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Changes in Resting State Measures after Associative Learning in Humans

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Abstract

This interdisciplinary master thesis investigates resting state measures after associative learning. Associative learning modulates functional brain connectivity and activity as signs of neuroplasticity. One of the strongest modulators of attention and memory is emotion. Thus, investigating the connection between emotional content and learning is of utmost importance. In this study, we examined the global functional connectivity (GFC), percent amplitude fluctuation (PerAF) and regional homogeneity (ReHo) of healthy subjects using resting-state functional magnetic resonance imaging (rs-fMRI). In a longitudinal design, experimental subjects were asked to study emotional or non-emotional associations for three weeks. Rs-fMRI measurements were conducted before and after this time period.

Our results are purely exploratory in nature as they are not FWE-corrected. GFC showed no changes due to associative learning, but PerAF and ReHo both increased in several brain regions. Increases in PerAF were found in the somatosensory gyrus, precentral gyrus, and the frontal superior gyrus as a suspected effect of object recognition, and the effect of learning or updating verbal representations, and decision-making and risk aversion, respectively. Furthermore, the middle frontal and frontal superior medial gyrus also showed increases that may be linked to the effects of post-retrieval monitoring.

In ReHo, the left postcentral gyrus and the right middle temporal gyrus showed an increase after associative learning. The left frontal superior gyrus showed differentiation measured in ReHo, based on the type of stimuli.

We provided insights and possible hypotheses for further research into the effects of learning and retrieval on rs-fMRI measures.

Contents

1 Learning Theories

1.1 Psychology

Memory and learning are widely studied sub-fields of psychology. According to Thompson, "Lasting changes in behaviour resulting from prior experience can be characterised as the result of learning, memory, and retrieval processes... At this point, it is useful to keep the basic definition of learning broad. Thus, bacteria have a kind of memory–their behaviour can change as a result of experience (for example, after exposure to certain molecules), and this change can persist after the experience." [1].

'Memory' raises a wide array of associations and connotations, which can be divided into two groups. Firstly, memory refers to our ability to remember the past. However, it also refers to the abstract concept of memory - the taste of the sea, an episode in the past - which is itself remembered.

If one looks at the memory as a process, the steps involved are encoding, storage and retrieval [2, 3] (Figure 1). Encoding is the process in which mental representations are created from sensory information; storage is the process by which this information is kept; and retrieval is when memories are pulled out of this storage, such as in the case of retrieving a memory into consciousness. Memory retrieval is a vital way of assessing and using learnt knowledge.

Memory retrieval can be assessed in several different ways using either recall tasks or recognition tests.

Recall tasks can be of three types: cued, free, or serial [3]. Cued recall refers to when different objects are paired (e.g., words in different languages: Apfel-apple). Later, the investigator cues the subject with one part of the pair and expects the other part as a response. In serial recall, the subject has to recall items from memory in a pre-defined order, like in a poem. Free recall has no

restrictions on the sequence; the subject can recite the elements in any order but is expected to recall all the elements.

During a recognition test, the subject will need to recognise certain stimuli. The number of objects recalled from memory varies depending on the test performed and the stimuli involved. In recognition tests [4], it was found that up to 2000 images could be recognised [5].

The types of memories formed can be divided into two main groups, declarative and non-declarative memories. Declarative memories are the collections of different events and facts, also called episodic and semantic memories. Episodic memories are memories of certain events in one's life, while semantic memories are concerned with basic facts about the world and one's environment.

Non-declarative memories include procedural patterns (e.g., movements) as well as effects of classical conditioning and priming [6]. A crucial difference between declarative and non-declarative memories is that declarative memories are recalled due to a conscious effort, whereas non-declarative memories are recalled unconsciously (Figure 2).

Non-declarative memories are further subdivided into associative and non-associative memories. Associative memories arise through the coupling of mul-

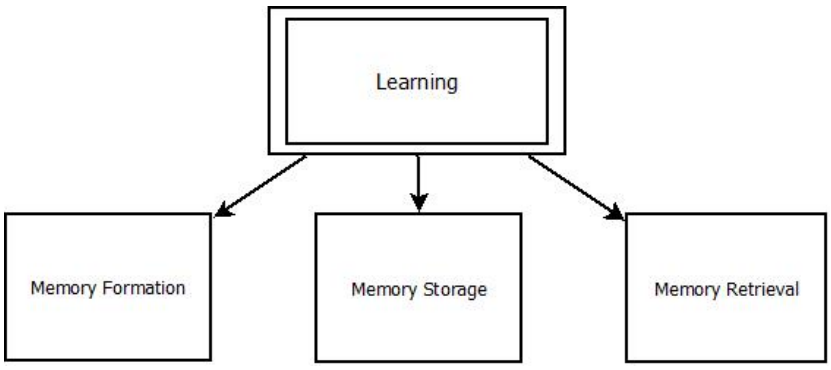

Figure 1: Different phases of learning

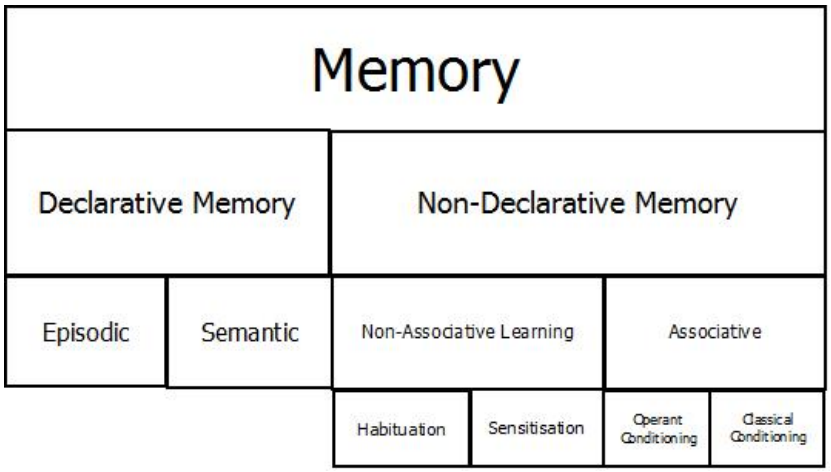

Figure 2: Classification of memories

tiple different stimuli that then lead to a response or learning. We talk about non-associative memory when there is only one single stimulus that leads to learning and, thus, a specific response. Non-associative memories are of two types: habituation or sensitisation.

Habituation is the process in which a stimulus is initially responded to with high sensitivity, but this decreases upon renewed repetition. A fitting example is the level of excitement one might feel upon a phone call in the lab, but after one gets many calls, especially ones not meant for them, this excitement lowers. In this case, the response is the excitement, and the unconditional stimulus is the call. A stimulus is seen as conditional when an unconditional stimulus is paired with an unrelated stimulus and delivers the same response. Critical factors are the time between the conditional and unconditional stimulus paired, the strength of the stimuli and the frequency of training [7, 6].

The repetition of the unrelated stimulus without the conditioned stimulus will lead to sensitisation over time. For example, behaviourally, one might hear a sudden, loud or frightening sound, after which the previous sounds and stimuli in one's area suddenly become more noticeable. Both sensitisation and habituation

have been found in very simple biological models as well as in primates, both on behavioural as well as on the neurological level [8].

Categories of associative memories are classical and instrumental or operant conditioning. The first investigations into classical conditioning were undertaken by Ivan Pavlov around the turn of the 20th century [6]. Pavlov showed that training a dog with a conditional stimulus (the sounding of a bell) followed by an unconditional stimulus elicited a response in the dog (salivation), and later merely the conditional stimulus alone would elicit the same response. It seems as if the conditional and unconditional stimulus had been paired in the dog's mind, producing the salivation response. This reaction may be erased by repeatedly sounding only the conditional stimuli without the unconditional one. This process is called extinction. The same effect was found in the "Little Albert experiment" conducted by Watson in 1920 [9], using a loud, frightening bang as the unconditional stimuli and a white rat as the conditional stimuli, as well as little Albert, a kid of nine months, as the experimental subject. This experiment has later been shown to have had several methodological and ethical issues [10].

There are also different types of associative memories. Instrumental conditioning was pioneered by Edward Thorndike and B. F. Skinner. This is the process of learning behaviour-response pairs using positive or negative reinforcement and punishment [11]. To strengthen behaviour, this theory proposes adding beneficial stimuli or removing noxious ones. To weaken a behaviour, one would add a noxious stimulus (punishment) or remove a positive one. Timing is just as important a factor as with classical conditioning, but with instrumental conditioning, a further key factor is motivation. As motivation is a complex study of its own, this kind of learning is regarded as more complex than classical conditioning and will not be discussed here [6].

A multitude of other memory models exist, some of which are presented below.

1.1.1 Shiffrin and Atkinson

According to Shiffrin and Atkinson [12], memories can be differentiated based on how long the stimulus lasts, where they are stored and for how long they are stored. Thus, memory storages can be divided into sensory, short-term and long-term stores [12]. However, it is important to note that the authors perceived it as theoretical and not actual storages, mainly as good mental models for furthering the understanding of memory.

An information processing sketch is shown in Figure 3. The sensory register or iconic store is a very limited-capacity, short-time registry of external stimuli. Sperling has tried to measure the capacity of this store for visual stimuli and found it to be 12 items [13]. Averbach and Coriell have found that memory in the sensory store can be erased/overwritten in case it is not transferred to another store [14]. This process is called backward visual masking in the case of vision. In case one is shown two stimuli at the same place in less than 0.1 seconds, then the images are overlayed [14]. For example, if one overlays a seven-segment figure 4 with a figure 0, one would see an 8. This is due to the processing speed of sensory information.

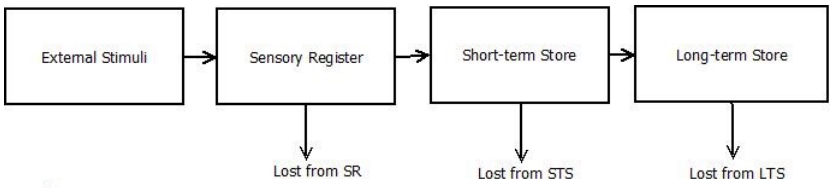

Figure 3: Schiffer-Atkinson model of memory SR: Sensory Register, STS: Short-term Store, LTS: Long-term Store

In short-term storage, one keeps memories from a couple of seconds up to about 30 seconds, and some control processes are also available, which regulate the flow of memory into the long-term store [3]. According to Baddeley, memories, especially of words, are stored here acoustically rather than visually, i.e. more based on how they sound than what they look like [15, 3].

Short-term storage has been found to be a limited resource [16] that, depending on the types of elements memorised, has a capacity of about 7 ± 2, but this varies based on the topic (differences in digits, words...). Furthermore, the definition of what constitutes an element is also non-trivial [17]. An early explanation for remembering more elements than the previously mentioned 7 is via memorising chunks of information and grouping stimuli into more meaningful groups. The number of chunks or groups could then be 7 ± 2. Newer research questions whether reporting only the working memory size, without the quality of the memories makes any sense at all [18]. Further evidence for memory capacity being much more complex to estimate stems from the fact that in the case of words, the syllables constitute a significant factor in determining how much memory one can retain [19]. More recent experiments put the size of this memory to be around 4 ± 1 [20]. This finding is further supported for visual memory [21] as well as for American Sign Language [22].

Long-term memory is meant to be for storing memories indefinitely, and there is no known limit to how much can be memorised [3]. However, the stability of long-term memories is not verified; they may be subject to flaws in retrieval or may be changed due to reconsolidation [23, 24]. Reconsolidation is the process of memories being recalled or situations replayed that can change the memory of the original event [25]. Several psychological approaches exist using this phenomenon for curing post-traumatic stress disorder(PTSD) and other anxiety-related diseases [26].

A specific, robust part of this storage is referred to as permastore, which includes the memory of languages as well as mathematics [27, 28].

1.1.2 Levels of Processing

The levels-of-processing theory posits that the correct way to think about memories is to consider the amount of encoding that goes into every created memory. There are no stores or storages, just some amount of encoding that will affect the robustness and reliability of the memory [29]. Verbal stimuli can be encoded on three levels, which are physical, phonological, and semantic. The physical level deals with the appearance of the word, the phonological with acoustic properties and the semantic with the actual meaning of the word. This enumeration also mirrors the depth of each layer, and thus, the semantic encoding is the most robust memory. The levels-of-processing model can also be adapted to non-verbal stimuli, for example, shallow or deep processing of faces [30].

Furthermore, the best encoding seems to happen when experimental subjects are asked to self-reference words or, even better, to find the words that are descriptive of themselves [31].

1.1.3 Working Memory

One of the prevailing memory models of today is the "working memory" model of Baddeley [32]. The main difference between this and the Shiffrin and Atkinson model is that in the working memory model, there is another, separate storage called "working memory", which not only stores recently activated memories as well as input but is a location where a certain amount of processing occurs [3]. Moreover, working memory interacts with long-term memory directly, for instance, to retrieve the meaning of words [33]. In this model, working memory is subdivided into five subsections, which can be seen in Figure 4.

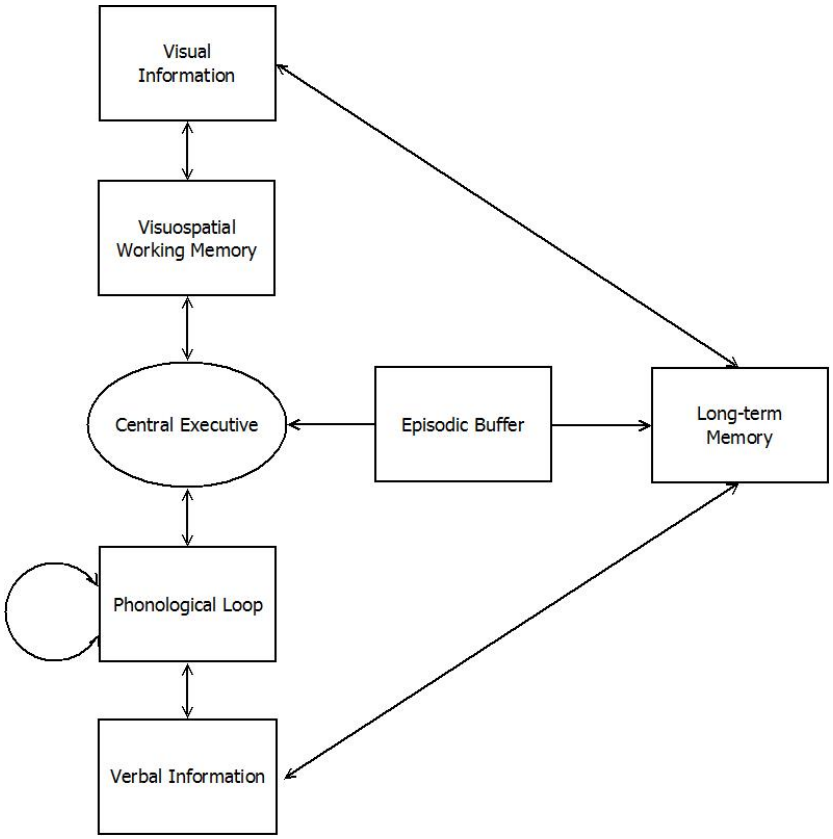

Figure 4: Working memory model

The phonological loop holds auditory information for a brief period of time, either after hearing or also when remembering auditory signals. A short, two-second stimulus is kept in phonological storage, and to keep the memory in place, sub-vocal rehearsal[1] is undertaken [3].

The visuospatial working memory analogously holds images for a brief period of time, when one sees or imagines something and holds not only visual but also spatial information. This information is somehow rehearsed to be kept in this memory, but it is not clear how [3]. Logie speculates [34] that this may retain information on movements and visual stimuli. Logie argues for the presence of

[1]The phenomenon when one talks to oneself but does not speak out loud

"visual cache" for perceptual visual information and of that of a "visual scribe" for information on movement sequences [34].

The next logical element is the central executive, which has the role of distributing attention and other resources between different tasks that need to be done simultaneously [32]. Bilingualism is said to strengthen the capabilities of the central executive as it constantly has to fend off mental intrusions of interfering languages. Evidence exists that monolinguals also need to exclude different, intruding stimuli [35].

The last element is the episodic buffer, which is meant to explain how memories from the visuospatial working memory or the phonological loop get transferred to long-term memory and helps to re-evaluate past experiences and to solve problems [36].

The importance of working memory has been evaluated in several studies as a good predictor of academic success [37, 38]. Working memory can also be trained, but the efficiency remains questionable [39].

1.1.4 Parallel Distributed Processing

The parallel distributed processing models (PDP) is a connectivist framework where information is stored in the connections between neurons or in activation patterns [40].

As opposed to simple serial connectivist models, which are biologically implausible, parallel distributed systems offer a more realistic model for the mind [3]. If one accepts the hypothesis that form influences function, then the brain's parallel processing is better represented by such a model. Activation can propagate when strengths between the sending and receiving unit (neurologically, this could be the pre- and postsynaptic neuron) are large or when the activation in the sending unit is large. When the activation is small or when the strength of the connection is small the chance of activation in the following unit is smaller;

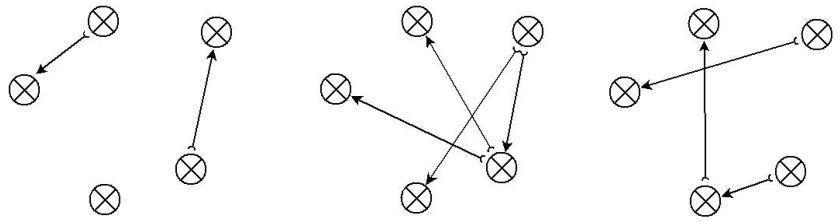

Figure 5: Examples of different connections in a connectivist model

thus, the signal would not propagate so far. The information is coded in the patterns of activation, not in the nodes themselves. Thus the three distinct patterns of connections in Figure 5 encode different information/memories even if the nodes are the same.

Nodes can send either excitatory or inhibitory signals to other connected nodes, and the connections used are strengthened the more often this signal is being sent [3]. The connections between nodes change based on either being exposed to new stimuli or from cognitive processes that activate the specific pattern, such as the effect of retrieving memories [3]. Memory is recalled based on a sufficiently large but possibly incomplete activation of the pattern [41].

The PDP model assumes a modular setup, where different modules have a somewhat overlapping set of nodes; the ones belonging to a single module are largely interconnected [41]. Each module would serve to encode different types of knowledge.

1.1.5 Other Models

According to Tulving [42], different memories might be stored in different places in the brain and can also be differentiated based on their contents. Tulving differentiated between episodic and semantic memories, as discussed in subsection 1.1. Others questioned [43, 44] whether semantic and episodic memories

were stored in anatomically different parts of the brain or are parts of distinct memory systems.

1.1.6 Encoding

Transforming sensory stimuli into mental representations is referred to as encoding [6]. Some theories on how memories get encoded in selected proposed models are reviewed in the following paragraphs.

Short-Term Memories

Working memory and short-term storage have been investigated by Conrad [45], who shows that letters, whether presented acoustically or visually, are initially encoded in an acoustic form[2], rather than a visual or semantic form. Baddeley has argued the same for words [46]. This is not to say that no semantic or visual encoding occurs; rather that these encodings are either fleeting or just contribute less to the memories formed [47, 48].

Long-Term Memories

While short-term and working memory seems to work with acoustic rather than visual or semantic encoding, in long-term memory, semantic encoding seems to be more critical [49]. Considering the "levels-of-processing" theory, one might say that semantic processing occurs on a deeper level than acoustic processing, as long-term memories (LTMs) are created by semantic processing [3].

Consolidation from Short-term to Long-term storage

A major variable determining how memories are moved from short to long-term storage is whether the memory is declarative or not [3]. Issues arising during encoding of declarative memories may be "interference" or "decay". Interference

[2] using psychophysical experiments

is the inability to remember a stored item from one's memory that is similar to other stored items [50]. Decay is the process we would more colloquially refer to as "forgetting" [3].

Non-declarative memories, such as priming or habituation, decay quickly. Other types are kept in memory by means of rehearsal [3].

The long-term storage of declarative memories is called "consolidation" and is the lengthy process of declarative memory being encoded and integrated with prior knowledge [51]. Several strategies exist to improve this process, such as elaborative rehearsal, the spacing effect, and sleep.

Rehearsal is the repeated recitation of an item of memory in either an obvious or a hidden way (such as sub-vocal rehearsal mentioned before) [3].

Elaborative rehearsal is when the subject connects more meaning to the item of memory by integrating it and connecting it to other concepts [3] this way of memorising fits exceptionally well with the levels-of-processing theory or the connectivist approach to memory.

The spacing effect underlines the importance of separate encoding steps that are distributed over time rather than massed stimuli over a short period of time [52].

1.1.7 Retrieval

There are several interesting questions regarding the retrieval of memories, including whether it occurs in a sequential or parallel manner or whether it occurs from short-term or long-term memory. Furthermore, the question of whether there is a self-terminating or an exhaustive recall of memories, meaning whether one stops on the point of finding the correct memory or whether one matches all to find the best fit [3]. In the case of short-term memories, Sternberg et al. found that humans use a serial and exhaustive method for recalling memory [53, 54].

In the case of long-term memory retrieval, it was shown that hierarchical recall and categorised, cued recall have much higher efficiency than free recall, where the subject has no explicit support in organising their knowledge of images and words [55, 56]. Khader et al. [57] showed that in memorising visual imagery, the same parts of the cortex were activated when retrieving the same information two days later.

1.1.8 Failure of Memory

One might regard declarative memory as the parts of sensory input successfully encoded into long-term memory. As was elaborated in subsection 1.1, the study of (declarative) memory is most often conducted through different recall and recognition tasks. In other words, we measure the quantity and quality of remembered stimuli. Quantity may be measured by counting the number of remembered associative pairs, whereas quality could be considered a subjective appraisal of how precisely a mental image of a picture could be retrieved.

An equally important phenomenon is the quality and quantity of what we do not recall. Important research questions arise that deal with forgetting and contamination of memories. In the following sections, interference and decay theory, as well as false memories, are discussed.

Interference Theory

As the presence of certain words can help retrieval in the case of cued recall, the opposite is also possible. This is referred to as ”interference” and describes the presence of a word impeding retrieval of the target memory. For example, when memorising trigrams (groups of 3 letters) [58] under interference from counting backwards, subjects' memory is strongly inhibited, and they forget nearly every trigram they have been taught after 18 seconds. This kind of immediate interfering task is called ”retroactive interference” [3]. The same

Proactive	**Retroactive**
More interference with more time between encoding and retrieval [63]	More mistakes with longer time since learning [58]
More interference with more learned material [64]	Interfering stimuli largely irrelevant [60]
Interference grows with age [65]	Interference grows with age [66]

Table 1: Proactive and retroactive interference comparison

effect has been found, largely independent of the stimuli and interference tasks [59, 60].

Another kind of interference is "proactive interference" from previous knowledge stored in memory [3]. A common example is the mixing of words from different languages, even though this also happens in other contexts [61, 62].

There are several similarities and dissimilarities between the two mentioned modes of interference, which are summarised in Table 1.

Decay Theory

The decay theory posits that if certain elements of memory are not activated through recall or other cognitive processes, they will slowly disappear altogether. This is in contrast to interference theory, which holds that the reason for forgetting is some sort of blockage of the original memory [3]. While some studies exist in this field [67, 68], it appears that the role of decay in memory loss is smaller than that of interference [67].

False Memories

False memories are recalled information which were never learned that way. Roediger et al. [24] give an example of free recall and recognition testing of a list of words revolving around a particular topic. For example, the topic could be "sleep", the term itself not being included in the list of words and the list of words could be "bed", "dreams", "pillows", "rest" ... Participants recalled "sleep"

40% of the time and recognised it also at a similar rate. Edelson [69] points out the importance of social factors in creating false memories, such as memory conformity in a group. Furthermore, Roediger discusses the effect of reciting embellished stories on one's own memory as well as that of individuals who are familiar with the actual story [70].

Further experiments have shown that the implanted, false memories lead to actual life actions, emotions and decisions [71, 72, 73].

1.2 Biology

From a neuroscientific point of view, one needs to answer how and where memories are stored as a result of learning. In the following, first, the brain areas associated with learning are revised, and afterwards, some molecular mechanisms which point to learning and neuroplasticity will be discussed.

1.2.1 Brain Areas

Certain brain areas are primarily concerned with memories and learning as seen from various lesion studies [74, 75]. Figure 6 shows a summary of the most important brain regions involved in memory [76]. Memories are not solely located in the cortex, some parts of the limbic system and other sub-cortical structures are also involved. It is important to note that certain regions have a crucial role in the encoding, storage or retrieval of memory, but that this is not synonymous with the memories physically being stored there. The "parallel distributed processing" or other connectivist models would also be affected by brain lesions and thus do not contradict lesion studies. The thinking has moved away from strictly location-based memories toward the idea of networks and distributed systems for the storage and retrieval of memories [77, 78].

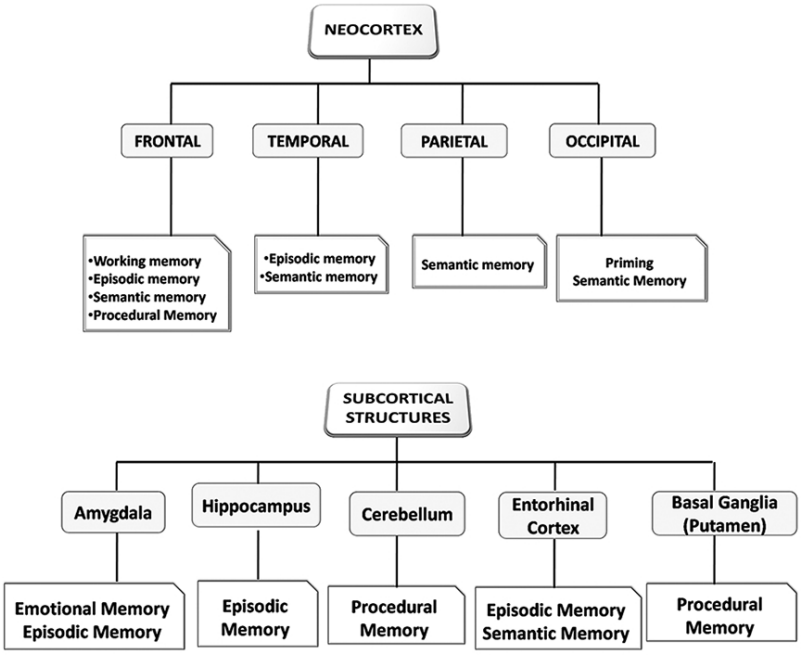

Figure 6: Classification of brain areas based on memory systems affected [79]

1.2.2 Dopaminergic System

Dopamine is a neurotransmitter involved in the reward system and in learning, as well as in Parkinson's and Alzheimer's disease, attention deficit hyperactive disorder (ADHD) and in schizophrenia [80].

Dopamine can bind to different receptors numbered from D_1 through D_5 [81]. These can be grouped into D_1-like family and D_2-like family [82]. The D_1-like sub-types are D_1 and D_5, which activate adenylyl cyclase, while the D_2-like sub-types (D_2 through D_4 inhibit adenylyl cyclase but activate K^+ channels [81]. D_1-like receptors are more often found in subcortical areas than are D_2-like receptors [83]. In case D1 and D2-like receptors are blocked using antagonists, then LTP and LTD are both blocked, but they are both strengthened by using

agonists for D_1 [82, 133, 134]. Furthermore, NMDA receptors are also involved in channel activation for LTP, besides D1-type receptors [135].

Three major dopaminergic pathways have been discovered, all connecting the midbrain to either the dorsal striatum, the ventral striatum, and the nucleus accumbens to the prefrontal cortex [84, 85].

The pathways to the dorsal striatum are involved in movement. Furthermore, they are involved in the parallel, recurrent loops linking the midbrain, the basal ganglia, the thalamus, and the cortex [86, 87].

The pathways connecting the midbrain to the cortex are rich in D_1 receptors and are involved in occulo-motor tasks and in working memory [82]. The amount of dopamine activity relates to working memory function in an inverted U manner. First, with growing activity, function also grows, but after crossing a threshold, the more dopaminergic activity occurs, the less function one gets [88].

Dopamine in the ventral striatum is involved in motivation, action and affect [89]. Furthermore, dopamine plays a decisive role in reward and reinforcement [90]. It has been shown that dopamine is relevant for different neural systems, which each contribute to reinforcement, learning and motivation [91]. The ventral striatum is also connected to the amygdala, and this connection plays a crucial role in Pavlovian learning [82].

The prefrontal cortex (PFC) plays a vital role in working memory [92, 93] and dopaminergic neurotransmission in modulating working memory [94, 95, 96]. Dopamine levels rose in non-human primates during working memory tasks [97] and depleted dopamine in rats and monkeys led to faults in working memory [98, 99]. There is a critical range of D_1 and D_2 receptor activation and the ratio of D_1 and D_2 that needs to occur in order to avoid cognitive impairment [100, 101, 80]. As D_1-type receptors are expressed at a much higher rate than

are D_2 receptors in the human prefrontal cortex [102] and the critical region of D_1 receptors, it seems that this is more important for mnemonic activity [80]. D_2 receptors may also affect working memory by regulating presynaptic dopamine release [80], and D_3 receptors may have a direct modulatory effect on working memory that is independent of D_1 receptors.

Dopamine also plays a role in spatial, aversive, reward/incentive learning, and in neuroplasticity [80].

In the case of spatial learning, studies in rodents suggest that D_1 and D_2 receptors play a modulating role through multiple memory systems. D_1 influences spatial navigation behaviours through memory processes, while D_2 receptors might be involved in procedural aspects and their consolidation [80, 103, 104].

In aversive, conditioned fear, dopamine also plays an important role [105, 106]. Primarily D_2 and D_{2L} [3] are involved, but D_1-like and D_2-like receptors may cooperate to facilitate fear memory [80]. D_3 inhibits fear memory, while D_4 fosters the consolidation of memory [80].

Incentive learning is the process during which previously neutral stimuli are associated with rewarding experience [107]. D_1 and D_2-like receptors seem to play different roles in food and drug abuse [80]. The roles of the specific receptors are inconclusive or controversial, but there seems to be a synergistic interaction between the different types of dopamine receptors. Furthermore, D_1 seems to have a prominent role in incentive learning regarding rewards [80, 108, 109, 110].

Dopamine is transduced via second messengers to regulate gene transcription [80]. Dopamine activates or inhibits adenylyl cyclase and cyclic adenosine monophosphate (cAMP), depending on whether D_1-type or D_2-type receptors are involved [80]. Activating cAMP and protein kinase A (PKA) pathways via D_1 or D_5 receptors has been shown to be a necessary and sufficient condition for neural plasticity, learning and memory formation to take place [80, 111, 112, 113, 114].

[3] a sub-type of D_2

Through several steps, dopamine also affects cAMP-response-element-binding protein (CREB), which regulates the expression of specific genes connected to neurons [80]. CREB has been found to be vital for long-term potentiation (LTP), learning and long-term memory [115, 116, 117, 118].

Synapses between the hippocampus and the PFC showcase LTP and long-term depression (LTD) both. On the other hand, these are known to be involved in the consolidation of memories and in working memory [82].

1.2.3 Neuroplasticity

According to Hebb [119], memories could be stored in neurons as a consequence of commonly occurring activation patterns. In his view, different stimuli, i.e., sensory input, would lead to different activations travelling along neural paths, which, as a result, would lead to functional strengthening in the connections along this path and also in structural change/growth.

When presynaptic neurons are active, and the postsynaptic one is strongly activated, then the synaptic coupling strength increases. However, when the postsynaptic neuron is only weakly activated, then the synaptic coupling strength decreases [6]. The saying "neurons that fire together wire together" summarises this view [119].

A matching molecular mechanism has been found in the form of LTP and LTD [120]. This mechanism aids the strengthening and weakening of synapses involved in creating memory engrams and thus supports Hebb's theory [78, 121, 122]. Furthermore, LTD and LTP modulate the synaptic weights of neurons firing simultaneously. Thus, not cells store the information or memories, but the strength of synaptic coupling between them.

In addition to the morphological changes on the synapses, recent research on dendritic spines [123, 124] also linked them to memory in different types of

learning and in different brain areas such as the auditory or association cortex [125, 126, 127].

The theories of LTP and LTD have been refined in later years, altering the theory from coincidence of spikes to the specific time-windows in which spikes have to occur in order for synaptic strengthening/weakening to happen [128, 129]. Additionally, the development of immature neural circuits from early childhood to the more organised adult circuits also occurs with the help of processes similar to LTP and LTD [78, 130].

It has been shown that not only the initial stimulus and ensuing synchronous pre and postsynaptic spiking leads to LTP/LTD, but that the brain replays particular segments of an episodic memory hundreds of thousands of times [78]. This repetitive re-activation is called a "hippocampal sharp wave-ripple" (SWR). SWRs occur during certain "off-line" states of the brain, such as non-REM sleep and consummatory behaviours like drinking, eating, grooming and immobility [131]. The interplay of pre-existing memories influences later decisions and recently acquired information during SWR [131]. The true nature of memory then can only be wholly investigated if one considers spines, as well as synapses, as the basic building blocks [131].

2 MRI Basics

2.1 Physical Background

Magnetic resonance imaging (MRI) is a non-invasive technique widely used for investigating living beings with sub-millimetre resolutions [132]. MRI can be used to differentiate between various tissues based on a quantum-mechanical property of elemental particles: spin. For the purpose of this thesis, it is enough to note that the spin is an intrinsic property of every elementary particle, which

can be understood as the angular momentum of the given particle and creates a magnetic field [133]. When such a particle is placed inside a magnetic field, it aligns with that magnetic field just like a magnetic dipole would. It is worth mentioning that only unbalanced nuclei in terms of protons and neutrons have non-zero spins, not all atoms. The alignment can happen in one of two ways for each particle: either the same (parallel) or the opposite (anti-parallel) direction as the magnetic field, but with a slight majority in the lower energy, parallel direction. This is also what happens when matter is placed inside the active MRI machine: the spins of hydrogen protons line up according to the main magnetic field and start precessing around its axis. While the spins never point in the direction of the magnetic field vector, the net result of one precession around it will point in the parallel direction of the magnetic field [134]. However, their phases are not necessarily aligned at this time. The slight difference in parallel and anti-parallel aligned spins in the external magnetic field can be measured. The precessing frequency of the spins is given by the *Larmor frequency* (ω), which is proportional to the external static magnetic field B_0 generated by the MRI machine with the *gyro-magnetic ratio* (γ). This constant has the value of about 42.58 MHz/T [135] in the case of a hydrogen nuclei and in case of a 3 Tesla machine resulting in a Larmor frequency of 127.74 MHz. The spins send out an electromagnetic wave with this frequency [136].

Suppose the investigated object is situated in the B_0 magnetic field, and an electromagnetic radio-frequency (RF) pulse is applied synchronously (with the Larmor frequency) with the precessing spins to create a magnetic field in the transverse plane, with regards to the direction of B_0 [134]. In that case the spins' direction will turn into the plane of the transverse plane, and their phases will also synchronise. This transverse plane is referred to as the B_1 plane (Figure 7).

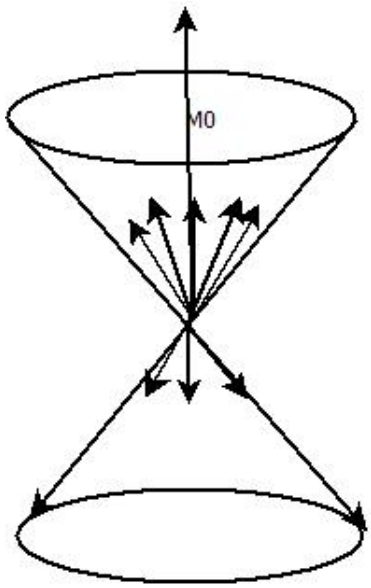

Figure 7: Precession after alignment with B_0 [137]

The phenomenon of large amplitude vibrations, caused by injecting little bits of energy into the system at precisely the right moment is known as resonance and allows for deflecting the spins with a much weaker magnetic field than B_0. When the RF pulse is turned off, the spins then emit electromagnetic energy of the Larmor frequency once they dephase and return to the lower-energy position in the plane of B_0.

The process in which the spins fall back into alignment with B_0 is called *relaxation*. Several relaxation processes can be differentiated and characterised based on their time constant (T_1, T_2, T_2^*). T_1, the spin-lattice relaxation time is the time it takes such that $1 - 1/e \approx 63.2\%$ of the maximum net magnetisation in the B_0 direction (longitudinal relaxation). T_2, the spin-spin relaxation time, is the time it takes for the transverse magnetisation to reach $1/e \approx 36.8\%$ of its maximum. $1/T_2^* = 1/T_2 + 1/T_{2\_inhomo}$ here the T_{2_inhomo} is derived from the magnetic properties of the scanned object, which disrupts the homogeneity

of the field. T_2^* is often used in fMRI recordings and also references relaxation. All three relaxations are exponential in nature. These different relaxation processes can be exploited to contrast different anatomical tissues such as: grey matter, white matter or cerebrospinal fluid in the brain or bone, joints, and other soft tissue in the body. Other characteristics used for creating contrasts in an MRI image are spin/proton density or the influence of water diffusion [134] by Brownian motion.

Different tissues have different proton densities and different relaxation times, which are determined by the composition of the matter (e.g., which molecules occur in which relative proximity to others).

2.2 Spatial Localisation

If there was only the B_0 field and an RF frequency pulse, one would simply record a single signal from the entire body, which would not be very useful for imaging purposes. So instead, several solutions are used to get a spatially resolved image from the signal.

A gradient magnetic field is also applied with the RF pulse in the z-direction (the direction of B_0). This gradient is used to select the slice to be recorded. Since the magnetic field is not constant anymore along the z-direction (the B_0 and gradient fields add up), the emitted RF pulse of a certain frequency range will only excite the protons in the region where the resonance criterion is still fulfilled. Thus, any signal recorded has to come from that slice. Afterwards, the RF pulse and the z-gradient are both switched off. Next, to localise the signals within one slice, the phase encoding gradient is switched on and finally, another frequency encoding gradient at the same time as recording the signal. The frequency-encoding step is done during sampling. As this changes the Larmor frequency, the signal can be encoded via different frequencies and hence, loca-

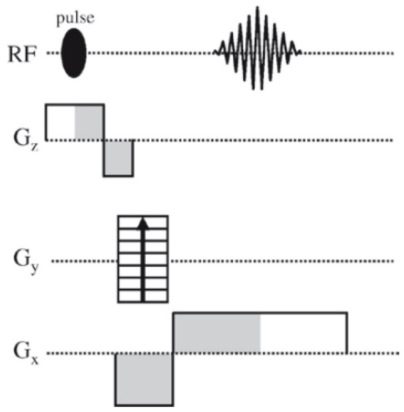

Figure 8: Spatial localisation of the magnetic resonance imaging signal. G_x, G_y and G_z are three different gradients. The multiple horizontal lines in G_y mark multiple gradient values being run one after another [136]. The solid ellipsis on the RF line denotes the RF pulse, and the alternating line, the acquired signal. The inversion of the gradient results in a gradient echo that can be measured. The signal is strongest when the negative and positive shaded areas on the gradients are equal.

tions calculated using the inverse Fourier transform [137]. The phase-encoding gradient is turned on for a short amount of time between the RF pulse and the frequency-encoding step and results in the spins dephasing by different amounts based on their location along the remaining dimension. The entire process is repeated several times but with different phase-encoding gradients [137] (See Figure 8). When using one phase gradient, the difference in phase between any two neighbouring regions along that gradient is equal. When one records with different phase gradient strengths, these differences become larger for stronger gradients and smaller for weaker ones, and this is the information that will result in the localisation in the phase-encoding direction.

The values that one records per slice are represented in the 3D k-space where the dimensions are k_x, k_y and the amplitude measured. The k_x and k_y can be determined in the following way: at every sampling, the value under the preceding gradient is measured, either under the read/frequency or the phase-

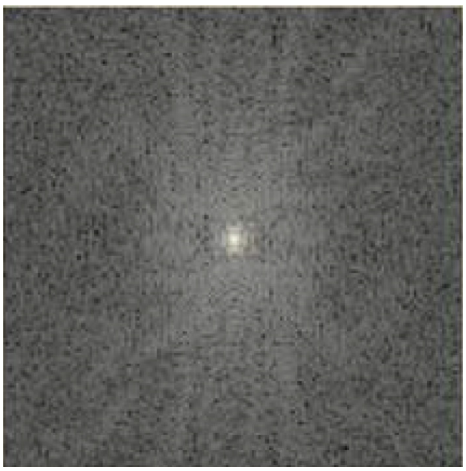

Figure 9: Values in k-space after one recording [137]

encoding gradient, and this is the so-called k-value. The gradient echo is the largest when the k-value is 0 for both dimensions. An example of the data recorded in one acquisition can be seen in 9.

As energy from the particles is released in the form of RF signals, this can be measured by an RF receiver coil. The spatial locations of the spins can be calculated based on the Larmor frequencies (which depend on both the gradient magnetic field and the original larger, B_0 field) emitted by the particles and the 2D inverse Fourier transform [134, 136]. The different emitted frequencies are crucial for spatial localisation. Usually, the brain is recorded slice-by-slice, not in one measurement, due to practical considerations. The thickness of the slice is determined by the frequency band used to synchronise the spins (i.e., the RF pulse) as well as the strength of the gradient field [137].

As the synchronisation and dephasing of spins are a relatively quick phenomenon compared to switching on the gradient magnetic field, one has come up with, amongst others, the technique of gradient echo to catch the spin synchronisation at its peak. The idea is that after the RF pulse, we switch on the gradients according to Figure 8. It requires a certain amount of rise time for

a gradient to reach its plateau level. As G_y is very short, the time it takes to physically alter the magnetic field is negligible. However, G_z takes longer and will thus ruin the signal before it reaches its desired strength. To regain the original signal (the echo), we invert this gradient magnetic field to rephase the spins and get the maximum amplitude, as seen in Figure 13.

This way, the spins will have rephased by the time the field has inverted, and the recorded signal amplitude is higher. The main difference to sampling at the very beginning is that turning on the read-gradient takes too much time; thus, the signal would decay significantly before one could measure it. The time between the RF pulse and the maximum echo is denoted by TE. The time between renewed scans is denoted by TR. Altering TE and TR leads to sampling at different times of signal decay and thus influences the signal amplitude received from different tissues with different relaxation times. For examples of different contrasts, see Figure 12.

Typical values for T_1 and T_2 in grey and white-matter and CSF can be found in the table below [138].

The spin-echo technique works similarly, but instead of inverting the readout, in this case, the RF is inverted. This also leads to the spins realigning and accounts for field inhomogeneities [139].

Echo-planar imaging (EPI) is a fast imaging technique that works on the principle that one main excitation should be enough for several echoes and thus being able to image a slice quicker. As shown in Figure 10, several short RF pulses are emitted after the initial one, each followed by a "blip" in the

	T_1	T_2
white matter	850ms	80ms
grey matter	1300ms	110ms
CSF	4500ms	2000ms

Table 2: T_1 and T_2 relaxation times of specific tissue in the brain [138]

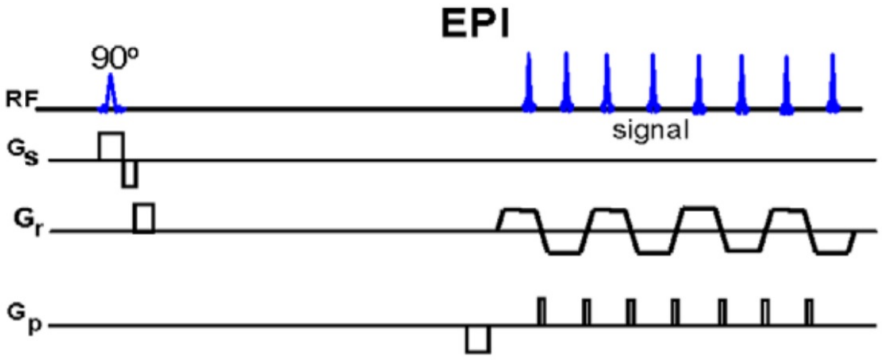

Figure 10: Gradient diagram of echo planar imaging, adapted from [137] R_F is the radio pulse and G_s, G_r, and G_p are the gradients (slice select, read and phase)

phase gradient, nudging the phase to a different value. This can be seen in the progression of k-values in Figure 11.

2.3 Limitations

During the generation of MRI images, one has to deal with different artefacts which may be present in the images. The five most important ones, according to Schneider and Fink, are discussed below [137].

Chemical shifts arise through the changing Larmor frequency of the proton's surroundings. As the frequency changes, the spatial localisation is also affected, and the shift between water and fat can be several voxels large [137]. This so-called fat-water-shift can be reduced by dephasing the fat cells before recording the MRI scan. This process is called "fat-suppression".

Motion artefacts arise when there is movement in the scanner during image acquisition. To some extent, this can be corrected by software algorithms or by stabilising the subject. There are other aspects, such as blood flow which can also be partially remedied by using fast sequences like EPI [137].

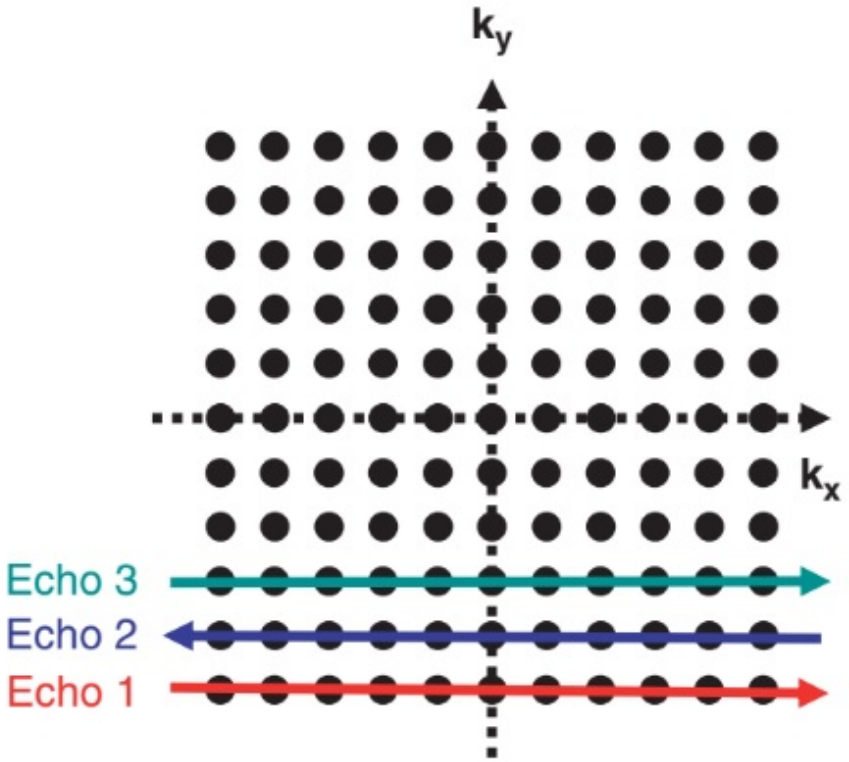

Figure 11: Echo-planar image acquisition in k-space [139]. The lines show the direction of recording and of writing into k-space. k_x stands for the read gradient and k_y stands for the phase encoding gradient.

Ghosting artefacts arise due to errors concerning the anti-parallel directions of recording in k-space and their results in phase encoding [140]. The consequence will be a ghost of the image translated by half of the field of view (FOV). It can be corrected for by phase-correction or via using calibration scans. Buonocore et al. suggest an algorithm that only uses odd or even lines of k-space to reconstruct the image [137, 140].

Susceptibility artefacts arise through inhomogeneities in the magnetic field. Materials with short T_2^* are especially susceptible to inhomogeneities of the

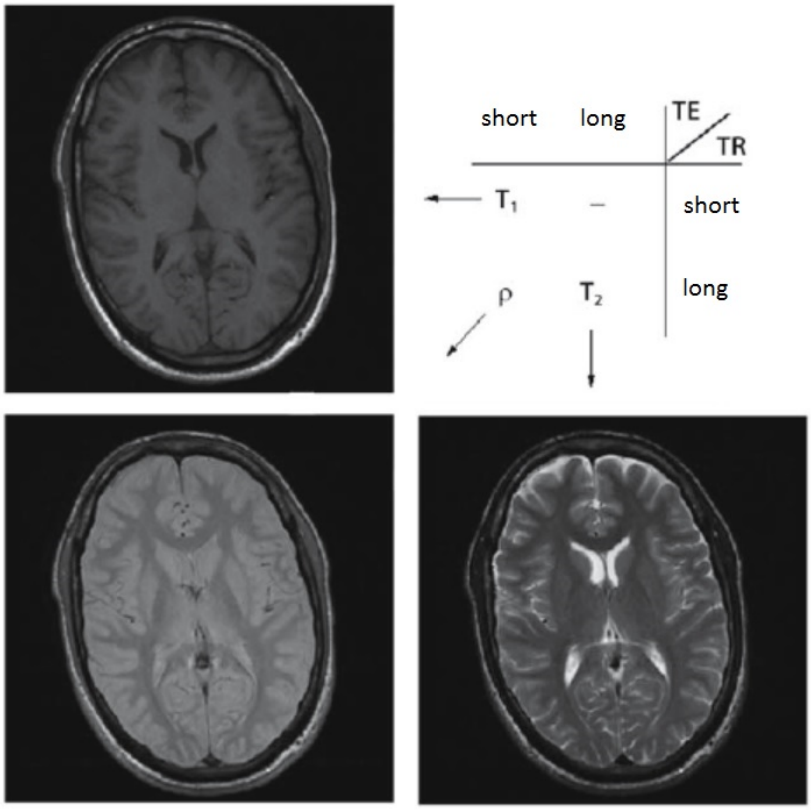

Figure 12: Different contrasts adapted from [137]

magnetic field; the solution is currently to shim - to measure the magnetic homogeneity of the field and try to correct it based on this [139].

Finally, aliasing occurs when the FOV is smaller than the object to be examined in the phase-encoding direction [137]. In such cases, the voxels are wrapped around or folded over onto the other side of the image.

2.4 BOLD - fMRI

Depending on the mental task, certain parts of the brain will activate more, i.e., consume more oxygen due to increased metabolic demand, than others. This is a result of the locally increased neuronal activity. Oxygen is transpor-

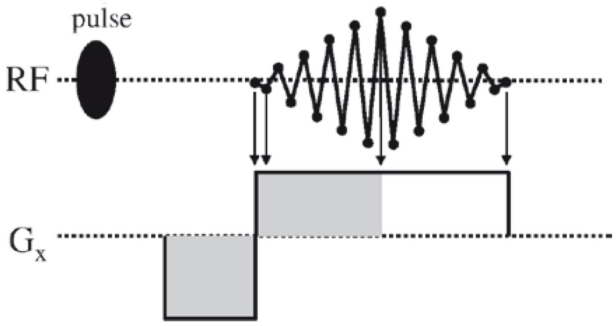

Figure 13: Gradient echo adapted from [136]

ted to the location of use in the blood using haemoglobin. In functional MRI, we use the different magnetic properties of oxyhaemoglobin (diamagnetic) and deoxyhaemoglobyn (paramagnetic) to locate which parts of the brain are using more oxygen while being active [137]. Tissue can usually be regarded as diamagnetic, so when it gets near a paramagnetic substance (i.e., deoxygenated haemoglobin) certain distortions and magnetic interference occur on the border of the two matters [136]. In essence, the signal intensity of the tissue is reduced through this effect. Following the haemodynamic response, the level of oxyhaemoglobin increases and the level of deoxyhaemoglobin decreases, which results in the magnetic field becoming more homogeneous and thus the signal intensity increasing, see Figure 14. Generally, the hemodynamic response function after a stimulus starts with an initial dip due to neuronal firing and consumption of the available oxygen. Subsequently, cerebral blood flow (CBF) is increased in the region of activation after roughly a second, which ultimately results in an oversupply of oxygenated blood. Other factors related to the haemodynamic response function are the cerebral blood volume and the metabolic rate of oxygen consumption. The peak of the HRF is at around 5-6 seconds after the stimulus. At this point, due to oxygen metabolism and the decrease of

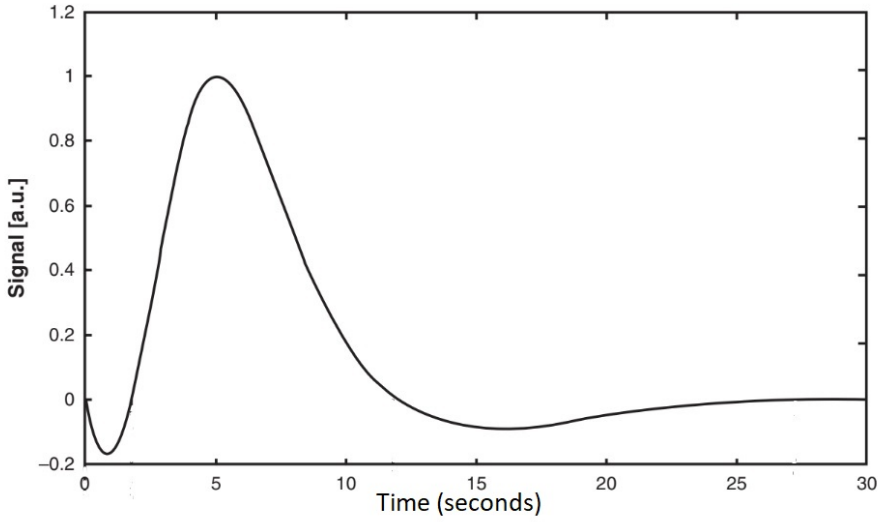

Figure 14: Haemodynamic response function adapted from [139], stimulus onset is at the time-point 0

CBF, the HRF level sharply decreases and results in an undershoot and a slow ascent back to baseline [136].

Imaging the BOLD signal is usually done via echo planar imaging. Figure 10.

2.4.1 Limitations of fMRI

While fMRI boasts higher spatial resolution than, e.g., positron emission tomography (PET) or electroencephalography (EEG), which are also used in the realm of neuroimaging, its temporal resolution, as it uses the BOLD signal as a proxy for brain activity, is considerably lower than that of EEG [141]. This is a limitation coming from the BOLD signal, not from the technical setup of acquisition.

Other issues arising from the use of the BOLD signal as a proxy are that the blood supply of the brain is not homogeneous, that the signal depends on

neurovascular coupling, and that smaller synaptic activity does not result in an increase of CBF and others [139].

As mentioned previously, specific pulse sequences are required for fMRI (often EPI is used), resulting in certain restrictions specific to fMRI. Due to the susceptibility artefacts discussed in section 2.3, parts of the image recorded are distorted. Furthermore, erroneously low signals might be measured from parts of the brain which are near air, such as ventral, temporal and the prefrontal cortical regions. Participants moving in the scanner too much (including eye-movement) can heavily compromise measurements, just like in other imaging modalities, although certain computational methods for correction exist [142]. The high magnetic fields require the use of special devices and stimuli delivery systems. Due to the loudness of the MRI scanner, it is challenging to conduct auditory studies [143, 144].

3 Objectives

The effects of daily, standardised associative learning on the brain are investigated in this study. We looked at changes in resting-state connectivity and changes in other resting state metrics after the first 3-week study regimen.

4 Materials and Methods

4.1 Study Design

A schematic summary of the study design can be seen in Figure 16.

This project is a part of the study "Enhancement of learning associated neural plasticity by SSRI" (PI: Univ. Prof. R. Lanzenberger), a longitudinal, double-blind, randomised, placebo-controlled study. In total, there are four

experimental groups investigated in this study: Half of the participants had to learn emotional and half of them non-emotional associations while receiving a placebo or SSRI during the relearning phase.

The study was conducted according to the Declaration of Helsinki and approved by the ethics committee of the Medical University of Vienna (ethics committee number EK 1739/2012). The study was registered at clinicaltrials.gov (NCT02753738).

4.2 Subjects

80 subjects should be recruited (with 10% expected dropouts to be replaced) through message boards at the University of Vienna and at local supermarkets and pharmacies. After an initial phone screening to establish adequacy for the study, prospective subjects visited the general hospital of Vienna (AKH) for a physical checkup, including a routine blood test, ECG and blood pressure assessment. Furthermore, they were scanned for illicit drug use and pregnancy and had to undergo a psychiatric assessment (structured clinical interview (SCID-I and II) according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)).

Participants were instructed to lead their lives as usual, to avoid stimulating events (like travels), and to schedule their learning at the same time of day, every day.

4.2.1 Inclusion Criteria

1. Non-smoking
2. Age 18-55
3. Right-handed

4. General physical health

5. Unremarkable clinical interview (DSM-IV SCID I and II)

6. Willingness and competence to sign an informed consent form

4.2.2 Exclusion criteria

1. Non-caucasian

2. Lifetime use of SSRI

3. Colour–blindness

4. Knowledge of Chinese/Japanese characters

5. Failure to comply with the study protocol

6. Current or former substance abuse

7. Any relevant internal, psychiatric, or neurological illness

8. Any stainless steel or other implant that contraindicates MRI

9. First-degree relatives with a history of psychiatric illness

4.3 Learning Paradigms

4.3.1 Association learning

After a baseline MRI assessment, 40 subjects entered a facial and hence, emotional associative learning paradigm (i.e., matching faces) to induce learning-related neuroplasticity.

The other 40 subjects entered another, non-emotional, associative learning paradigm, where they learned to match Chinese characters with random German nouns.

Associative learning lasted 3 weeks, and during this time, participants were instructed to learn associations for approximately 7 minutes each day, followed by about 3 minutes of retrieval.

4.3.2 Online learning paradigms

After receiving detailed instructions on a laptop during the preliminary examination, study subjects (N=80) got access to the web-based learning tool.

Facial/emotional pairs - association learning

During the first associative learning phase (days 1 to 21), subjects in the facial/emotional paradigm learned to associate two faces with each other. As the faces differ in their emotional expression, this task includes learning associations between emotional expressions.

From a pool of 200, 52 associative pairs were shown in each session, each pair for 5s, with pseudo-ransom sampling with repetitions over 21 days. The retrieval section also consisted of testing 52 pairs per day but sampled from everything seen up until then.

During the retrieval task, the matching image (face-face, Chinese character-German noun) to the presented stimulus should be selected from a given set of 4 possible answers (Figure 15, bottom). Learning times and retrieval scores were logged in the learning program.

Chinese character-German noun association learning

To differentiate neuroplastic changes induced by learning from the additional one caused by emotional content, half of the subjects (N=40) performed a Chinese character/random German noun learning paradigm. The participants were asked to associate a typed word with a Chinese character and vice versa.

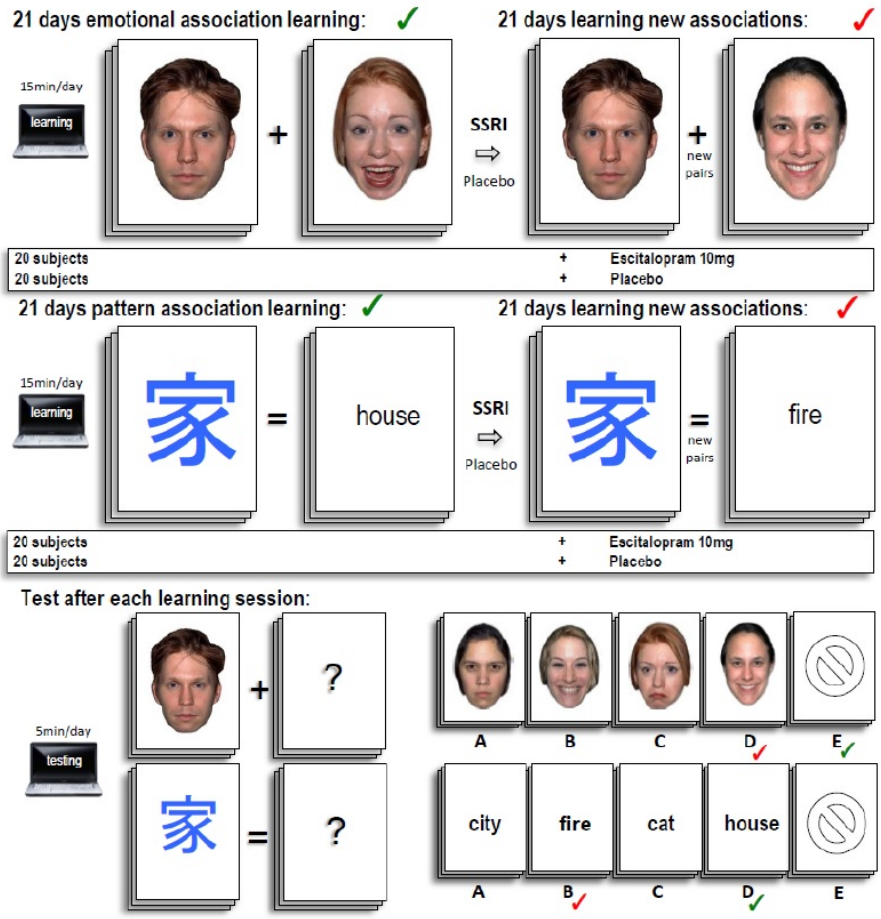

Figure 15: Study schedule with representative examples of (re-)learning content and the retrieval phase. (adapted from the study proposal "Enhancement of learning associated neural plasticity by SSRI" (PI: R. Lanzenberger))

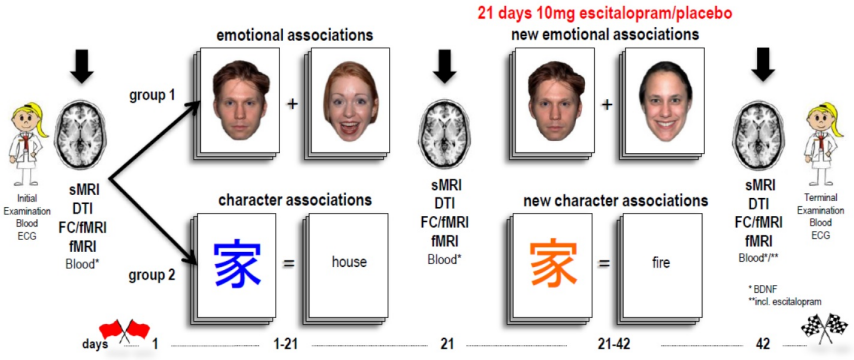

Figure 16: The course of the study adapted from the study proposal "Enhancement of learning associated neural plasticity by SSRI" (PI: Univ. Prof. R. Lanzenberger)

Learning new associations

On day 21, the same MRI scans as conducted for the baseline were repeated and the subjects were assigned new, shuffled dyads to learn. Presentation times, the number of learned items and retrieval remained identical to the previous association learning phase. The main difference to the previous part is that starting on the first day of the relearning phase, participants in both learning groups were either administered 10 mg escitalopram or placebo for the following 21 days ($\pm$ 4 days).

On the 42nd day of learning, the MRI protocol was run a last time.

4.4 MRI measurements

MRI measurements were performed on a 3 Tesla MAGNETOM PRISMA scanner (Siemens Medical, Erlangen, Germany). Subjects underwent 3 MRI scanning sessions, 1st at baseline, 2nd after association learning and the 3rd after learning new associations under the administration of placebo or escitalopram.

4.5 Hypotheses

$H_0(1)$: There will be no difference between the baseline brain activity before and after learning as measured via GFC, ReHo or PerAF.

$H_0(2)$: There will be no difference between GFC or PerAF, or ReHo metrics of subjects with emotional stimuli vs the Chinese characters learning group.

$H_0(3)$: There will be no interaction effect of time and groups neither in GFC, PerAF, and ReHo.

5 Pre-processing

Which preprocessing steps are performed as well as their order varies widely between different references. The steps are described here as they have been implemented for the current analysis that utilised the Statistical Parametric Mapping toolbox (SPM12).

A simple flow chart can be found in Figure 17, with detailed descriptions in the following sections.

5.1 Slice Time Correction

It takes the MRI machine usually seconds to acquire all the slices of an image. Thus, the first and last recorded slice of the brain show BOLD signals nearly an entire TR apart. To correct for this, the phase of the signals has to be shifted. This step uses a Fourier transform and adds a constant to each slice to shift the phase of the signals of each slice in such a way so that the acquired image portrays one specific point in time [145].

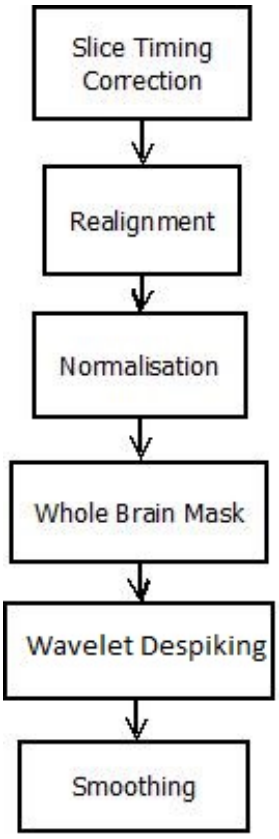

Figure 17: Pre-processing

5.2 Realignment

This step is conducted to correct for motion in the scanner. The algorithm corrects for rigid-body movement (rotations and translations) by minimising the least-squares difference between any given image and a specified reference image, e.g. the calculated mean of images after realignment to the first recorded one.

While the recorded brain will generally move in a rigid fashion, the same cannot be said about ghosting artefacts and other distortions, and realignment does not correct those [136].

5.3 Normalisation

Brain shapes and sizes differ between individuals, thus complicating the comparison of the brains. Normalisation is the process that standardises the 3D brain images so that they may be compared. In essence, this means to warp the images onto a kind of Tissue Probability Map (TPM). The tissue probability atlas [145] used was from the Montreal Neurological Institute (MNI), which has been created as an average of a large number of subjects. Thus the individual brains are transformed via nonlinear transformations to best fit the TPM.

5.4 Masking and Despiking

This step is to remove noise from the image. First, the brain is masked in order to limit the computationally expensive despiking to voxels containing only the signal of interest. A custom brain mask was used in this study. Next, the Wavelet Transform [146] is used to transfer the image to the wavelet space and remove biologically unrealistic intensity changes before transforming it back.

5.5 Smoothing

The image is smoothed with a Gaussian kernel with a specified full width at half maximum (FWHM) parameter. The image, as a result, is suitable for use in Gaussian random field theory. Additionally, the spatially random noise is distributed. An added benefit of smoothing is that since normalisation will alter the location of certain intensities of activation (due to the different contortions of the brain), these might be in a slightly different position than originally. This may also occur based simply on the natural differences between structural and functional changes in different brains, and smoothing will provide more signal intensity on the original place of activation [136].

6 Statistical Analysis in Resting State

Prior to the actual modelling, the susceptibility of RS data to various forms of noise requires further cleaning of the signal. In this study, this was achieved by regressing out nuisance signals. To this aim, the Friston-24 model for motion artefacts [147] and the CompCor approach for modelling physiological influences by heartbeat and respiration from white matter and cerebrospinal fluid signals were employed. Furthermore, sine and cosine regressors were added to the matrix in order to apply a bandpass filter from 0.01-0.10 Hz simultaneously to the nuisance regression [148]. Lower frequencies are removed as they mostly contain scanner drifts, and higher frequencies as they stem from physiological influences such as heartbeat and respiration. The resulting matrix is regressed out from every voxel time course, and the residuals constitute the cleaned signal. The signals are then run through one of the algorithms detailed in the following sections. For statistical analysis, the resulting models are fed into and tested via a General Linear Model (GLM) as implemented in SPM.

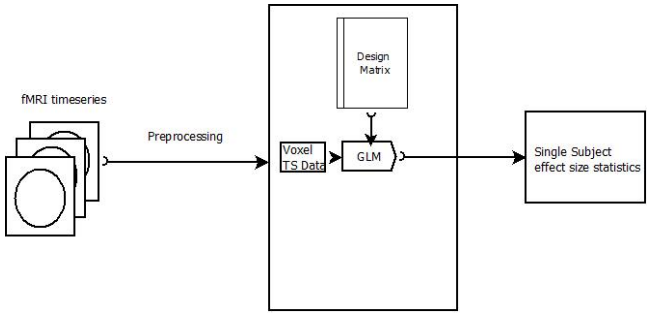

Figure 18: First level statistics, individual time series data is tested, voxel-wise in a general linear model with the design matrix, and results in single subject effect size statistics

6.1 Global Functional Connectivity

Global Functional Connectivity (GFC) is defined as the average pair-wise temporal Pearson correlation between one voxel and all other voxels. A mathematical trick for faster computation is calculating the correlation with the average of all standardised time courses [149].

6.2 PerAF

Percent Amplitude of Fluctuation (PerAF) [150] is a measure for RS-fMRI and calculates the percentage of BOLD fluctuations relative to the mean BOLD signal intensity for each time point and averages across the whole time series. The formula used to calculate the PerAF values is the following:

$$PerAF = \frac{1}{n} \sum \left| \frac{X_i - \mu}{\mu} \right| * 100\%$$

Here X_i stands for the intensity of a voxel at the i-th time-point, μ stands for the average of the time-series and n is the length of the time-series. In other words, it is the average scaled distance from the mean for each voxel and in per cent.

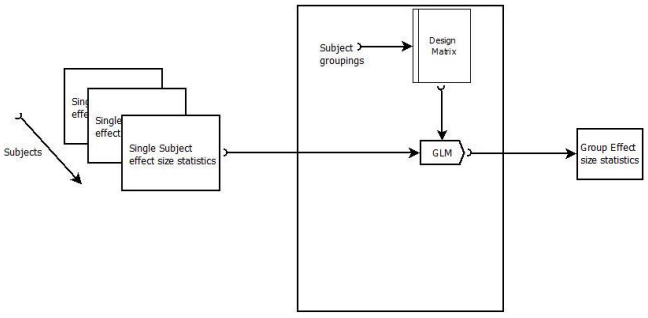

Figure 19: Second level statistics, the single subject effect size statistics are estimated with a general linear model, with a design matrix that contains the different subject groupings.

6.3 Regional Homogeneity

Regional Homogeneity (ReHo) is a similar approach to PerAF mentioned above, but instead of calculating local activity via fluctuations, the temporal similarity of neighbouring active regions, i.e., a localised form of connectivity, is exploited. Kendall's Coefficient of Concordance (KCC) for each voxel and its nearest neighbours is computed for this model [151]. This can be calculated as follows:

$$W = \frac{\sum((R_i)^2 - n \cdot (\bar{R})^2)}{1/12 \cdot K^2(n^3 - n)}$$

where W denotes KCC, n the number of ranks, K denotes the number of voxels taken into account during the calculation (number of neighbours plus the voxel itself), R_i is the sum rank of the i-th time point [152], and $\bar{R}$ is the average of these.

Since calculating local similarities automatically leads to a certain degree of smoothing, the model is usually calculated on unsmoothed data and afterwards smoothed to the desired overall degree.

7 Results

136 participants were recruited for the study, out of which 87 could be used for this analysis. The sample contained 37 male and 50 female participants with age mean and standard deviation of 25.34 ± 3.25 years.

43 participants were in the Chinese character group and 44 in the faces group. In the Chinese character group, 19 participants were male and 24 female, with age, mean and standard deviation of 25.30 ± 4.28 years.

	Age (± std) Male	Age (± std) Female	Number of Male/Female
Total	24.41/3.20	26.04/5.51	37/49
Chinese	24.10/2.69	26.25/5.07	19/24
Faces	24.72/3.72	25.84/5.99	18/25

Table 3: Demographic statistics

In the faces group, 18 male and 25 female participants took part with age mean and standard deviation of 25.38 ± 5.16 years. Further information can be collected from Table 3.

No data had to be excluded due to generally good to excellent image quality.

F-tests and t-tests were performed for all three resting-state models. An uncorrected threshold of $p \leq 0.001$ was used for peak-level significance.

There were no clusters which, corrected for multiple comparisons, reached a corrected $p \leq 0.05$, neither in the main effect of time nor in the interaction between group (Chinese character or faces) and time factors.

Thus, clusters of size larger than 30 voxels are reported on an exploratory basis. For variance stabilisation and to create unbound distributions, the GFC and ReHo maps were Fisher-z-transformed prior to testing. This transformation centres the data with a mean of 0 and a standard deviation of 1.

7.1 Global Functional Connectivity

An image of the averaged GFC signal from the first (baseline) measurement can be seen in image 20.

F-tests and t-tests were both performed to investigate the main effect of time on GFC among all participants, disregarding group assignment. No significant effect of time could be found.

Furthermore, we also found no significant interaction effects between time and groups when analysing for differences between groups over time.

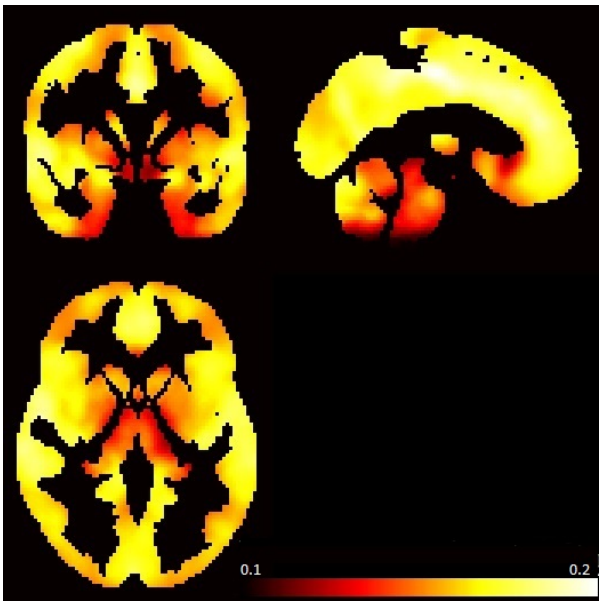

Figure 20: Mean global functional connectivity baseline measurement. The colour bar shows z-transformed correlation coefficients.

7.2 Percent Amplitude Fluctuation

An image of the averaged PerAF measure from the first (baseline) measurement can be seen in Figure 21

For the main effect of time, we found two clusters in the left postcentral and the left middle frontal gyrus. A more detailed overview of the regions with changes in PerAF can be found in Table 4.

The following images show the left postcentral gyrus and the left middle frontal gyrus (Figure 22, 23).

There were no clusters for the interaction effect between time and group.

7.3 Regional Homogeneity

An image of the averaged ReHo from the first (baseline) measurement can be seen in Figure 24.

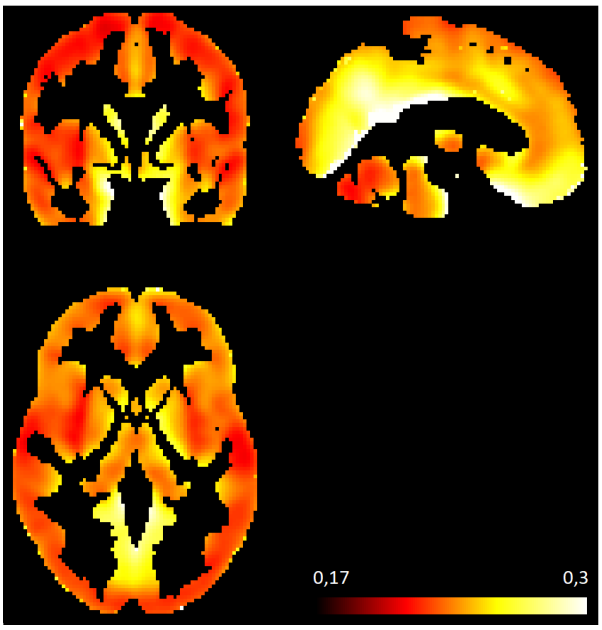

Figure 21: Mean percent amplitude fluctuation baseline measurement

For the main effect of time, we found an increase in ReHo in the left post-central gyrus and the right middle temporal gyrus. More details can be found in Table 5 and in Figure 25

As an interaction effect of time and groups, we found an increase in ReHo in the left frontal superior gyrus. More details can be found in Table 6 and Figure 26

Anatomical region	BA	Size [voxels]	MNI coordinates	$p_{uncorrected}$	DoC
L postcentral gyrus	3	126	-48;-26;56	1.53E-05	increase
L middle frontal gyrus	9	119	-24;32;34	4.03E-05	increase
L frontal superior medial gyrus	32	38	-4;28;36	1.19E-04	increase
L precentral gyrus	6	34	-32;-10;68	2.71E-05	increase
L superior frontal gyrus orbital part	11	31	-12;58;-20	5E-05	increase

Table 4: Percent amplitude fluctuation main effect of time. DoC: Direction of change L: left, R: right

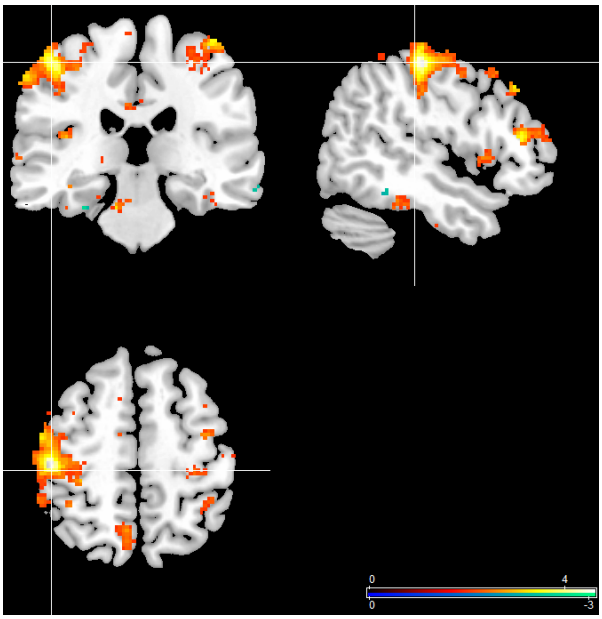

Figure 22: Percent amplitude fluctuation main effect of time shown at 48;-26;56 in the left postcentral gyrus

Anatomical region	BA	Size [voxels]	MNI coordinates	$p_{uncorrected}$	DoC
L postcentral gyrus	3	46	-46;-26;54	2.96E-05	increase
R middle temporal gyrus	21	36	66;-16;-8	7.24E-06	increase

Table 5: Regional homogeneity main effect of time DoC: Direction of change L: left, R: right

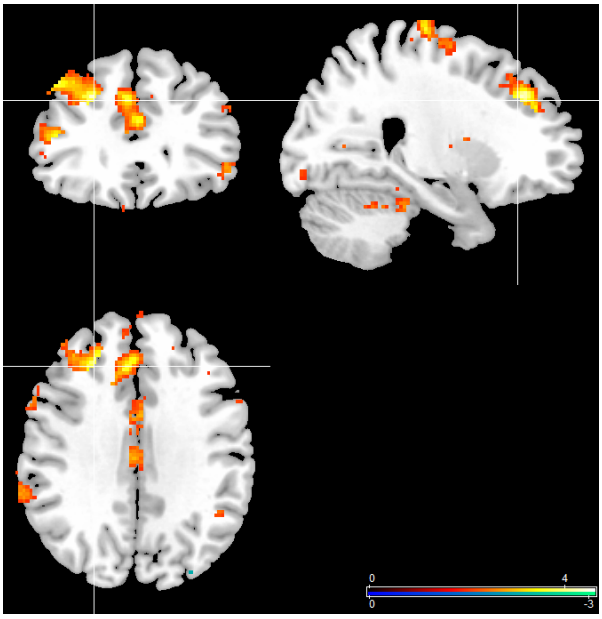

Figure 23: Percent amplitude fluctuation main effects of time shown at -24;32;34 in the left middle frontal gyrus

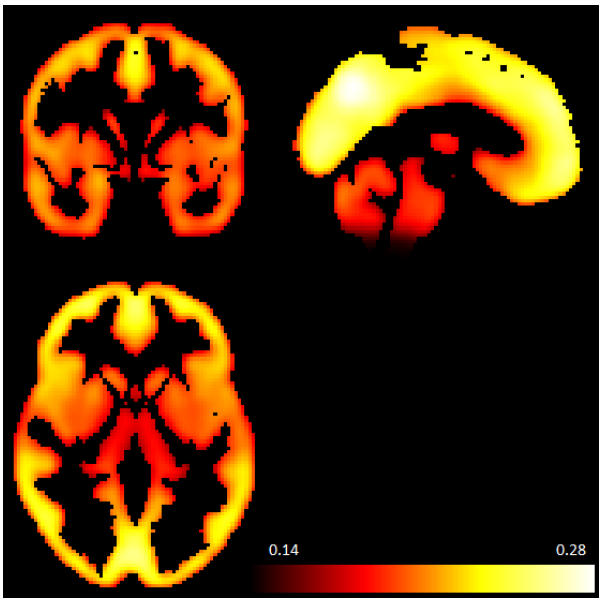

Figure 24: Mean regional homogeneity baseline measurement

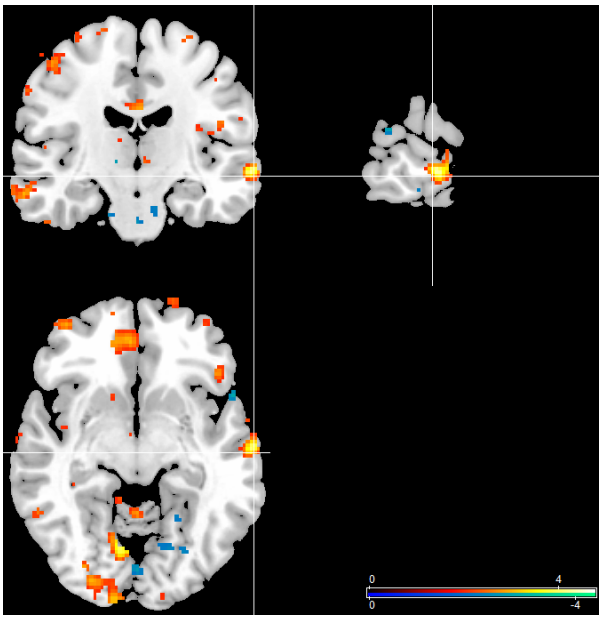

Figure 25: Regional homogeneity main effect of time at 66;-16;-8 in the right middle temporal gyrus

Anatomical region	BA	size [voxels]	MNI coordinates	$p_{uncorrected}$	DoC
L frontal superior gyrus	10	35	-24;64;4	2.43E-05	increase

Table 6: Regional homogeneity interaction between time and group DoC: Direction of change L: left, R: right

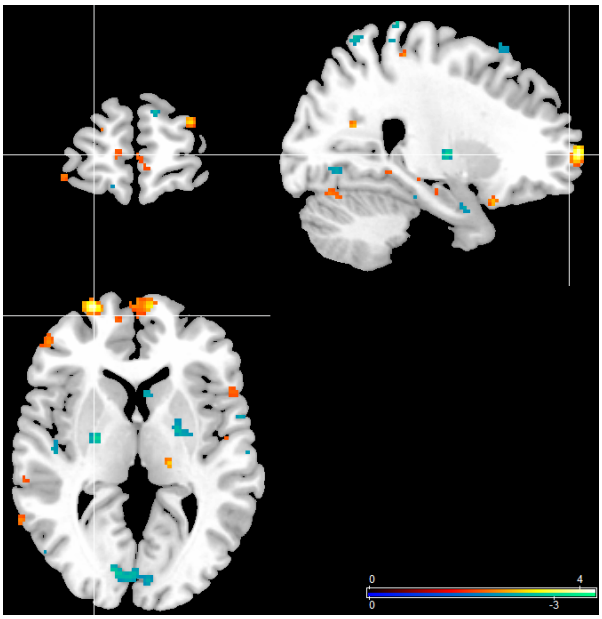

Figure 26: Regional homogeneity interaction effect of time and groups at -24;64;4 in the left frontal superior gyrus

8 Discussion

8.1 General

In this study, we aimed to investigate the effects of associative learning on different resting state metrics and to reveal whether any differentiation based on emotional connotations in the learning content can be detected.

Two rs-fMRI measurements were conducted, one in the beginning of the experiment as a baseline scan and one after three weeks of training to assess the differences.

8.2 GFC

There were no significant differences in GFC over the three-week period, which could be explained by not enough impact of the experiment to cause any change and the effects of individual differences averaging out.

Jolles et al. have conducted a study consisting of using a verbal strategy to memorise a sequence of objects [153]. After six weeks of working memory practice, young adults showed increased functional connectivity between the right middle frontal gyrus (MFG) and other regions of the frontoparietal network, including the paracingulate gyrus, anterior cingulate cortex, and bilateral superior frontal gyrus. In addition, they showed reduced functional connectivity between the medial PFC and the right posterior middle temporal gyrus.

Serra et al. [154] found that in amnestic mild cognitive impairment patients, ventral tegmental area (VTA) disconnection was predominantly found with the right parietal lobule (BA7), while in Alzheimer Dementia patients, it involved the posterior cingulate cortex (PCC), precuneus, bilateral parietal lobe, in other words, the posterior nodes of the default-mode network.

Cole and colleagues [155] reported that GFC in the lateral PFC and posterior parietal cortex were found to be more volatile in terms of GFC than other brain regions.

For the current study, this means that one would have expected GFC changes in at least some of the above-mentioned regions.

8.3 PerAF

Regarding the main effect of time on PerAF, areas around Brodmann's area (BA) 6 showed an increase after learning. BA6 is a non-primary motor area and is composed of the premotor cortex and the supplementary motor area [159], which does not immediately connect to the task of associative learning.

However, Taneka et al. [156] have found involvement of this region in updating spatial and verbal representations. Buschkuehl et al. conducted a working memory study and found more activation after training than before [157]. However, Dreyer et al. [158] and Leveroni et al. [159] have found the postcentral gyrus to be involved in the representation of faces in the macaque and in humans. Therefore, one might expect a PerAF increase in BA6 to appear as an interaction effect and not as a main effect, as seen here. Thus, we could hypothesise that this effect was due to the updating of verbal representations or an effect of learning rather than facial representations.

In BA9 (frontal association cortex, FrA, part of dorsolateral prefrontal cortex), PerAF was increased after three weeks of studying. This region is known to be involved in stimulus integration and associative memory [160]. Lai et al. [126] have shown that this region undergoes plastic changes in response to context-specific paired stimuli. Leube et al. conducted a study on the recognition of faces in humans and have also found activation in BA9/32 and attributed their findings to the recognition of faces. However, the authors have not controlled for recognition in general and also mention that the fusiform gyrus plays a role in the recognition of a wider scope of objects than solely faces [161]. Rodriguez et al. [162] have similarly found that recognition of faces caused activation in BA9. Achim et al. [163] found effects of working memory monitoring as well as post-retrieval monitoring in this area, which is used to evaluate the relevance of retrieved memory. Achim et al. [164], Nolde et al. [165], and others [166, 167] have also noted a primarily left-hemispheric activation in monitoring. Consequently, one would expect some change in activation patterns due to our experiment as well. Krieger-Redwood et al. [168] have found that the "left anterior IFG and pMTG work together to maintain a meaningful context that shapes ongoing semantic processing, and that this process is more strongly

taxed by word than picture associations." In our case, we had no differentiation in PerAF based on the type of stimuli. A word was paired with a Chinese character, potentially appearing as a picture to the participants, similarly as in the case of faces. Possibly the added text did not sufficiently affect PerAF, which might be the reason for no interaction effect between group and time, but rather a time effect only.

BA11, the superior frontal gyrus, orbital part, is involved in emotional processing [169]. The main effect of time showed an increase in PerAF in this region. From this evidence, one might expect to see changes here during the emotional faces task only. However, as Kringelbach et al. [170] point out, this area is also involved in the reward system, and as self-monitoring may have amounted to some feedback on the correct answers, this area would be relevant as well. Canessa et al. report that decision making and risk aversion in gambling activated the orbitofrontal cortex [171]. In the current study, an element of choice also exists, where the subjects similarly want to score higher and avoid losses.

PerAF and ReHo both showed an increase over time in the somatosensory gyrus (BA3) Thorensen et al. [172] and others [173, 174, 175] have also found activations in this area to similar stimuli as the one in the current study, but they do not discuss its meaning or possible relevance. Rodriguez et al. [162] have shown that correct recognition of faces activates this region but failing to recognise one does not. It can be concluded that the activation in this area is most probably related to object recognition rather than more specific facial recognition, but the literature on its meaning in the current context is insufficient to speculate any further.

8.4 ReHo

An increase in ReHo was found in the posterior division of the left middle temporal gyrus (BA21). The temporal lobe plays an essential role in processing both semantic and episodic memories [176, 177]. Activity in BA21, in particular, has been shown to be correlated with semantic processing efficiency [178] in language as well as in music [179]. Evidence from lesion studies points to damage to the medial temporal lobe resulting in "genuine forgetfulness" [177]. Clark et al. [174] found that a group of people doing working memory (WM) training had a more activated MTG during the dual 2-back (a moderately difficult WM test) compared to a simple dual 1-back test. However, it was not simply based on the difficulty of the tasks as it did not show up in the dual 3-back vs 1-back or 3-back vs 2-back versions. This may point to different strategies between trivial, simple, and difficult or overloaded memory tasks. In our study, the regional homogeneity of the MTG increased after associative learning, which confirms the results of Ranganath et al. [180], who found increased connectivity of the hippocampus and other surrounding structures, including the MTG, upon successful encoding of memories. Although in our experiment, the hippocampus showed no changes in ReHo, the MTG did. Rodriguez et al. [162] conducted an experiment regarding the recognition of faces and found that the MTG was active in both the correctly recognised and the "uncertainty about face presentation" conditions suggesting that this area is involved in unconscious and conscious processing. One might hypothesise that this area is required at least for a minimal amount of processing but not necessarily for the recognition of faces. In our experiment, changes in the MTG were not selectively found in the group viewing faces, but for all study participants, one might further hypothesise that its function is not necessarily limited to faces.

In the frontal superior gyrus, in BA10, an increase in ReHo for the group learning faces was found. Donaldson et al. [181] showed that this area is active in recognition as well as in the old-new distinction of semantic stimuli. BA10 is well known to be involved in retrieval success [182]. Rodriguez et al. [162] showed that the frontal superior gyrus was active when correctly recognising faces. As other parts known to be used in facial recognition (for instance, parts of the fusiform gyrus and the DLPFC) did not show higher ReHo, one should be cautious with interpreting this finding as a sign for processing of faces. It could be hypothesised that there is more semantic information in faces than in Chinese characters for people unable to make sense of them and that the recognition of this semantic information is what causes the effect to show up for the faces group.

8.5 Limitations

As the results are not FWE-corrected, this analysis needs to be seen as purely exploratory. It is possible that the emotional faces stimuli were not expressive, emotional or engaging enough to induce a significant difference. Memorising Chinese characters could have also been too easy, such that the varying difficulty of the learning tasks had a considerable influence. Furthermore, participants were requested but not required to learn every 24 hours, so large fluctuations in times between learning sessions are possible, inducing unwanted variance.

9 Conclusion

We provide potential pointers to increases in PerAF and ReHo, possibly as a consequence of associative learning for a three-week period (the main effect of time) in several parts of the cortex. Increases in PerAF were found in the somatosensory gyrus, precentral gyrus, and the frontal superior gyrus as a suspected

effect of object recognition and the effect of learning or updating verbal representations, and decision making and risk aversion, respectively. Furthermore, the middle frontal and frontal superior medial gyrus also showed increases that may be linked to effects of post-retrieval monitoring and its shaping of semantic processing.

ReHo showed an increase in the middle temporal gyrus, which could be explained as the unconscious processing of semantic stimuli. In addition, an increase in the group learning associations between emotional faces was found in the superior frontal gyrus orbital part, which points to faces having more semantic content than Chinese characters if the latter has no linguistic meaning to the observer. For future studies on associative memory, less complex material might be chosen in order to avoid contributions from different, difficult to control for sources. This might be particularly important for the comparison of different stimuli and their effects not only on memory but other neuroscientific and psychological aspects like affect or involvement of different brain regions.

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10 Appendix

10.1 Deutsche Zusammenfassung

In dieser interdisziplinären Masterarbeit wurden Ruhezustandsmessungen des Gehirns vor und nach assoziativem Lernen verglichen. Assoziatives Lernen moduliert die funktionelle Konnektivität und Aktivität des Gehirns, welche als Surrogate für Neuroplastizität genutzt werden können. Lernen erfordert Aufmerksamkeit, und um Effekte des Lernens zu testen, wird in unserer Studie das Gedächtnis verwendet. Einer der stärksten Modulatoren von Aufmerksamkeit und Gedächtnis sind Emotionen. Daher ist die Untersuchung des Zusammenhangs zwischen emotionalen Inhalten und lernen von großer Bedeutung. In dieser Studie untersuchten wir die globale funktionelle Konnektivität (GFC), die prozentuale Amplitudenfluktuation (PerAF) und die regionale Homogenität (ReHo) in gesunden Probanden mit Hilfe der funktionellen Magnetresonanztomographie im Ruhezustand (rs-fMRI). In einem Längsschnittdesign wurden die Versuchspersonen gebeten, drei Wochen lang emotionale oder nichtemotionale Assoziationen zu lernen. Rs-fMRI-Messungen wurden vor und nach dieser Zeitspanne durchgeführt.

Die Tests im Rahmen dieser Arbeit wurden auf explorativer Basis durchgeführt. Die GFC zeigte keine Veränderungen durch das assoziative Lernen, aber sowohl PerAF als auch ReHo nahmen in mehreren Hirnregionen zu. Ein Anstieg von PerAF wurde im somatosensorischen Gyrus, im präzentralen Gyrus und im frontalen superioren Gyrus als vermutete Auswirkung der Objekterkennung und als Effekte des Lernens und des Aktualisierens verbaler Repräsentationen bzw. der Entscheidungsfindung und Risikoaversion im Sinne falscher Antworten bei der Abfrage festgestellt. Darüber hinaus wiesen im mittleren frontalen und im

frontalen superioren Gyrus ebenfalls Zunahmen auf, die mit Effekten des Post-Abruf-Monitorings erklärt werden können.

Bei ReHo zeigten der linke postzentrale Gyrus und der rechte mittlere temporale Gyrus einen Anstieg nach assoziativem Lernen. Der linke Gyrus frontalis superior zeigte bei ReHo eine Differenzierung, die auf der Art der Stimuli beruhte.

Wir haben Einblicke und mögliche Hypothesen für die weitere Erforschung der Auswirkungen von Lernen und Abrufen auf rs-fMRI-Messungen geliefert.