RSP), the mPFC, the medial temporal lobes, the amygdala and hippocampus, the TPJ, the Precuneus and the lateral temporal cortex (Carhart-Harris et al., 2014; Fossati, 2013; Svoboda, McKinnon, & Levine, 2006). Most of the brain regions from the AM network can also be found as regions or sub-regions in the Default Mode Network (DMN) and the amygdala is one of the core regions from the Salience Network (Chand & Dhamala, 2016; Kim, 2016; Menon, 2015). There is some evidence that these activity patterns can be influenced by factors like the valence of the memory, where some studies showed an increased response in the autobiographical memory (AM) system and emotional brain regions, like the amygdala, orbitofrontal cortex and medial PFC, during the recollection of positive memories relative to negative memories (Piefke, Weiss, Zilles, Markowitsch, & Fink, 2003; St Jacques, Botzung, Miles, & Rubin, 2011). Moreover, in the case of negative relative to positive memories, executive regions like the dorsal and lateral PFC are activated (Anderson et al., 2004). There are many factors that have the possibility to affect our performance and the required brain regions during memory tasks like this. One factor that has such an influence is Early Life Stress (ELS). It affects the neurodevelopment of certain memory regions and therefore has an impact on memory functions later in life.

ELS stands for Early Life Stress and refers to the experience of stressful events early in childhood. ELS includes events like being bullied severely, physical or emotional abuse, or sexual abuse or assault before the age of ten. Poorer cognitive function in memory domains and executive functioning has been linked to exposure to ELS, both with and without the occurrence psychopathology (Navalta, Polcari, Webster, Boghossian, & Teicher, 2006). This can also be associated with problems with verbally mediated higher cognitive abilities, a deficient inhibitory capacity, and distractibility and impaired sustained attention (Beers & De Bellis, 2002; Bremner et al., 1995; Mezzacappa, Kindlon, & Earls, 2001; Palmer et al., 1997). The laboratory of Navalta et al. have studied these effects of ELS extensively as well, finding a strong graded association between the duration of childhood sexual abuse and memory functions (Navalta et al., 2006). Aside from the studies focussing on the behavioural consequences of ELS, there is also already quite a body of literature focused on the neurobiological effects of ELS. Some of this has shown a reduced activity in the nucleus accumbens and dorsolateral and ventrolateral PFC and an increased activity in the dorsal mPFC during social rejection in individuals who have experienced ELS (Herzberg & Gunnar, 2020). The group of Navalta et al. also reported findings of both their own research and other papers they studied which indicate that a history of abuse can be related to reduced volume of the left hippocampus, a smaller size of the corpus callosum, abnormalities in cortical size, symmetry and neural density and a highly lateralized hemispheric response to memory recall (Bremner et al., 1997; Carrion et al., 2001; De Bellis et al., 1999; De Bellis et al., 2002; Driessen et al., 2000; Stein, Koverola, Hanna, Torchia, & McClarty, 1997; Teicher et al., 2004; Teicher et al., 1997; Vythilingam et al., 2002). Moreover, there is consistent evidence that ELS exposure in individuals without psychiatric disorders is associated with volumetric and functional changes in brain regions relevant to executive functions and more importantly memory functions such as the Anterior Cingulate Cortex (ACC), the medial prefrontal cortex (mPFC), the caudate and the insula (Saleh et al., 2017).

So experiencing these traumatic events so early in life influences the neurodevelopment of some key memory and emotion related brain regions. Some of these regions play an important role in memory functions while other regions are related to emotion and stress related circumstances, which are both also relevant components of PTSD. This could explain the outcome of the recent studies that the alteration in neurodevelopment of such relevant brain regions caused by ELS predisposes these victims of ELS to develop PTSD later in life when they experience a traumatic event (Garrett et al., 2019; Villain et al., 2018). There have also been studies investigating the effects of PTSD on AMR,

which consistently show that there is an increased amygdala and reduced mPFC response while doing an AMR task with trauma-related scripts in PTSD patients relative to controls (Carhart-Harris et al., 2014; Lanius, R.L., & Frewen, 2011). PTSD is characterized by hyper arousal, hypervigilance and dissociative symptoms (Thome, Terpou, McKinnon, & Lanius, 2020). These can cause the patient to suffer from symptoms like intrusions in the form of dreams or thoughts, avoidance, anxious arousal or general distress (Marshall et al., 2019). The probability of developing this disorder relies on a multitude of factors, for example gender, the type of trauma and the combination of these factors (Shalev, Liberzon, & Marmar, 2017; Villain et al., 2018). These factors could possibly play an important role in finding new ways to prevent or possibly treat PTSD better in the future. There already are several methods of treatment currently applied to help PTSD patients, including prolonged exposure to trauma-related stimuli (Cusack et al., 2016). However, even though there is a reduction in symptomatology, only 50% of the patients fully remit, with some experiencing relapses and leaving some still suffering from symptoms right after treatment has been finished (Bisson et al., 2013; Kessler, 2000). The most common residual PTSD symptoms after treatment are detachment, insomnia and trauma flashbacks, which are all related to general distress (Larsen, Fleming, & Resick, 2019). Evidently there is a necessity to increase the rate of remission of PTSD, and novel or additional treatments are needed to achieve full recovery in all patients. Recently there have been studies investigating whether adding a pharmacological intervention to these existing treatments could lead to an improvement of the treatment outcome. It has not been proven yet, but there are some promising results for drugs like Hydrocortisone (Yehuda, Bierer, Pratchett, & Malowney, 2010), Propranolol (Smith, Doran, Sippel, & Harpaz-Rotem, 2017) and MDMA (Sessa, 2017). Another way to try and improve the PTSD treatments is to try and control for factors influencing PTSD and the outcome of the treatment, in this case focussing on ELS.

It is therefore crucial to gain a better understanding of how stress and trauma early in life affect the development of the memory systems. This allows us to expand our knowledge and enables us the search for more and better ways to help PTSD patients, personalized to their life experiences. There is already the implication that ELS can affect the AMR performance, which could therefore imply an indirect effect on the probability to develop PTSD in the case of a traumatic event, and moreover even the success rate of current PTSD treatments. And since there is no consensus yet on how ELS influences the way individuals deal with traumatic events later in life and how memory consolidation and retrieval is connected with this, there is a need for additional

data on this subject. How this affects the probability of developing PTSD, or the effectivity of the current treatments available remains unknown as well so far. All together this calls for more research to discover the answers to these questions that are so important for PTSD patients and their future.

This study will provide more data on this particular subject, while the larger main study was designed to determine whether a glucocorticoid manipulation is effective to facilitate fear memory extinction retention in an experimental model of exposure therapy in healthy individuals with ELS compared to healthy controls without ELS. One of the main goals of the study will be to further investigate the interactive effects of hydrocortisone and ELS on neural correlates of memory. However, since the study is not finished yet, this current paper will not focus on the difference between with and without ELS or the drug effects on the AMRT, but on verifying the effectivity of the AMRT task in causing differences in neural activity during emotional memory retrieval. Looking at all the information that was collected, we would expect activity during the recall of autobiographical memory, for both the ELS and non-ELS group, in the hippocampal complex, the Precuneus, and the amygdala (Fossati, 2013; Holland & Kensinger, 2010; Martinelli, M., & Piolino, 2013) from the limbic structures. Furthermore, an activity pattern is expected in both the medial and lateral PFC, including the perigenual ACC, the insula, and the cerebellum, specifically the Culmen (Fossati, 2013; Holland & Kensinger, 2010; Martinelli et al., 2013; Thome et al., 2020), or at least the posterior cerebellar lobule VI (Thome et al., 2020). Activation is expected in the sensory cortex of the occipital lobe (Fossati, 2013; Holland & Kensinger, 2010), the middle temporal gyrus, the TPJ and sensory cortex of the temporal lobe as well (Holland & Kensinger, 2010; Martinelli et al., 2013). If the AMRT is proven to be effective, the main study can proceed their data collection and analysis with the assurance that the task paradigm functions properly. Their results will help us gain a better understanding of the effects of ELS on different memory functions later in life.

Research Objective

The main objective of this study is to verify if the Autobiographical Memory Task paradigm is effective in eliciting activity in neural correlates of memory and emotion. The participants with and without ELS will be combined and analysed as one group because the data that has been collected so far is from a rather small group. Taking the groups with and without ELS together will increase the power of the analysis and will allow us to study which brain regions will be activated during the AMR task in the data so far collected. Activity in the regions of interest during the AMR Task will be analysed first and then other regions that are possibly interesting from the DMN and SN will be explored.

Considering all the information that was collected from previous studies, we expect that the mPFC, the hippocampal complex, the Precuneus, the cerebellum, the TPJ, the insula, amygdala and ACC and the sensory cortex from the occipital and sensory cortex of the temporal lobe will be activated during the Autobiographical Memory Recall Task in a group including people with and without Early Life Stress. If compared to the complete AM network that was mentioned before, you can find many regions represented either in the Default Mode Network or the Salience Network. The mPFC, Hippocampus, TPJ and Precuneus can be found in the DMN, while the Amygdala is part of the SN. Thus, we hope to see activity patterns in our data, but we should keep in mind that this is a preliminary dataset with a limited sample-size and power analysis. However, we expect to found enough neural activity to verify the task and predict whether the task will be sufficient for the main study.

Methods

This paper is part of a larger study that is still running. The complete study paradigm will be explained shortly, but the focus will be on the details of the tasks relevant to this paper. The key objective of the main study was to determine whether a glucocorticoid manipulation using Hydrocortisone is effective to facilitate fear memory extinction retention in an experimental model of exposure therapy in healthy individuals with ELS compared to healthy controls without ELS. Another goal of the main study is to further investigate the interactive effects of hydrocortisone and ELS on neural correlates of memory. This paper is an analysis on preliminary data and will therefore focus on verifying the effectivity of the AMRT task in causing activation in neural correlates of memory and emotion during emotional memory retrieval compared to rest. This will be done by using a 2*2 mixed design, namely a placebo-controlled double-blind cross-over design. However, for this paper we only analysed the data of the first session of each participant that was included so far, without taking into account whether that session was the placebo or Hydrocortisone session.

Study Population

The inclusion criteria for both groups was that they were healthy men and women between 18 and 45 years old with predominant right-handedness and a history of taking cannabis at least once in their lifetime. A person was considered healthy if they were not suffering from any neurological or psychiatric disorder at this moment or in the recent past. The main study is still running and is aiming to include 58 participants, 50% having ELS and 50% without ELS. The sample size was calculated based on the main goal of the study, which originally included the use of THC in a third session which was thus considered during the calculation. Two previous studies with similar outcome measures and drug treatments were used to determine an expected effect size of the drug effect. One study of Rabinak et al. reported a drug effect size for THC (Cohen's d) of .88, and another study of de Quervain et al. reported a drug effect size for Cortisol of .6 (de Quervain et al., 2011; Rabinak et al., 2013). This first led to a sample size of 24 for each group and thus a total of 48 participants. This would have an effect size .6, an alpha of .05 and a power (1-ß) of .8. Ultimately, we came to a sample size of 58 participants, taking into account an expected drop-out rate of 20%.

To determine whether someone belonged in the ELS group or the control group, we used the criteria of the Maltreatment and Abuse Chronology of Exposure Scale (MACE-X) questionnaire before the age of 10 (Teicher & Parigger, 2015).

The exact exclusion criteria can be found in Supplementary 1 and the following inclusion criteria were used for the selection of the participants;

For ELS group:

- There are 10 subscales in MACE-X, the inclusion criteria for each subscale is listed below and they all had to be fulfilled before the age of ten. There were six subscales which are relevant to Severe Childhood Maltreatment (SCM): Emotional Neglect, Parental Nonverbal Emotional Abuse, Parental Physical Maltreatment, Parental Verbal Abuse, Sexual Abuse, or Witnessing Interparental Violence. Participant had to fulfil the criteria for at least one of these subscales to be included:
  - Emotional neglect: the cut-off is 2 items out of 5
  - Parental non-verbal emotional abuse: the cut-off is 4 out of 6
  - Parental physical maltreatment: the cut-off is 4 items
  - Parental verbal abuse: the cut-off is 3 items out of 4
  - Sexual abuse: the cut-off is 2 items out of 7
  - Witnessing interparental violence: the cut-off is 2 items out of 5
- There are four remaining subscales which were not relevant to SCM, the criteria of each subscale are listed here below and again had to have happened before the age of ten. If participants only fulfil the criteria of any of these four subscales and none of the SCM subscales, they were excluded:
  - Peer emotional abuse: the cut-off is 4 items out of 5
  - Peer physical bullying: the cut-off is 2 items out of 5
  - Physical neglect: the cut-off is 2 items out of 5
  - Witnessing violence to siblings: the cut-off is 1 item out of 4

For Non-ELS group:

- In the control group we sought participants with no experiences of early-life stress, thus people were only included when they scored zero items on the six SCM subscales and could not fulfil the criteria for any the other four subscales of the MACE-X.

Study Procedures

Pre-screening

The participants were recruited by distributing posters around the city of Nijmegen and posting these on several internet pages like Nextdoor.nl and Facebook. The information on these posters would lead to a website about our study, http://jeugdtraumacannabis.nl , where they could find some basic information about our study and a link to our anonymized pre-screening questionnaire on www.soscisurvey.de. This pre-screening questionnaire would include questions about the crucial inclusion and exclusion criteria. Passing this online pre-screening would lead to an appointment for the on-site screening.

Screening

The screening would be started with signing the informed consent by the participant and collecting the code to access the anonymized data from the pre-screening. The participant would then fill in the MACE-X (Teicher & Parigger, 2015), the Spielberger's State-Trait Anxiety Inventory (STAI) (Defares, van der Ploeg, & Spielberger, 1980; Spielberger, Gorsuch, & Lushene, 1970), Beck's Depression Inventory (BDI) (Whisman, Judd, Whiteford, & Gelhorn, 2013), the NEO Five Factor Inventory (NEO-FFI) (McCrae & Costa, 1999), Behavioural Inhibition and Activation Scales (BIS-BAS) (Carver & White, 1994), the Positive and Negative Affect Schedule (PANAS) (Watson, Clark, & Tellegen, 1988), and the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV) (Wechsler, 1997). Afterwards, the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) was used as a guideline for an interview to assess any current or past possible mental health issues and allow us to determine if participation was possible and whether there were any circumstances from their past that needed to be taken into consideration during testing. Afterwards, an appointment would be made for both test sessions if the participant met all criteria.

They were compensated with a monetary payment if they completed the screening and both test sessions. The study was approved by the local medical ethical committee (CMO region Arnhem-Nijmegen, the Netherlands) and conducted in accordance with the Declaration of Helsinki (2007-2008)
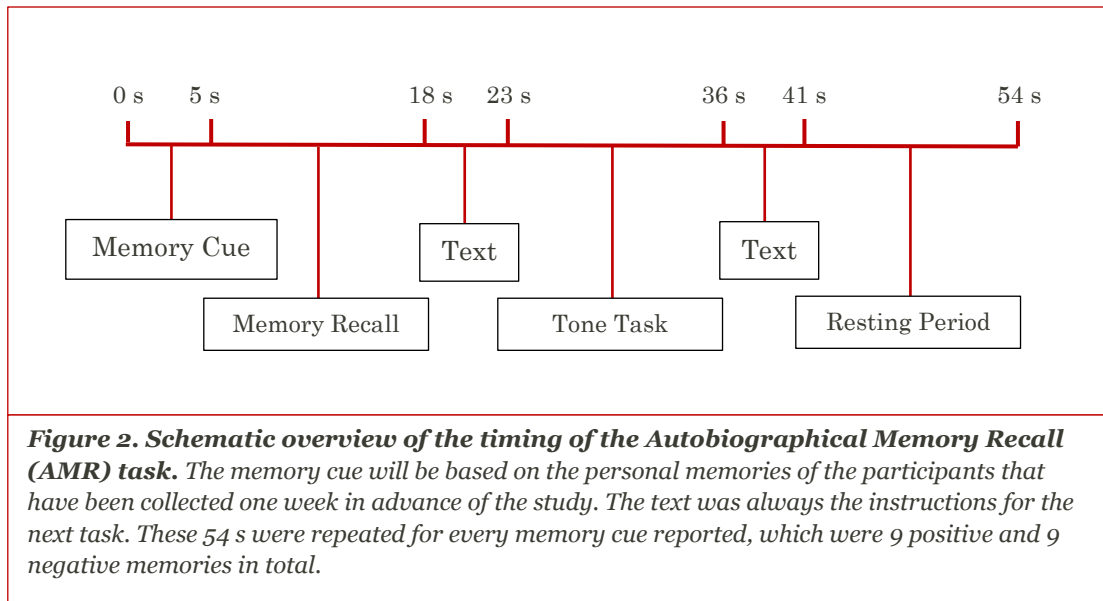
Experimental Procedures

The study consisted of two sessions with at least two weeks between them. Participants would come in at 09:00 and do a drug and pregnancy test and we would take a hair and blood sample. This was followed by a fear conditioning session and a two hour break. In the middle of the break we would take a saliva sample and give the drug intervention. After the break we would again collect a saliva and blood sample, followed by the fear extinction session. Then they went to the MRI scanner where a saliva sample was collected before starting the MRI session. We would acquire a structural T1 or Diffusion Tensor Image, depending on the session, and a Resting State scan. During fMRI acquisition they would perform the AMR task and a Dynamic Face task. Then another saliva sample would be collected and they would stay until 17:00 so we could check for any adverse drug effects. The next day they would collect a saliva sample themselves at home and come back once more for the Fear Recall session. The timeline of one complete study session is shown in figure 1. As mentioned before, the complete study will not be explained in detail because of the irrelevance to the topic of the current paper and the focus will solely be on the autobiographical memory recall (AMR) task and the fMRI acquisition of the first session.
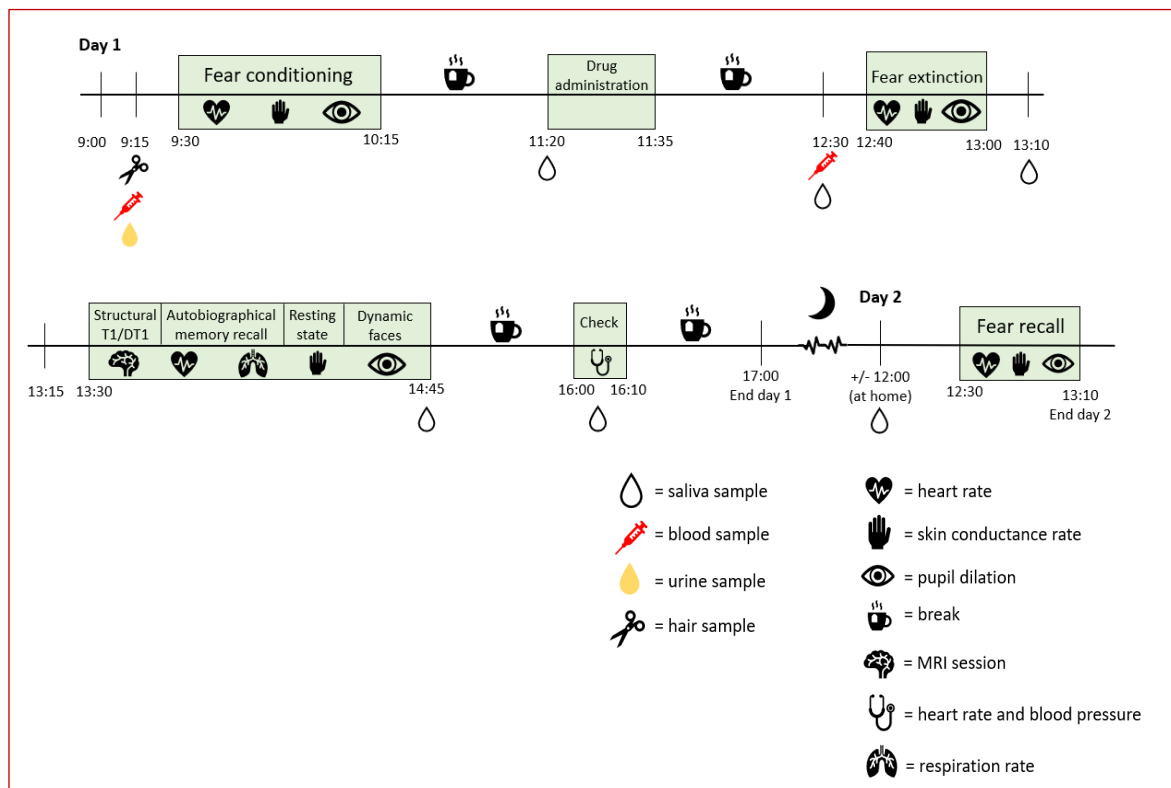
Figure 1. Schematic overview of the testing sessions of the complete study session. This paper will focus on the Autobiographical Memory Recall Task during the MRI session. The drug administration consisted of either a placebo or 20 mg of Hydrocortisone that was dissolved in different fruit juices, grapefruit and strawberry-orange juice respectively.

The MRI sequence was started with the structural T1W scan and a field map scan to adapt participants to the MRI environment, which was then followed directly by the AMR task. The purpose of the AMR task was to measure neuronal activity during the retrieval of a personal past event recollected in the context of a particular time and place. Personalized memory cues were collected a week in advance of the testing day by sending a questionnaire, asking them to list nine of their worst and nine of their best memories in three to five key words, at which age this event occurred and the valence of the event on a one to five numerical scale. The questionnaire also included a question regarding the vividness of the memory, but they were only asked to fill this in after performing the task in the MRI scanner (Supplementary 2). The AMR task itself was programmed in Presentation (version 20.2). The task was explained right before starting. The task was a block-design of 18 blocks and each block started with instructions that told the participant to remember and relive a personal past event, based on one of their personalized memory cues, as vividly as possible with their eyes closed. The cue would be presented for 5 seconds, followed by a period of 13 seconds to recall the memory. The participant would be reminded by an auditory cue after those 13 seconds, asking them to open their eyes. New instruction would appear on the screen for 5 seconds again, asking them to listen to a sequence of low and high tones with their eyes closed for 13 seconds. Then they were instructed by text to indicate if they heard more high or low tones by pressing a button box. Then another instruction appeared on the screen for 5 seconds, telling the participant to close their eyes and rest for 13 seconds without thinking about anything specific. This was already indicated before the MRI session, plus it was stressed that they should not think about any of the memories that we collected. The auditory cue to open their eyes was played again afterwards and this whole sequence restarted with a new memory cue. The order of the memory cues is randomized for every participant. The sequence of one memory cue is displayed in a simplified timeline in Figure 2. The goal of the tone task was to distract the participant from the memory they just recalled and possibly to use as a contrast to the brain activation during memory recall. The rest period was used only as a contrast to compare the neural activity between the recall period and rest period.

Figure 2. Schematic overview of the timing of the Autobiographical Memory Recall (AMR) task. *The memory cue will be based on the personal memories of the participants that have been collected one week in advance of the study. The text was always the instructions for the next task. These 54 s were repeated for every memory cue reported, which were 9 positive and 9 negative memories in total.*

MRI parameters

The MRI data was acquired at the Donders Centre for Cognitive Neuroimaging with a Siemens Skyra 3T MRI scanner (Siemens, Germany) that has a 32-channel head coil. The anatomical T1-weighted (T1W) brain volumes were collected with a T1W-3D magnetization prepared gradient echo sequence (MPRAGE). It was performed with a voxel size of 1 x 1 x 1 mm³, 192 slices, a repetition time (TR) of 2300 ms, an Echo Time (TE) of 3.03 ms, a flip angle (FA) of 8°, a Field of View (FOV) of 256 x 256 mm², a matrix size of 256 x 256 x 256 and a total scan time of 5 min and 21 s. All functional images were acquired with Multiband Short-Echo sequence with multi-sliced interleaved slices, with a TR of 945 ms, a TE of 28 ms, a FA of 60°, a FOV of 213 mm and it consisted of 66 slices, with a voxel size of 2.05 x 2.05 x 2 mm³ and a Multiband Acceleration Factor of 6. Furthermore, there was an Echo Spacing of 0.77 used, a bandwidth of 1602 Hz/Px, an EPI factor of 104 and the total acquisition time was 24 min and 7 s. Lastly, the field map scan was performed with multi-sliced interleaved slices, with a TR of 620 ms, a TE of 4.70 ms, a FA of 60°, a FOV of 210mm and it consisted of 66 slices, with a voxel size of 2.4 x 2.4 x 2 mm³, a bandwidth of 800 Hz/Px and it lasted 1 min and 52 s.

Analysis

Pre-processing

The program SPM 12 was used to perform all data processing and analyses. The MRI data was first realigned with estimation and re-slicing, which was followed by co-registration with estimation. The images were registered to the mean for the first estimation and had a 2nd degree B-spline interpolation, no wrapping was done. All images and the mean image were resliced with a 4th degree B-spline interpolation without wrapping but with masking. The co-registration was done with Normalised Mutual Information with a 4 x 2 separation of samples. The tolerance was set to 1x2 double and histogram smoothing of 7 x 7 was used. This first step of pre-processing was saved as a batch to pre-process all the data correctly and consistently per participant. The next step was to normalise the data with estimation and writing followed by smoothing of the images. The images were aligned to the T1 image of the same participant to normalize the data. Bias regularisation was used and the Full Width Half Maximum (FWHM) Bias had a 60mm cut off. The International Consortium of Brain Mapping (ICBM) space template for European Brains was used for the Affine Regularisation and 1 x 5 double was used for the Warping Regularisation. There was no smoothness added yet, but a sampling distance of 3 mm was used. For the writing of the normalisation, the double bounding box was set to 2 x 3 with voxel sizes of 3 x 3 x 3 with an Interpolation of the 4th degree B-spline. The last step of the pre-processing was to smooth the image, for which an 8 x 8 x 8 FWHM was used with no implicit masking.

fMRI activation analysis

The First-level analysis was started with fMRI model specification. Our interscan interval was 0.945 seconds with a microtime resolution of 16 s and an onset of 8 s. Four conditions were added to create contrasts later on. First there were the memory conditions, the positive and negative memories were separated which resulted in 9 trials each with a duration of 13 s and no time modulation. Then there were the control conditions, for which both the tone task and the resting period were used, which consisted of 18 trials each that also lasted 13 s. The onset time of all conditions was calculated using the log files created by the Presentation script for the AMRT and all of them had orthogonalized modulations. Furthermore, we added the multiple regressors which were created during pre-processing and a high-pass filter of 128 s. The regressors were necessary to correct for factors like head movement and included the six motion parameter regressors, three translations and three rotations, the zero-centered squares and the first derivatives of the motion

parameters and the zero-centered squares of those derivatives. An autoregressive model was used for the serial correlations. Lastly for the first-level analysis, a classical model estimation was performed. This led to the following contrasts by comparisons of conditions: Positive (Memories) to Negative (Memories), Negative to Positive, Positive to Control: Tone Task (CTT), Negative to CTT, Positive to Control: Resting Period (CRP), Negative to CRP, Both Positive and Negative (Memories) to CTT and lastly Positive and Negative to CRP. The CTT and CRP were also compared as an extra comparison to later on check the quality of the control conditions.

Finally, the second-level analysis was done, for which all scans were taken together to perform a one-sample T-test. The one-sample T-test was chosen because we are dealing with numerical data from one group of participants and we are interested in the mean difference in brain activation of certain regions. Only an implicit mask was used for the Factorial design specification and the Restricted Maximum Likelihood (ReML) method was used for the model estimation, this model assumes the error correlation structure is the same at each voxel. Then the images were created and no masking, no False Discovery Rate (FDR) correction and no p-value adjustment was applied. A whole-brain analysis was done with a threshold of $p < 0.001$ and the FWE-corrected p-values were used. No extent threshold was added either. After the results were studied like this, a small volume correction was performed for the Regions of Interest (ROI) with several brain region and network masks and some brain region coordinates. These masks from the DMN network and SN network were used from the Functional Imaging in Neuropsychiatric Disorders (FIND) Lab at Stanford University (Shirer, Ryali, Rykhlevskaia, Menon, & Greicius, 2012), which included most of our ROI. Coordinates were used as well for the smaller important regions. The Montreal Neurological Institute (MNI) coordinates (x, y, z) for the Hippocampus were -26, -20, -16 for the left hemisphere and 26, -12, -20 for the right hemisphere (Martinelli et al., 2013). The coordinates of the Amygdala were -18, 0, -12 for the left hemisphere (Whalley, Rugg, & Brewin, 2012) and 30, -4, 16 for the right hemisphere (St Jacques et al., 2011). Finally, we checked whether activated regions could also be found in the AM network, the DMN and the SN to verify if the hypothesized regions were activated during the AMRT.

Results

Demographics

Twelve participants completed the first sessions, of which 6 belonged to the ELS group and the other 6 to the non-ELS group. The demographic information of these participants can be found in Table 1. The intervention was not deblinded yet since the study was still running, so we do not know whether they were given the Hydrocortisone or the placebo.

		Non-ELS group N = 6		ELS group N = 6		Total N = 12	
Age		26.50	(3.19)	28.17	(2.57)	27.33	(1.97)
BMI		23.5	(1.33)	26.03	(1.86)	24.76	(1.16)
Gender	Male	3	(50)	4	(66.7)	7	(58.3)
	Female	3	(50)	2	(33.3)	5	(41.7)
Education	VMBO	1	(16.7)	1	(16.7)	1	(8.3)
	HAVO			1	(16.7)	1	(8.3)
	VWO			1	(16.7)	2	(16.7)
	HBO	2	(33.3)			2	(16.7)
	WO	3	(50)	3	(50)	6	(50)

Table 1. Demographic data of all participants. *Age and BMI is described as the Mean (Std. Error) and Gender and Education is described as the number (Percent %).*
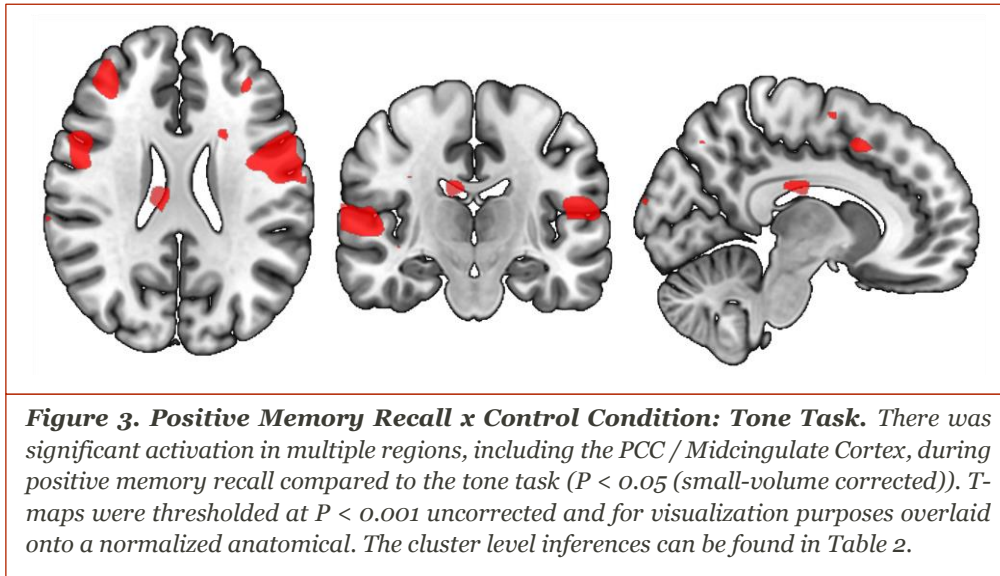
MRI results

The purpose of this study was to verify the effectivity of the AMRT task in causing neural activity in relevant brain regions during emotional memory retrieval by performing a 2*2 mixed design study design. We investigated the acute response to the AMRT task during the first session of all 12 participants, using a whole-brain activation analysis first and then adding a small volume correction for the ROIs from our hypothesis, using the brain network and region masks from both the DMN and SN from the FIND Lab at Stanford University, which include these ROIs (Shirer, Ryali et al.), and the coordinates of the Amygdala and Hippocampus (Martinelli, M et al., Whalley, Rugg et al., St Jacques, Botzung et al.). Afterwards we explored more regions with these masks that seemed interesting because of their association to the AM network, like regions from the SN or DMN. We looked at the cluster-level statistics to calculate our FWE-corrected p-values.

Negative vs. Positive Memory Contrast

Analyses started with comparing neuronal activation after negative vs. positive memories, which did not result in any significant data.
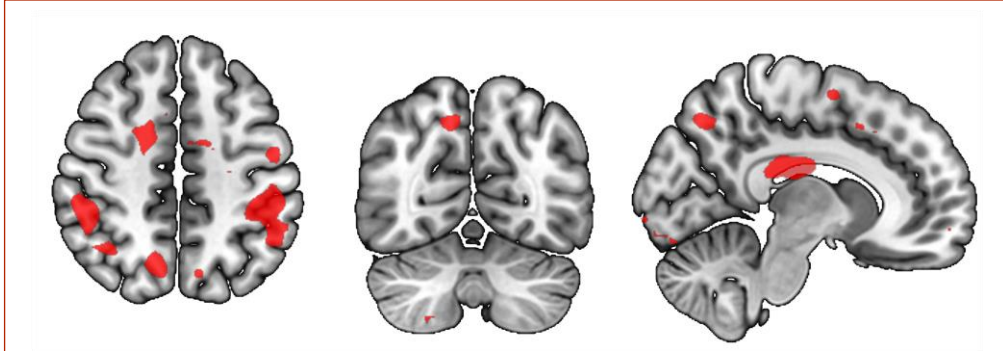
Positive Memory vs. Control Condition: Tone Task

Next, the different valenced memories were compared to the Tone Task as a control condition (CTT). When comparing the positive memory recall to the CTT condition, there were no significant results during the whole-brain analysis, but a significant difference in activation was found in a few regions when using a small-volume correction for the ROIs. These regions were the Inferior Frontal Gyrus (T = 5.85, cluster size 278 mm^3, P$_{FWE-corr}$ = 0.001), the Inferior Parietal Lobule (T = 4.16, cluster size 2 mm^3, P$_{FWE-corr}$ = 0.044) and the PCC / Midcingulate (T = 4.52, cluster size 4 mm^3, P$_{FWE-corr}$ = 0.022). The activation around the PCC / Midcingulate Cortex is shown in Figure 3.

Figure 3. Positive Memory Recall x Control Condition: Tone Task. There was significant activation in multiple regions, including the PCC / Midcingulate Cortex, during positive memory recall compared to the tone task (P < 0.05 (small-volume corrected)). T-maps were thresholded at P < 0.001 uncorrected and for visualization purposes overlaid onto a normalized anatomical. The cluster level inferences can be found in Table 2.

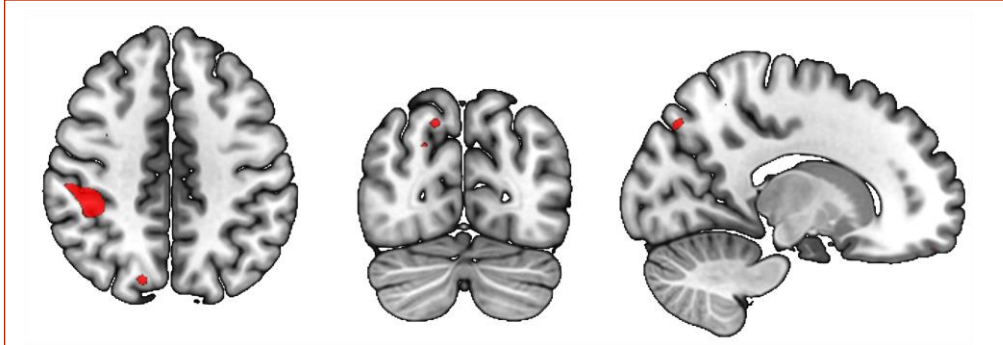## Negative Memory vs. Control Condition: Tone Task

There were no significant results when comparing Negative memory recall to the CTT condition with whole brain analysis, but with small volume correction for the ROIs, significant activation was found in the Inferior Parietal Lobule (T = 4.72, cluster size 9 mm^3, P$_{FWE-corr}$ = 0.026), PCC / Midcingulate Cortex (T = 7.97, cluster size 15 mm^3, P$_{FWE-corr}$ = 0.01) and right Precuneus (T = 4.66, cluster size 4 mm^3, P$_{FWE-corr}$ = 0.049). The activation surrounding the Precuneus can be seen in Figure 4.

Figure 4. Negative Memory Recall x Control Condition: Tone Task. *There was significant activation in multiple regions, including the Precuneus , during positive memory recall compared to the tone task (P < 0.05 (small-volume corrected)). T-maps were thresholded at P < 0.001 uncorrected and for visualization purposes overlaid onto a normalized anatomical. The cluster level inferences can be found in Table 2.*

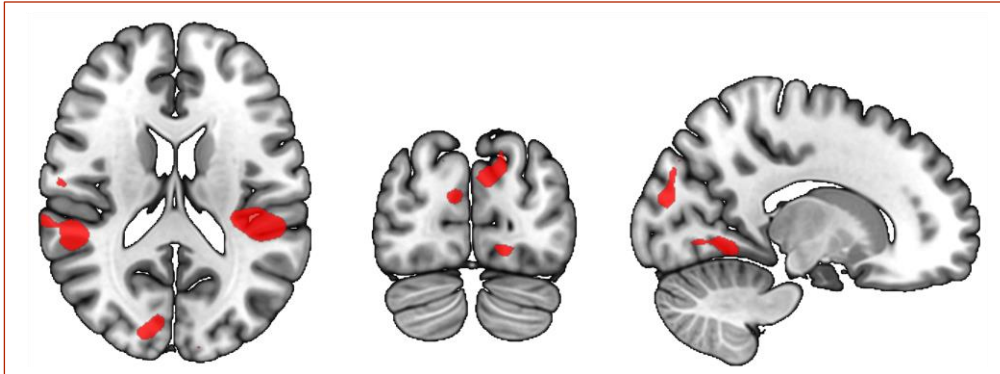## *Positive Memory vs. Control Condition: Resting Period*

Then we compared the Positive Memories to the other control task condition, the resting period (CRP). During the comparison between Positive Memory Recall and CRP with a whole-brain analysis, significant activation was found in the left Superior Temporal Gyrus (T = 11.98, cluster size 1074 mm^3, $P_{FWE\text{-}corr}$ = 0.000), in the right Superior Temporal Gyrus (T = 11.72, cluster size 1202 mm^3, $P_{FWE\text{-}corr}$ = 0.000) and the right Supramarginal Gyrus (T = 11.57, cluster size 219 mm^3, $P_{FWE\text{-}corr}$ = 0.000). When adding the small-volume correction masks for the ROIs, we also found activation in the right PCC / Midcingulate (T = 4.48, cluster size 2 mm^3, $P_{FWE\text{-}corr}$ = 0.033), in the left PCC / Midcingulate (T = 4.14, cluster size 1 mm^3, $P_{FWE\text{-}corr}$ = 0.04), the right Precuneus (T = 5.64, cluster size 12 mm^3, $P_{FWE\text{-}corr}$ = 0.023), the mPFC (T = 4.89, cluster size 2 mm^3, $P_{FWE\text{-}corr}$ = 0.006), the right Postcentral Gyrus / Middle Frontal Gyrus (T = 5.57, cluster size 15 mm^3, $P_{FWE\text{-}corr}$ = 0.014) and the Inferior Parietal Lobule (T = 4.41, cluster size 2 mm^3, $P_{FWE\text{-}corr}$ = 0.024). The activation in the right Precuneus can be seen in Figure 5.

Figure 5. Positive Memory Recall x Control Condition: Resting Period. *There was significant activation in multiple regions, including the Precuneus, during positive memory recall compared to the tone task (P < 0.05 (small-volume corrected)). T-maps were thresholded at P < 0.001 uncorrected and for visualization purposes overlaid onto a normalized anatomical scan. The cluster level inferences can be found in Table 2.*

### *Negative Memory vs. Control Condition: Resting Period*

When comparing the Negative Memory Recall to the CRP with whole brain analysis, activation was found in the left Middle Temporal Gyrus (T = 8.49, cluster size 735 mm^3, $P_{FWE-corr}$ = 0.000), the left Culmen (T = 8.38, cluster size 189 mm^3, $P_{FWE-corr}$ = 0.000), the right Middle Temporal Gyrus (T = 8.37, cluster size 908 mm^3, $P_{FWE-corr}$ = 0.0000), the right Intraparietal Sulcus (T = 7.61, cluster size 115 mm^3, $P_{FWE-corr}$ = 0.002), the left Cuneus (T = 6.78, cluster size 170 mm^3, $P_{FWE-corr}$ = 0.000) and the right Middle Occipital Gyrus (T = 5.49, cluster size 109 mm^3, $P_{FWE-corr}$ = 0.002). When adding a small-volume correction for our ROIs, more regions were found, which were the right Precuneus (T = 4.60, cluster size 6 mm^3, $P_{FWE-corr}$ = 0.041), the Paracentral Lobule (T = 4.04, cluster size 1 mm^3, $P_{FWE-corr}$ = 0.007) and the right Intraparietal Lobule / Precentral Gyrus (T = 4.18, cluster size 3 mm^3, $P_{FWE-corr}$ = 0.047). Part of the activation pattern around the Right Precuneus can be found in Figure 6.

Figure 6. Negative Memory Recall x Control Condition: Resting Period. There was significant activation in multiple regions, including the right Precuneus, during positive memory recall compared to the tone task (P < 0.05 (small-volume corrected)). T-maps were thresholded at P < 0.001 uncorrected and for visualization purposes overlaid onto a normalized anatomical scan. The cluster level inferences can be found in Table 2.

Memory Recall vs. Control Condition: Tone Task

This was followed by combining the Positive and Negative memories together for the Memory Recall condition and comparing it to the CTT. When using a whole brain analysis, activation was only found in the right Fusiform Gyrus (T = 5.60, cluster size 177 mm^3, P$_{FWE-corr}$ = 0.001). Then adding a small volume correction mask for our ROIs, the PCC / Midcingulate (T = 6.88, cluster size 11 mm^3, P$_{FWE-corr}$ = 0.013) and the Inferior Parietal Lobule (T = 4.36, cluster size 2 mm^3, P$_{FWE-corr}$ = 0.046) also showed up. Some of the activation pattern around the PCC / Midcingulate Cortex can be seen in Figure 7.
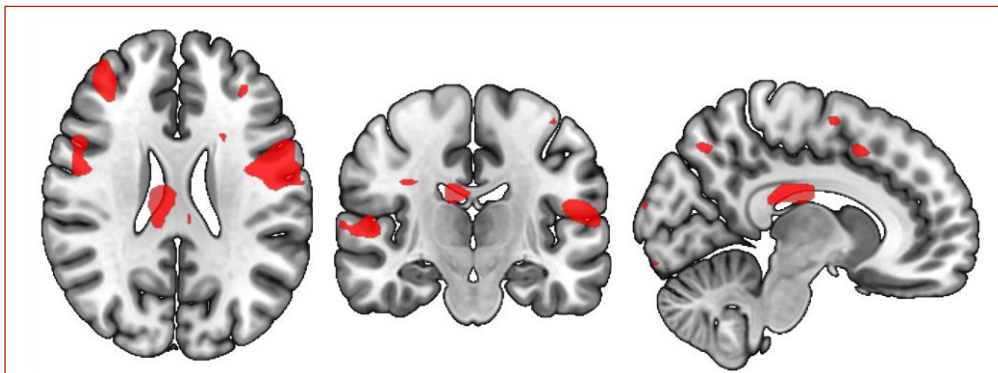
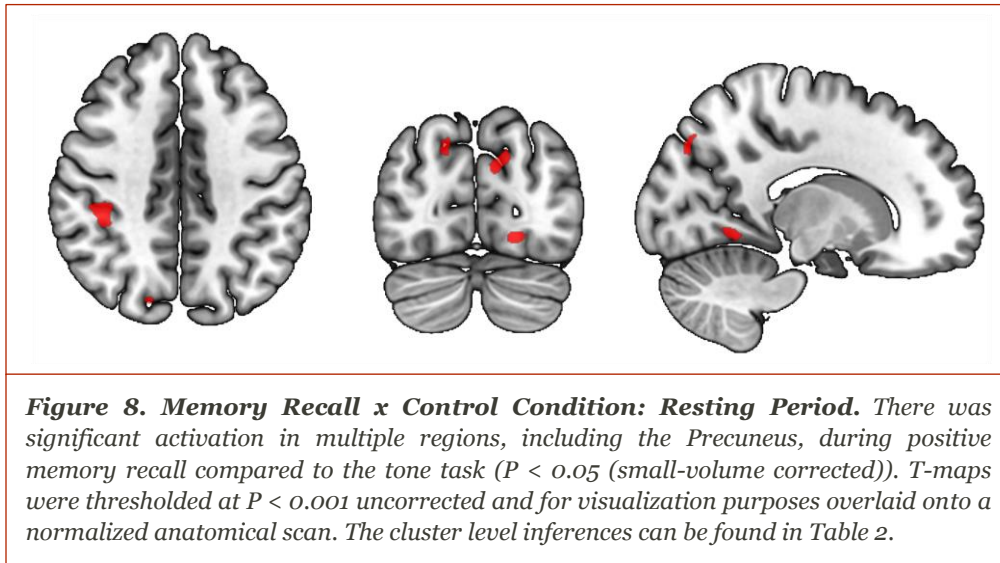*Figure 7. Memory Recall x Control Condition: Tone Task. There was significant activation in multiple regions, including the PCC / Midcingulate, during positive memory recall compared to the tone task (P < 0.05 (small-volume corrected)). T-maps were thresholded at P < 0.001 uncorrected and for visualization purposes overlaid onto a normalized anatomical. The cluster level inferences can be found in Table 2.*
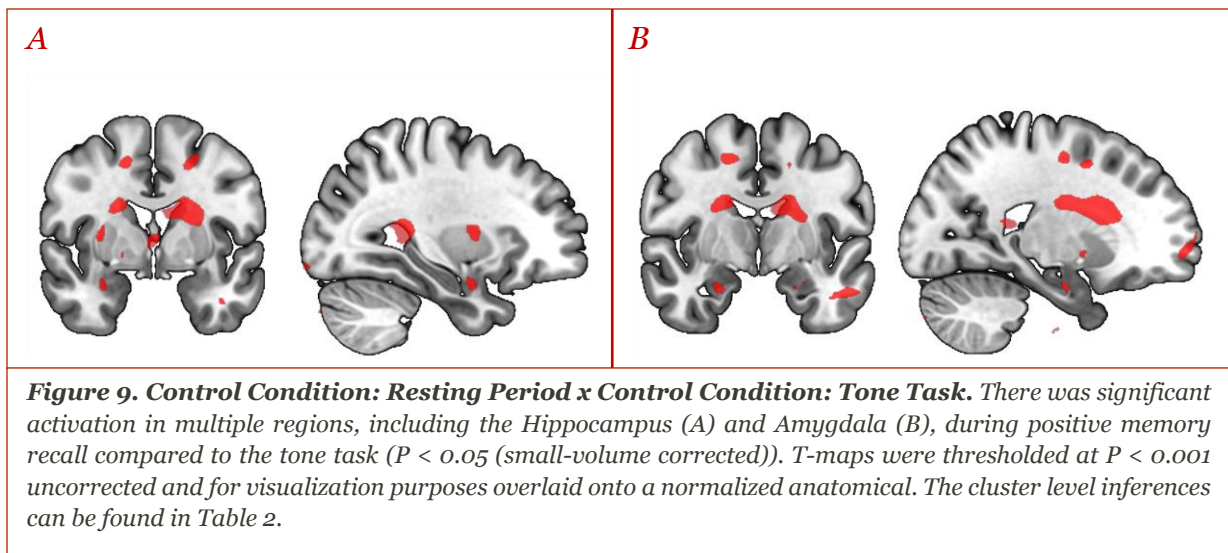
<u>*Memory Recall vs. Control Condition: Resting Period*</u>

Then the Memory Recall was compared to the CRP with a whole-brain analysis, showing significant activation in the left Fusiform Gyrus / Lingual Gyrus (T = 11.01, cluster size 191 mm³, $P_{FWE-corr}$ = 0.000), right Superior Temporal Gyrus (T = 9.72, cluster size 1127 mm³, $P_{FWE-corr}$ = 0.000), the Intraparietal Sulcus (T = 9.67, cluster size 184 mm³, $P_{FWE-corr}$ = 0.000), the left Superior Temporal Gyrus (T = 9.54, cluster size 954 mm³, $P_{FWE-corr}$ = 0.000), left Cuneus (T = 7.83, cluster size 178 mm³, $P_{FWE-corr}$ = 0.000), right Fusiform Gyrus / Lingual Gyrus (T = 7.37, cluster size 161 mm³, $P_{FWE-corr}$ = 0.000) and the left Inferior Parietal Lobule (T = 6.45, cluster size 115 mm³, $P_{FWE-corr}$ = 0.001). When adding a small-volume correction for our ROIs, the following additional regions showed significant activation; the right Precuneus (T = 5.46, cluster size 13 mm³, $P_{FWE-corr}$ = 0.022), the mPFC (T = 5.47, cluster size 2 mm³, $P_{FWE-corr}$ = 0.006), the right Postcentral Gyrus / Middle Frontal Gyrus (T = 4.91, cluster size 4 mm³, $P_{FWE-corr}$ = 0.042), the Inferior Parietal Lobule (T = 4.37, cluster size 5 mm³, $P_{FWE-corr}$ = 0.038), the Supramarginal Gyrus (T = 4.88, cluster size 4 mm³, $P_{FWE-corr}$ = 0.042) and the Insula (T = 4.08, cluster size 1 mm³, $P_{FWE-corr}$ = 0.014). Some of the activation pattern near the Precuneus can be seen in Figure 8.

Figure 8. Memory Recall x Control Condition: Resting Period. *There was significant activation in multiple regions, including the Precuneus, during positive memory recall compared to the tone task (P < 0.05 (small-volume corrected)). T-maps were thresholded at P < 0.001 uncorrected and for visualization purposes overlaid onto a normalized anatomical scan. The cluster level inferences can be found in Table 2.*

Control Condition: Resting Period vs. Tone Task

Lastly, we compared the two control conditions to each other to check for differences between those. When comparing CRP to CTT during the whole brain analysis, we just found significant activation in the left Caudate Nucleus / Putamen (T = 5.15, cluster size 103 mm^3, $P_{FWE-corr}$ = 0.007), but with a small volume correction added for ROIs, activation was also found in the Hippocampus (T = 4.90, cluster size 2 mm^3, $P_{FWE-corr}$ = 0.024) and the Amygdala (T = 4.28, cluster size 2 mm^3, $P_{FWE-corr}$ = 0.024). The activation of the Hippocampus and Amygdala and the surrounding areas can be seen in Figure 9. No significant activation was found when comparing CTT to CRP.

Figure 9. Control Condition: Resting Period x Control Condition: Tone Task. *There was significant activation in multiple regions, including the Hippocampus (A) and Amygdala (B), during positive memory recall compared to the tone task (P < 0.05 (small-volume corrected)). T-maps were thresholded at P < 0.001 uncorrected and for visualization purposes overlaid onto a normalized anatomical. The cluster level inferences can be found in Table 2.*

When all data is taken together, we see a trend of activation in some of the predicted regions. The group effect is rather small at this moment since we only have the data of 12 participants without being able to take the ELS status or drug effect into account, but the results suggest that the AMRT task caused at least partly the expected results. The results and cluster levels of all the comparisons and analyses can also be found in Table 2.

Contrast				Brain region	Peak T value	Cluster size (mm³)	MNI coordinates (x, y, z)
Positive	–	**Control: Tone Task**		*Inferior Frontal Gyrus*	5.85	278†	-54 0 24
				Inferior Parietal Lobule	4.16	2†	-54 -30 45
				PCC / Midcingulate	4.52	4†	9 -18 24
Negative	–	**Control: Tone Task**		*Inferior Parietal Lobule*	4.72	9†	-51 -51 48
				PCC / Midcingulate Cortex	7.97	15†	9 -21 24
			R	Precuneus	4.66	4†	9 -66 48
Positive	–	**Control: Resting Period**	R	PCC / Midcingulate	4.48	2†	9 -36 24
			L	PCC / Midcingulate	4.14	1†	-6 -24 27
			R	Precuneus	5.64	12†	15 -75 45
				mPFC	4.89	2†	9 -30 45
			R	Postcentral Gyrus / Middle Frontal Gyrus	5.57	15†	60 -21 18
				Inferior Parietal Lobule	4.41	2†	54 -30 36
				Superior Temporal Gyrus	11.98	1074*	-39 -33 15
				Superior Temporal Gyrus	11.72	1202*	63 -15 0
			R	Supramarginal Gyrus	11.57	219*	42 -33 45
Negative	–	**Control: Resting Period**	R	Precuneus	4.60	6†	15 -81 39
				Paracentral Lobule	4.04	1†	9 -30 48
			R	Intraparietal Lobule / Precentral Gyrus	4.18	3†	60 -24 18
			L	Middle Temporal Gyrus	8.49	735*	-48 -27 6
			L	Culmen	8.38	189*	-21 -57 -6
			R	Middle Temporal Gyrus	8.37	908*	48 -33 12
			R	Intraparietal Sulcus	7.61	115*	42 -33 45
			L	Cuneus	6.78	170*	-9 -84 33
			R	Middle Occipital Gyrus	5.49	109*	15 -87 18

Comparison			Region	T	Cluster	MNI (x, y, z)
Recall	–	**Control: Tone Task**	PCC / Midcingulate	6.88	11†	9 -18 24
			Inferior Parietal Lobule	4.36	2†	-54 -30 45
				4.28	1†	-51 -51 48
	R		Fusiform Gyrus	5.60	177*	-51 -3 24
Recall	–	**Control: Resting Period**	Precuneus	5.46	13†	15 -78 42
			mPFC	5.47	2†	9 -30 45
	R		Postcentral Gyrus / Middle Frontal Gyrus	4.91	4†	60 -21 18
			Inferior Parietal Lobule	4.37	5†	57 -30 21
				4.16	4†	54 -33 33
			Supramarginal Gyrus	4.88	4†	60 -48 30
			Insula	4.08	1†	-36 -21 0
	L		Fusiform Gyrus / Lingual Gyrus	11.01	191*	-24 -60 -9
	R		Superior Temporal Gyrus	9.72	1127*	63 -12 0
	R		Intraparietal Sulcus	9.67	184*	42 -33 45
	L		Superior Temporal Gyrus	9.54	954*	-42 -30 9
	L		Cuneus	7.83	178*	-12 -81 33
	R		Fusiform Gyrus / Lingual Gyrus	7.37	161*	27 -60 -6
	L		Inferior Parietal Lobe	6.45	115*	-36 -39 48
Resting Period	–	**Tone Task**	Hippocampus	4.90	2†	30 0 -24
			Amygdala	4.28	2†	21 -6 -24
	L		Caudate Nucleus / Putamen	5.15	103*	-21 3 21

Table 2. Brain Region Activity during the AMRT while comparing several memory and control conditions. *The brain activity during the AMRT task when comparing different conditions. The data is categorized per comparison between Negative and Positive Memory Recall or both combined as Memory Recall in general, and the Resting Period and Tone Task control conditions. Results are noted per brain region, reporting the peak T-value, Cluster Size and MNI (Montreal Neurological Institute) coordinates (x, y, z) of the peak voxel. The results of both the whole-brain analysis and small-volume correction analysis have been grouped together. A one-sample T-test was performed with no masking, no correction or p-value adjustment and a cluster-forming threshold for the T and p value of 0.001. No extent threshold was added either.*
* P < 0.05 (whole brain corrected); † P < 0.05 (small volume corrected for region of interest). Positive and Negative stands for the Positive and Negative Memory Recall. Recall is the combined condition of positive and negative memories, which is the Memory Recall Condition. L stands for Left and R for Right.

Discussion

Verifying the Autobiographical Memory Task

The aim of this study was to validate the AMR task which was used during this study and our hypothesis was that activation would be found in the mPFC, the hippocampal complex, the Precuneus, the cerebellum, the TPJ, the insula, the amygdala, the ACC, and part of the sensory cortex from the occipital lobe and part of the sensory cortex from the temporal lobe during the Autobiographical Memory Recall Task performed by individuals both with and without Early Life Stress. To test this hypothesis, we analysed the fMRI data during the AMRT task of the first session of 12 participants both with and without ELS and without taking the drug effect of Hydrocortisone into account, since the study was not finished yet and thus not deblinded. When contrasting the positive memories to the tone task we found activation in the PCC/Midcingulate Cortex and when contrasting negative memories to the tone task it resulted in activation in the PCC/Midcingulate Cortex as well as the Precuneus. The contrast of positive memories and the resting period resulted in activation in both the left and right PCC/Midcingulate Cortex, the Precuneus and the mPFC. Contrasting the negative memories with the resting period showed activation in the Precuneus, Culmen and Middle Occipital Gyrus. When taking both positive and negative memory trials together, which we called the recall condition, and contrasting it with the tone task resulted in activation in just the PCC/Midcingulate Cortex. But contrasting the Recall condition to the resting period resulted in activation in the Precuneus, mPFC and Insula. Furthermore the Resting Period was put in contrast with the Tone Task, which resulted in activation in the Hippocampus and Amygdala. These results were generated with a cluster-forming threshold of $p < 0,001$, on both the whole-brain and ROI analyses, with a FWE correction on cluster-level. We did a whole-brain analysis as well as a small-volume correction analysis based on our ROI's, using their coordinates or the masks from the FIND lab. These results showed a trend in activation in our hypothesized regions. However, the group effect was rather small, but this can be explained by the small sample size and not being able to take drug effect or ELS status into account.

The most surprising result was the lack of activation in the hippocampus during a memory task, the AMRT. None of the contrasts showed any hippocampus activity except the comparison between the Resting Period with the Tone Task. The next few paragraphs will explore several reasons that could explain these findings. The first factor that could influence the

Hippocampus activity is the use of Hydrocortisone and in our case the fact that some did and some did not take it and we could not deblind the intervention and thus not take this into account during the analysis. There have been multiple studies investigating the effect of hydrocortisone on the neural activation during memory tasks because it is known that the Hippocampus and PFC have a high density of glucocorticoid receptors (GR) and these brain regions are thus very likely to be influenced by the administration of cortisol or hydrocortisone (Fleischer et al., 2019). There already was extensive evidence that cortisol enhances the consolidation of memory but impairs retrieval after acute administration of glucocorticoids or after psychosocial stress (Wolf, 2017). Fleischer et al. studied this by giving participants either hydrocortisone or a placebo before performing an AMRT during an fMRI scan. Surprisingly, they only found a main effect of hydrocortisone on the reduction of neural activity in the anterior medial PFC (Fleischer et al., 2019). However, this study only included women, which is just under half of our subjects, so the use of a single gender sample could play a role in the effects they found. Additionally they used only 10 mg of hydrocortisone while we used 20 mg, so we can only speculate whether the effects of the hydrocortisone will be the same in our study sample. Another study investigated whether there was a dose-dependent effect of Hydrocortisone (Young, Drevets, Schulkin, & Erickson, 2011). Healthy volunteers would perform the AMR task twice after an infusion of either Hydrocortisone or a placebo. The hydrocortisone was either a moderate dose, of which the mean total dose was 10.9 mg, or a high dose, of which the mean total dose was 31.8 mg. Their behavioural data showed that Hydrocortisone affected the AMR recall in a dose-dependent manner, since the high dose caused a decrease in the recall of specific memories and increasing the reaction times to recall categorical memories while there was no effect for the moderate dose. Unfortunately they only collected behavioural measures, so there was no fMRI data to match these results. One other study did administer 20 mg of Hydrocortisone and did acquire fMRI data (Oei et al., 2007). However, their memory task was a word recognition task with an encoding-phase beforehand and a recognition phase inside the MRI scanner. Nonetheless, they did find that the hydrocortisone led to reduced brain activation in both the PFC and the hippocampus. Since this is a fairly new direction of memory research, there are no other studies that match our approach sufficiently to make any prediction on what the exact effects of the Hydrocortisone intervention is on our results. However, it probably will affect the activation of the Hippocampus and PFC during the AMRT, since all previously mentioned studies found at least some evidence that hydrocortisone altered memory

processes and reduced activation in these regions. However, this issue can easily be resolved once the study is finished and the intervention can be deblinded. This will allow us to compare the results between the Hydrocortisone and the placebo session and thus further investigate the effects of Hydrocortisone on neural activation.

There is one more difference between all of these studies that could be relevant to these findings, which is the timing between the administration of the Hydrocortisone and the performance of the AMR task. There is approximately 120 minutes between our drug administration and AMR task, while Fleischer et al. have only 45 minutes and Oei et al. only 60 minutes. The participants of the Young et al. study performed the AMRT 75 minutes after the administration, but the more important difference here is that they used an infusion instead of an oral administration. However, as it is believed that the glucocorticoid induces a time-dependent increase of activation in the Amygdala which underlies these memory effects of Hydrocortisone, it might also influence the Hippocampus activity indirectly (Roozendaal & McGaugh, 1997). But because the timing between the drug administration and the AMRT differs between all these studies, it is difficult to deduce any possible effects on our data.

Another possible explanation for the lack of Hippocampus activity depends on two conflicting theories on memory consolidation, related to the effects of memory age and vividness on the involvement of the Hippocampus during memory recall. The earlier memory models indicate that hippocampal-neocortical connections weaken over time when storage of the memories gets transferred to the cortical regions from the Hippocampus (Bayley, Hopkins, & Squire, 2003; Niki & Luo, 2002; Piefke et al., 2003). One study of Sheldon and Levine investigated this and indeed found evidence of different patterns of hippocampal–neocortical connectivity for remote and recent memories, irrespective of vividness even (Sheldon & Levine, 2013). Another study by Piefke et al. also researched this theory as well, but they actually found differential involvement of both the hippocampal and the retrosplenial region during recent vs. remote memory retrieval. Their data also clearly showed that both the emotional valence and the differential remoteness from the date of information encoding have a role in modulating the neural activity in key regions of the AM network (Piefke et al., 2003) These two studies urge us to look into the memory age in our study and in our case the participants' memories differed from quite recent to remote memories from months or even years ago. For example, there was one 42 year old participant who had both a memory that was a few months old and a memory that dated back to when he was 6 years old. Even when some of the memories are more recent and some

more remote, this taken together with the small sample size can explain why there is no activation found in the Hippocampus, or at least not yet. The other theory suggests that the episodic elements of autobiographical memory will always engage the hippocampus, regardless of the age of this memory. However they suggest that the difference in activation is caused by the difference in vividness that is partially caused by the age difference of the memory (Sheldon & Levine, 2013). Unfortunately, even though the vividness of the memories was collected in our study, it was not done during the task. Participant were asked to fill in the vividness of all memories after completing the MRI session, which meant that the subjective measure of the vividness of the recalled autobiographical memory could be less accurate due to the passage of time and having performed a different task before the scores were collected. Nonetheless, it could be interesting to investigate the influence of remote vs. recent memories and the level of vividness of the memories on neural activity in our fMRI data in the future.

The last finding to be considered, is the results of the contrast between the two control conditions, the Resting Period and the Tone Task. The results show activation in the Hippocampus and Amygdala, which could have two implications. First, it might indicate that participants had trouble abstaining from thinking about memories that they had just recalled or were anticipating to show up in the task. However, it could also mean that the tasks are too close together which could lead to remnants of the BOLD response in these regions showing up during the control task. Unfortunately, there are no studies that specify the activation found during the resting period to compare our findings to. But there are studies comparing the AMR task to a resting period that do find signification activation in the hippocampus (Carhart-Harris et al., 2014; Svoboda et al., 2006). These findings suggest that the resting period can be a suitable control condition, but only the final analysis will reveal what the effects are of the activation currently found during the resting period. However, specifically for the Amygdala response seen during this period, there could be one other reason. Many of the participants that were included had never been in an MRI scanner before, which could lead to a slight fear or at least stress during the scan, especially when there is no task to focus on. Nonetheless, when the sample size has increased, we expect these small effects to disappear during the analysis. Furthermore, there is a great benefit to having two control conditions. The results so far indicate that both control conditions have their advantages and disadvantages. The two conditions will

therefore again be compared in the final analysis. If certain activity patterns show up again, we could consider actually using this information to perform a correction on either control condition to create an optimized control condition for the analysis.

Strength and Limitations

First and foremost, most of the limitations of this paper are caused by the small sample size. This is due to the fact that data acquisition was not finished yet by the time that data analysis had to start for this paper. Therefore, only the first session of 6 participants were analysed for both the ELS and non-ELS group. When analysed separately or when compared this would have had no strength, so they were grouped together to one group of 12 participants. But despite our lack of strength, we still found some significant results and a strong trend in activation. This is very promising for the main study, since the intended sample size of 58 participants will be acquired for the final analysis.

The first consequence of the small sample size is that there was no chance to look into the main effect of ELS, leading us to combine the data of the different groups. This could slightly affect the current data analyses and thus the results, since the fact that one has or has not experienced ELS does affect their neurodevelopment. For example, a meta-analysis done by Svoboda, McKinnon and Levine presented a prediction of predominant engagement of the left-lateralized and medial brain regions for healthy people without ELS during an AMR task which we were unable to find during our analysis (Svoboda et al., 2006). Accordingly, another study by Saleh et al. has shown that the mPFC, the ACC, caudate and insula are often affected by ELS exposure (Saleh et al., 2017). Thus, it can be said that the ELS status for the participants is likely to affect the neural activity during the AMRT, which in turn could alter our results on a group level since half of our study sample had experienced ELS. However, it must also be considered that our sample size still exists of only 6 ELS and 6 non-ELS subjects. The fact these groups are of equal size could also lead to a balanced effect on the results. Furthermore, it is not of too great importance yet since our aim is to verify if the AMRT paradigm works for now, and not to study the difference in neural activity between the two groups.

Another issue that was caused by the unfinished dataset, is that the intervention could not be de-blinded. Therefore we do not know how many and which of these participants got 20 mg of Hydrocortisone and who got the placebo on the sessions we analysed. Either way, there is a considerable chance that this influenced the results of the current data analysis. As mentioned before, there is quite a bit of evidence showing that the use of Hydrocortisone affects the neural activation in the Hippocampus and PFC, which are both

areas that did not show up as much as expected in our results (Fleischer et al., 2019; Oei et al., 2007; Young et al., 2011). However, it is still uncertain as to what level these effects of Hydrocortisone are dose-dependent, there is no data yet on the exact same study paradigm as we performed and there is no consensus yet on what the effect of Hydrocortisone exactly is. Therefore, it cannot be determined whether this has affected our results and if it caused the lack of activity patterns in the PFC and Hippocampus or not. However, this also indicates that this can be solved once the intervention is deblinded and we can actually compare the results between the Hydrocortisone and the placebo session and thus investigate the drug effects on neural activity in regions like the PFC and Hippocampus.

The last possible limitation to be considered, is the fact that the contrast between the two control conditions, the Resting Period and the Tone Task, shows activation in the Hippocampus and Amygdala. This might indicate that participants might have been anticipating certain memories or were still thinking about previous ones. However, the activation found could also be remnants of the previous memory recall period, meaning that the tasks were too close together. Fortunately, it is very likely that these small effects will disappear once the sample size increases. Furthermore, this current limitation will turn into a great benefit once we reached the intended sample size. The results so far indicate that both conditions would suffice as a control, but also have their limitations. The two conditions will therefore again be analysed for the final analysis. If the memory activity presents itself again during the control periods, we could consider actually using this information to correct the data on either control condition to create a near-perfect control condition.

Apart of these limitations, there are a lot of strengths to the AMR task and our study paradigm. As mentioned before, the use of both the active tone task and a resting period as control conditions can be very beneficial for the analysis afterwards. This allows us to thoroughly determine if there are any remnants of memory related neural activity in our control condition and to use this information during the analysis of our fMRI data. Another advantage is that we collected personal memory cues. This enhances the strength of the memory recall and ensures that the participant has a specific memory to recall following all of the memory cues. Furthermore, since the valence is determined up front, there is a better spread of both positive and negative memories and the valence scores are more trustworthy as well. Many studies use generalized cues, and hopefully our study will show that having personalized memory cues will lead to stronger results. Lastly, this is one of the first studies to compare ELS to non-ELS participants so directly on a memory task and in addition even investigate the influence of ELS on the drug effects of Hydrocortisone on

memory functions. This is not relevant for the current paper yet, but that is only because the study has not been finished yet. So far our data already shows a strong trend of activation with a rather small sample size, which indicates the statistical power will increase once the study is finished.

Conclusion

We found a strong trend of activation in the hypothesized areas and even some extra regions that are certainly relevant to the AMRT. The most prominent regions that were predicted and show up in several contrasts during the analysis, despite the small sample size, are the PCC/Midcingulate cortex, mPFC and the Precuneus. Other predicted regions that show up in some contrasts are the Middle Occipital Gyrus, the Temporal Lobe and Insula. Unfortunately, there were also some regions that we failed to find even though we mentioned them in our prediction. These include the Amygdala, Hippocampus, TPJ and Cerebellum. Taking all this information together leads to the conclusion that even though the sample size was small, there is a trend of activation in relevant brain regions and our version of the Autobiographical Memory Recall Task holds promise for significant and relevant results once data acquisition is finished.

There are only two recommendations that can be taken from these preliminary results. The first is to collect the vividness score of the memory sooner in future studies, leading to a more reliable score that is not vulnerable to change due to the delay between recalling the memory and scoring the vividness. The other one is to specify how remote or recent the memories should be, as to decrease the variation in this per participant and even between memories of a single participant. If the vividness scores are more reliable and there is a clear difference between remote vs. recent memories, and they can be equally separated in two groups of approximately the same size as well, it could be interesting to investigate the difference in remote vs. recent memories and its' role in the involvement of the Hippocampus in autobiographical memory. It is rather challenging to make any further recommendations for future studies since this is a preliminary dataset. Even though the results of this analysis are promising, it is yet to be seen how this translates to the full sample size and final data analyses and results.

References

Anderson, M. C., K.N., O., Kuhl, B., Cooper, J., Robertson, E., Gabrieli, S. W., . . . Gabrieli, J. D. E. (2004). Neural systems underlying the suppression of unwanted memories. *Science, 303*(1095-9203 (Electronic)), 232 - 235. doi:10.1126/science.1089504

Atsak, P., Hauer, D., Campolongo, P., Schelling, G., Fornari, R. V., & Roozendaal, B. (2015). Endocannabinoid signaling within the basolateral amygdala integrates multiple stress hormone effects on memory consolidation. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 40*(1740-634X (Electronic)), 1485-1494. doi:10.1038/npp.2014.334

Bayley, P. J., Hopkins, R. O., & Squire, L. R. (2003). Successful Recollection of Remote Autobiographical Memories by Amnesic Patients with Medial Temporal Lobe Lesions. *Neuron, 38*(1), 135-144. doi:https://doi.org/10.1016/S0896-6273(03)00156-9

Beers, S. R., & De Bellis, M. D. (2002). Neuropsychological function in children with maltreatment-related posttraumatic stress disorder. *American Journal of Psychiatry, 159*(3), 483 - 486. doi:American Journal of Psychiatry

Bisson, J. I., A, E., Matthews, R., Pilling, S., Richards, D., & Turner, S. (2013). Psychological treatments for chronic post-traumatic stress disorder. Systematic review and meta-analysis. *The Cochrane database of systematic reviews, 12*(0007-1250 (Print)). doi:10.1002/14651858.CD003388.pub4

Bremner, J. D., P., R., Scott, T. M., Capelli, S., Delaney, R., McCarthy, G., & Charney, D. S. (1995). Deficits in short-term memory in adult survivors of childhood abuse. *Psychiatry Research, 59*(1 - 2), 97 - 107. doi:10.1016/0165-1781(95)02800-5

Bremner, J. D., Randall, P., Vermetten, E., Staib, L., Bronen, R. A., Mazure, C., . . . Charney, D. S. (1997). Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse--a preliminary report. *Biological psychiatry, 41*(1), 23-32. doi:10.1016/s0006-3223(96)00162-x

Carhart-Harris, R. L., Wall, M. B., Erritzoe, D., Kaelen, M., Ferguson, B., De Meer, I., . . . Nutt, D. J. (2014). The effect of acutely administered MDMA on subjective and BOLD-fMRI responses to favourite and worst autobiographical memories. *The international journal of neuropsychopharmacology, 17*(1469-5111 (Electronic)), 527–540. doi:10.1017/S1461145713001405

Carrion, V. G., Weems, C. F., Eliez, S., Patwardhan, A., Brown, W., Ray, R. D., & Reiss, A. L. (2001). Attenuation of frontal asymmetry in pediatric posttraumatic stress disorder. *Biol Psychiatry, 50*(12), 943-951. doi:10.1016/s0006-3223(01)01218-5

Carver, C. S., & White, T. L. (1994). Behavioral Inhibition, Behavioral Activation, and Affective Responses to Impending Reward and Punishment. *Journal of Personality and Social Psychology, 67(2).*

Chand, G. B., & Dhamala, M. (2016). Interactions Among the Brain Default-Mode, Salience, and Central-Executive Networks During Perceptual Decision-Making of Moving Dots. *Brain connectivity, 6*(2158-0022 (Electronic)), 294 - 254. doi:10.1089/brain.2015.0379

Cusack, K., Jonas, D. E., Forneris, C. A., Wines, C., Sonis, J., Middleton, J. C., . . . Gaynes, B. N. (2016). Psychological treatments for adults with posttraumatic stress disorder: A systematic review and meta-analysis. *Clinical psychology review, 43*(1873-7811 (Electronic)), 128–141. doi:10.1016/j.cpr.2015.10.003

De Bellis, M. D., Keshavan, M. S., Clark, D. B., Casey, B. J., Giedd, J. N., Boring, A. M., . . . Ryan, N. D. (1999). A.E. Bennett Research Award. Developmental traumatology. Part II: Brain development. *Biological psychiatry, 45*(0006-3223 (Print)), 1271-1284. doi:10.1016/s0006-3223(99)00045-1

De Bellis, M. D., Keshavan, M. S., Shifflett, H., Iyengar, S., Beers, S. R., Hall, J., & Moritz, G. (2002). Brain structures in pediatric maltreatment-related posttraumatic stress disorder: a sociodemographically matched study. *Biol Psychiatry, 52*(11), 1066-1078. doi:10.1016/s0006-3223(02)01459-2

de Quervain, D. J. F., Bentz, D., Michael, T., Bolt, O. C., Wiederhold, B. K., Margraf, J., & Wilhelm, F. H. (2011). Glucocorticoids enhance extinction-based psychotherapy.

Proceedings of the National Academy of Sciences, 108(16), 6621. doi:10.1073/pnas.1018214108

Defares, P. B., van der Ploeg, H. M., & Spielberger, C. D. (1980). Handleiding bij de Zelf-beoordelings Vragenlijst ZBV. Een nederlandstalige bewerking van de Spielberger State-Trait Anxiety Inventory. . *Lisse: Swets & Zeitlinger*.

Driessen, M., Herrmann, J., Stahl, K., Zwaan, M., Meier, S., Hill, A., . . . Petersen, D. (2000). Magnetic resonance imaging volumes of the hippocampus and the amygdala in women with borderline personality disorder and early traumatization. *Archives of General Psychiatry, 57*(12), 1115. doi:10.1001/archpsyc.57.12.1115

Fleischer, J., Metz, S., Düsenberg, M., Grimm, S., Golde, S., Roepke, S., . . . Wingenfeld, K. (2019). Neural correlates of glucocorticoids effects on autobiographical memory retrieval in healthy women. *Behavioural brain research, 359*(1872-7549 (Electronic)), 895–902. doi:10.1016/j.bbr.2018.06.024

Fossati, P. (2013). Imaging autobiographical memory. *Dialogues in clinical neuroscience, 15*(4), 487–490. doi:10.31887/DCNS.2013.15.4/pfossati

Garrett, A., Cohen, J. A., Zack, S., Carrion, V., Jo, B., Blader, J., . . . Agras, W. S. (2019). Longitudinal changes in brain function associated with symptom improvement in youth with PTSD. *Journal of psychiatric research, 114*(1879-1379 (Electronic)), 161–169. doi:10.1016/j.jpsychires.2019.04.021

Hamann, S. (2001). Cognitive and neural mechanisms of emotional memory. *Trends in Cognitive Sciences, 5*(9), 394-400. doi:https://doi.org/10.1016/S1364-6613(00)01707-1

Herzberg, M. P., & Gunnar, M. R. (2020). Early life stress and brain function: Activity and connectivity associated with processing emotion and reward. *NeuroImage, 209*(1095-9572 (Electronic)). doi:NeuroImage

Holland, A. C., & Kensinger, E. A. (2010). Emotion and autobiographical memory. *Physics of life reviews, 7*(1), 88–131. doi:10.1016/j.plrev.2010.01.006

Kensinger, E. A., & Ford, J. H. (2020). Retrieval of Emotional Events from Memory. *Annual review of psychology, 71*(1545-2085 (Electronic)), 251-272. doi:10.1146/annurev-psych-010419-051123

Kessler, R. C. (2000). Posttraumatic stress disorder: the burden to the individual and to society. *The Journal of clinical psychiatry, 61*(0160-6689 (Print)), 4-12.

Kim, H. (2016). Default network activation during episodic and semantic memory retrieval: A selective meta-analytic comparison. *Neuropsychologia, 80*(1873-3514 (Electronic)), 35–46. doi:10.1016/j.neuropsychologia.2015.11.006

LaBar, K. S., & Cabeza, R. (2006). Cognitive neuroscience of emotional memory. *Nature Reviews Neuroscience, 7*(1), 54-64. doi:10.1038/nrn1825

Lanius, R. A., R.L., B., & Frewen, P. A. (2011). How understanding the neurobiology of complex post-traumatic stress disorder can inform clinical practice: a social cognitive and affective neuroscience approach. *Acta psychiatrica Scandinavica, 124*(5), 331–348. doi:10.1111/j.1600-0447.2011.01755.x

Larsen, S. E., Fleming, C. J. E., & Resick, P. A. (2019). Residual symptoms following empirically supported treatment for PTSD. *Psychological trauma : theory, research, practice and policy, 11*(1942-969X (Electronic)), 207-215. doi:10.1037/tra0000384

Marshall, G. N., Jaycox, L. H., Engel, C. C., Richardson, A. S., Dutra, S. J., Keane, T. M., . . . Marx, B. P. (2019). PTSD symptoms are differentially associated with general distress and physiological arousal: Implications for the conceptualization and measurement of PTSD. *Journal of anxiety disorders, 62*(1873-7897 (Electronic)), 26–34. doi:10.1016/j.janxdis.2018.10.003

Martinelli, P., M., S., & Piolino, P. (2013). Neural substrates of the self-memory system: new insights from a meta-analysis. *Human brain mapping, 34*(7), 1515–1529. doi:10.1002/hbm.22008

McCrae, R. R., & Costa, P. T., Jr. . (1999). A five-factor theory of personality. . *Handbook of personality: Theory and research, 2*, 139-153.

Menon, V. (2015). Salience Network. In A. W. Toga (Ed.), *Brain Mapping: An Encyclopedic Reference.* (Vol. 2, pp. 597 - 611). Elsevier.

Mezzacappa, E., Kindlon, D., & Earls, F. (2001). Child abuse and performance task assessments of executive functions in boys. *Journal of Child Psychology and Psychiatry, 42*(8), 1041-1048. doi:10.1111/1469-7610.00803

Navalta, C. P., Polcari, A., Webster, D. M., Boghossian, A., & Teicher, M. H. (2006). Effects of childhood sexual abuse on neuropsychological and cognitive function in college women. *the Journal of neuropsychiatry and clinical neurosciences, 18*(1), 45–53. doi:10.1176/jnp.18.1.45

Niki, K., & Luo, J. (2002). An fMRI Study on the Time-Limited Role of the Medial Temporal Lobe in Long-Term Topographical Autobiographic Memory. *Journal of Cognitive Neuroscience, 14*(3), 500-507. doi:10.1162/089892902317362010

Oei, N. Y. L., Elzinga, B. M., Wolf, O. T., de Ruiter, M. B., Damoiseaux, J. S., Kuijer, J. P. A., . . . Rombouts, S. A. R. B. (2007). Glucocorticoids Decrease Hippocampal and Prefrontal Activation during Declarative Memory Retrieval in Young Men. *Brain imaging and behavior, 1*(1-2), 31–41. doi:10.1007/s11682-007-9003-2

Palmer, L., Armsworth, M., Swank, P., Bush, G., Frantz, C., & Copley, J. (1997). The neuropsychological sequelae of chronically psychologically traumatized children. *Archives of Clinical Neuropsychology, 12*(4), 379 - 380. doi:10.1093/arclin/12.4.379a

Piefke, M., Weiss, P. H., Zilles, K., Markowitsch, H. J., & Fink, G. R. (2003). Differential remoteness and emotional tone modulate the neural correlates of autobiographical memory. *Brain : a journal of neurology, 126*(3), 650–668. doi:10.1093/brain/awg064

Rabinak, C. A., Angstadt, M., Sripada, C. S., Abelson, J. L., Liberzon, I., Milad, M. R., & Phan, K. L. (2013). Cannabinoid facilitation of fear extinction memory recall in humans. *Neuropharmacology, 64*, 396-402. doi:https://doi.org/10.1016/j.neuropharm.2012.06.063

Roozendaal, B., & McGaugh, J. L. (1997). Glucocorticoid Receptor Agonist and Antagonist Administration into the Basolateral but Not Central Amygdala Modulates Memory Storage. *Neurobiology of Learning and Memory, 67*(2), 176-179. doi:https://doi.org/10.1006/nlme.1996.3765

Saleh, A., Potter, G. G., McQuoid, D. R., Boyd, B., Turner, R., MacFall, J. R., & Taylor, W. D. (2017). Effects of early life stress on depression, cognitive performance and brain morphology. *Psychological Medicine, 47*(1), 171-181. doi:doi:10.1017/S0033291716002403

Sessa, B. (2017). MDMA and PTSD treatment: "PTSD: From novel pathophysiology to innovative therapeutics". *Neurosci Lett, 649*, 176-180. doi:10.1016/j.neulet.2016.07.004

Shalev, A., Liberzon, I., & Marmar, C. (2017). Post-Traumatic Stress Disorder. *The New England journal of medicine, 376*(25), 2459–2469. doi:10.1056/NEJMra1612499

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., . . . Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The Journal of clinical psychiatry, 59*(0160-6689 (Print)), 22-57.

Sheldon, S., & Levine, B. (2013). Same as it ever was: vividness modulates the similarities and differences between the neural networks that support retrieving remote and recent autobiographical memories. *NeuroImage, 83*(1095-9572 (Electronic)), 880-891. doi:10.1016/j.neuroimage.2013.06.082

Shirer, W. R., Ryali, S., Rykhlevskaia, E., Menon, V., & Greicius, M. D. (2012). Decoding subject-driven cognitive states with whole-brain connectivity patterns. *Cerebral Cortex, 22*(1), 158-165. doi:10.1093/cercor/bhr099

Smith, N. B., Doran, J. M., Sippel, L. M., & Harpaz-Rotem, I. (2017). Fear extinction and memory reconsolidation as critical components in behavioral treatment for posttraumatic stress disorder and potential augmentation of these processes. *Neurosci Lett, 649*, 170-175. doi:10.1016/j.neulet.2017.01.006

Spielberger, C. D., Gorsuch, R. L., & Lushene, R. (1970). State-Trait Anxiety Inventory. *Palo Alto*.

St Jacques, P. L., Botzung, A., Miles, A., & Rubin, D. C. (2011). Functional neuroimaging of emotionally intense autobiographical memories in post-traumatic stress disorder. *Journal of psychiatric research, , 45* (5), 630–637. doi:10.1016/j.jpsychires.2010.10.011

Stein, M. B., Koverola, C., Hanna, C., Torchia, M. G., & McClarty, B. (1997). Hippocampal volume in women victimized by childhood sexual abuse. *Psychological Medicine, 27*(4), 951 - 959. doi:10.1017/s0033291797005242

Svoboda, E., McKinnon, M. C., & Levine, B. (2006). The functional neuroanatomy of autobiographical memory: a meta-analysis. *Neuropsychologia, 44*(12), 2189-2208. doi:doi.org/10.1016/j.neuropsychologia.2006.05.023

Teicher, M. H., Dumont, N. L., Ito, Y., Vaituzis, C., Giedd, J. N., & Andersen, S. L. (2004). Childhood neglect is associated with reduced corpus callosum area. *Biol Psychiatry, 56*(2), 80-85. doi:10.1016/j.biopsych.2004.03.016

Teicher, M. H., Ito, Y., Glod, C. A., Andersen, S. L., Dumont, N., & Ackerman, E. (1997). Preliminary evidence for abnormal cortical development in physically and sexually abused children using EEG coherence and MRI. *Annals of the New York Academy of Sciences, 821*(0077-8923 (Print)), 160-175. doi:10.1111/j.1749-6632.1997.tb48277.x

Teicher, M. H., & Parigger, A. (2015). The 'Maltreatment and Abuse Chronology of Exposure' (MACE) scale for the retrospective assessment of abuse and neglect during development. *PloS one, 10*(e0117423). doi:10.1371/journal.pone.0117423

Thome, J., Terpou, B. A., McKinnon, M. C., & Lanius, R. A. (2020). The neural correlates of trauma-related autobiographical memory in posttraumatic stress disorder: A meta-analysis. *Depression and anxiety, 37*(4), 321-345. doi:10.1002/da.22977

Villain, H., Benkahoul, A., Birmes, P., Ferry, B., & Roullet, P. (2018). Influence of early stress on memory reconsolidation: Implications for post-traumatic stress disorder treatment. *PloS one, 13*(1932-6203 (Electronic)). doi:10.1371/journal.pone.0191563

Vythilingam, M., Heim, C., Newport, J., Miller, A. H., Anderson, E., Bronen, R., . . . Bremner, J. D. (2002). Childhood trauma associated with smaller hippocampal volume in women with major depression. *American Journal of Psychiatry, 159*(12), 2072-2080. doi:10.1176/appi.ajp.159.12.2072

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the PANAS scales. *Journal of personality and social psychology, 54*(6), 1063-1070. doi:10.1037//0022-3514.54.6.1063

Wechsler, D. (1997). WAIS-III: Wechsler adult intelligence scale. *Psychological Corporation*.

Whalley, M. G., Rugg, M. D., & Brewin, C. R. (2012). Autobiographical memory in depression: an fMRI study. *Psychiatry Research: Neuroimaging, 201*(2), 98-106. doi:10.1016/j.pscychresns.2011.08.008

Whisman, M. A., Judd, C. M., Whiteford, N. T., & Gelhorn, H. L. (2013). Measurement invariance of the Beck Depression Inventory-Second Edition (BDI-II) across gender, race, and ethnicity in college students. *Assessment, 20*(4), 419-428. doi:10.1177/1073191112460273

Wolf, O. T. (2017). Stress and memory retrieval: mechanisms and consequences. *Current Opinion in Behavioral Sciences, 14*, 40-46. doi:https://doi.org/10.1016/j.cobeha.2016.12.001

Yehuda, R., Bierer, L. M., Pratchett, L., & Malowney, M. (2010). Glucocorticoid augmentation of prolonged exposure therapy: rationale and case report. *Eur J Psychotraumatol, 1*. doi:10.3402/ejpt.v1i0.5643

Young, K., Drevets, W. C., Schulkin, J., & Erickson, K. (2011). Dose-dependent effects of hydrocortisone infusion on autobiographical memory recall. *Behavioral neuroscience, 125*(5), 735-741. doi:10.1037/a0024764

SUPPLEMENTARY 1: INCLUSION CRITERIA

Exclusion Criteria

For both groups:

- A Body Mass Index lower than 18,5 or higher than 30.
- Abnormal hearing or abnormal vision that was not uncorrected.
- Habitual smoking, so more than a package of cigarettes per week and in case they smoked they had to be able to stop 24 hours prior to testing.
- Psychotropic medication or recreational drugs use once a week or more.
- Using said drugs less within one week prior to testing.
- Use of alcohol within the last 24 hours before each measurement.
- Regular use of corticosteroids, any endocrine treatment or medication that may interact with hydrocortisone.
- Contraindication for systemic hydrocortisone.
- History of repeated loss of consciousness.
- History of psychiatric treatment or current psychiatric treatment
- History of psychiatric treatment or current psychiatric treatment
- Cognitive impairment (Mini-Mental State Examination < 25).
- Pregnancy or any plans for pregnancy.
- Contraindication for the MRI, f.e. claustrophobia or any metal implants.

Supplementary 2: AMRT questionnaire

Schrijf in de **eerste kolom van de linker tabel**, jouw 9 meest **negatieve** herinneringen gedurende je leven op. Schrijf in de **eerste kolom van de rechter tabel**, jouw 9 meest **positieve** herinneringen gedurende je leven op. Probeer deze herinneringen zo kort (bijvoorbeeld in 1 woord) en duidelijk mogelijk te maken, zodat ze alleen door jou begrepen kunnen worden.

Antwoord vervolgens voor iedere **negatieve** herinnering de volgende vraag en omcirkel het nummer in de **tweede kolom** van de **linker** tabel.

"Hoe negatief zijn de gedachtes aan deze herinnering/gebeurtenis?"

1. *Zeer negatief*
2. *Negatief*
3. *Een beetje negatief*
4. *Neutraal*
5. *Helemaal niet negatief*

Beantwoord ook de volgende vraag voor iedere **positieve** herinnering en omcirkel het nummer in de **tweede kolom** van de **rechter** tabel.

"Hoe positief zijn de gedachtes aan deze herinnering/gebeurtenis?"

1. *Zeer positief*
2. *Positief*
3. *Een beetje positief*
4. *Neutraal*
5. *Helemaal niet positief*

Geef in de derde kolom "leeftijd" aan hoe oud je was toen deze herinnering plaatsvond.

Beantwoord de volgende vraag pas **NA** de MRI-sessie voor zowel de negatieve als de positieve herinneringen.

"Hoe helder/levendig waren de herinneringen aan deze gebeurtenis gedurende de MRI-sessie?"

1. *De herinneringen waren afwezig*
2. *De herinneringen waren zeer vaag*
3. *De herinneringen waren een beetje helder/levendig*
4. *De herinneringen waren levendig*
5. *De herinneringen waren zeer levendig*

Omcirkel het nummer voor de **negatieve** herinneringen in de **laatste** kolom van de **linker** tabel en het nummer voor de **positieve** herinneringen in de **laatste** kolom van de **rechter** tabel.

Negatieve herinneringen			
Herinneringen	Negatief	Leeftijd	Helder /levendig
	1 2 3 4 5		1 2 3 4 5
	1 2 3 4 5		1 2 3 4 5
	1 2 3 4 5		1 2 3 4 5
	1 2 3 4 5		1 2 3 4 5
	1 2 3 4 5		1 2 3 4 5
	1 2 3 4 5		1 2 3 4 5
	1 2 3 4 5		1 2 3 4 5
	1 2 3 4 5		1 2 3 4 5
	1 2 3 4 5		1 2 3 4 5

Positieve herinneringen			
Herinneringen	Positief	Leeftijd	Helder /levendig
	1 2 3 4 5		1 2 3 4 5
	1 2 3 4 5		1 2 3 4 5
	1 2 3 4 5		1 2 3 4 5
	1 2 3 4 5		1 2 3 4 5
	1 2 3 4 5		1 2 3 4 5
	1 2 3 4 5		1 2 3 4 5
	1 2 3 4 5		1 2 3 4 5
	1 2 3 4 5		1 2 3 4 5
	1 2 3 4 5		1 2 3 4 5