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"The role of obesity on the structural integrity of the human hippocampus"

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1. Introduction

"What do you mean, a child doesn't get a hot meal in Austria? [...] Do you know what the cheapest hot meal in Austria is? It's not healthy, but it's cheap. [...] A hamburger at McDonald's, 1.40 euros."

Karl Nehammer (Kurier.At, 2023)

Around the time this thesis was written, the Austrian Chancellor Nehammer was exposed for proposing unconventional ideas to help parents bring a warm meal to the table of their families. His proposition: If one can't afford other food, one should opt for McDonald's meals.
Nehammer rightly states that this would not be considered healthy. Obesity has been linked to a wide range of health complications such as cardiovascular diseases, respiratory diseases, cancers, Metabolic syndrome, stroke, Type 2 diabetes, non-alcoholic fatty liver disease, osteoarthritis and other musculoskeletal complications. Obesity has also been linked to depression and neuropathy (WHO, 2022).
From a cognitive standpoint, the question arises, of how neurological function might be impacted by obesity. How do the metabolic changes manifest neurologically? What would these changes imply for cognitive functioning? What cognitive implications would it have to rely on Nehammer's proposed diet? Are there other factors influencing cognitive function that have to be addressed? Do lifestyle factors impact neuronal health more than genetic components?
In an attempt to better understand the potential impact of obesity on cognitive function, this master thesis delves into the influence of specific biological parameters and inflammatory markers on hippocampal structural integrity.

1.1 The hippocampus

The hippocampus is a common target of investigation in cognitive science for its crucial role in learning and memory, which has been described since at least 1957 (Scoville and Milner, 1957). Since then, the role of the hippocampus in memory and learning has been further understood to be linked to physiological memory formation, the stabilization of long-term memories in the process of system consolidation and the redistribution of memory representations from hippocampal short-term storage to neocortical long-term storage (Frankland & Bontempi, 2005; O'Reilly and McClelland, 1995). Other functions of the hippocampus are linked to processes that are related to pattern separation and pattern completion, as well as the regulation of emotion, fear, anxiety, and stress (Bartsch &Wulff, 2015). Research focussing on the Hippocampus led to the discovery of key concepts, that shaped the field of cognitive science as we know it, such as: Hebbian Learning (Hebb, 1949/2002), long-term potentiation (Bliss & Lomo, 1973), the place cell system (O'Keefe & Dostrovsky, 1970) as well as adult neurogenesis (Altman & Das, 1965). Those have first been observed in the Hippocampus (Bartsch, 2012; Taupine, 2007).

The hippocampus has been observed to be altered by neurological diseases such as Alzheimer's, limbic encephalitis, neurodevelopmental disorders, schizophrenia or depression (Bartsch, 2012; Wenbo et al., 2020).

One of the factors for this to happen is attributed to the vulnerability associated with neuroplasticity that is characteristic of the hippocampus (Bartsch & Wulff, 2015). This makes the hippocampus a region of special interest, firstly because adult neurogenesis and neuroplasticity to the extent that they can be observed in the hippocampus are rare (Kempermann et al., 2015; Bartsch & Wulff, 2015), and secondly because effects of lifestyle choices can be observed, for example in intervention studies.

Besides neuroplasticity, the hippocampus is known for its circuitry, anatomical projections as well as neurotransmitter components, which potentially contribute to its prominent role in neuropsychiatric disorders such as ischemia, epilepsy, chronic stress as well as neurodegeneration and ageing. All of these are reflected in alterations of the hippocampal structure, function and performance in cognitive tasks (Bartsch & Wulff, 2015).

However, it is not decided if those alterations are part of a cause or an effect of neuropsychiatric diseases (Bartsch & Wulff, 2015).

The hippocampus is critically involved in:

- learning and memory
- physiological memory formation
- stabilization of long-term memories
- redistribution of memory representations from hippocampal short-term storage to neocortical long-term storage
- Pattern separation
- Pattern completion
- Spatial learning

It is, among other structures, involved in:

- regulation of emotion, fear, anxiety, and stress
- Contextual Memory
- decision-making
- imagination and creativity

In effect, healthy hippocampal functions form the basis for a self-sufficient, independent and fulfilling life. Being able to orient oneself as well as having unimpaired memory function is vital not only for an individual’s ability to live independently but also for an individual’s self-perception and identity.

The hippocampus significantly contributes to the general quality of life; preserving normal function means improving the quality of life while ageing.

1.1.1 Anatomical organization of the hippocampal formation and connectivity with the trisynaptic circuit

The hippocampus can be divided into dorsal, intermediate and ventral parts. It has a longitudinal axis that extends in a curve resembling a C (Stuchlik et al., 2022). The hippocampal formation encompasses the dentate gyrus, hippocampus, subiculum, presubiculum, parasubiculum, and entorhinal cortex (Lavenex, 2012). It is embedded within the medial temporal lobe (Knierim, 2015; Lavenex, 2012). The hippocampus itself comprises the dentate gyrus (DG) and the Cornu Ammonis (CA). The Cornu Ammonis or CA region is divided into four subfields, CA1, CA2, CA3 and CA4 (Taupin, 2007). The CA and the DG both have multiple layers: the principal cell layer, the granule and the pyramidal cell layers (Knierim, 2015; Taupin, 2007).

The hippocampus receives most of its synaptic input from cells within the formation. CA2 and CA3 are well connected via their axons, while CA1 receives strong inputs from CA2 and CA3 (Lavenex, 2012).
The hippocampus is known for its anatomic connectivity, including the trisynaptic loop. The first major connection is from the entorhinal cortex, which provides the major cortical input to the hippocampus, via the perforant path to the dentate gyrus (DG) region

Secondly, the information is projected from the DG to the CA3 regions via the mossy fibre pathway. From there the CA3 region projects to the CA1 via the Schaffer Collateral pathway. Completing the loop, CA1 projects back to the entorhinal cortex (Knierim, 2015).

This circuitry is complimented by another associative network, that interconnects the largest area in the hippocampus, the CA3.

The CA3 forms the largest tract for information flow and has extensive interconnections between the principal cells, which form a circulating collateral fibre system (Gilbert and Brushfield, 2009). The resulting associative network is composed of axon collateral branches of CA3 pyramidal cells, that connect directly via synapses with the apical dendrites of CA3 pyramidal cells in other regions (Knieriem 2016). The CA3 receives projections from the DG, the EC and other CA3 neurons (Yassa and Stark, 2011). The interconnection of the CA3 might serve to support memory function by connecting multiple CA3 neurons, each representing different aspects of a memory. The CA3 has also been proposed to play a vital role in pattern separation and spatial memory (Gilbert and Brushfield, 2010). It receives projections from subcortical areas, and projects to the lateral septal nucleus (Lavenex, 2012).

The dentate Gyrus (DG) is involved in learning and memory and is one of the few sites, where adult neurogenesis can be observed (Stuchlik et al., 2022; Clelland et al. 2009; Lavenex, 2012). In the molecular layer, mainly dendrites of the dentate granule cells are found, as well as fibres of the perforant path. Those fibres originate in the entorhinal cortex. Densely packed granule cells enclose and form the polymorphic cell layer (Stuchlik et al., 2022; Lavenex, 2012). Those are the

only cells originating in the DG, that project to other areas (namely the CA3) (Lavenex, 2012). The DG receives projections from the presubiculum and parasubiculum, which then reach the molecular layer and end up in entorhinal cortex projections. Adding to that, projections from subcortical areas also reach the DG (Lavenex, 2012). At the hillus of the DG the **CA4** region can be found, it consists of pyramidal neurons (Taupin, 2007). At the same time, the CA4 can also be described as the most superficial cells of the CA3 (Cauhan et al., 2021) (see Fig. 1).

The CA1 area is characterized by receiving projections, such as projections from the CA3 (via the Schaffer collaterals) EC and cortical areas such as perirhinal and parahippocampal cortices, contrasting that, the CA1 is interconnected to a lesser degree (Lavenex, 2012). It is mainly formed by densely packed large pyramidal neurons, whose involvement is paramount for long-term memory as well as related behaviour and spatial tasks. Its major role is in transferring excitatory information via the deep layers of the EC or subiculum, it is a key output node of the whole hippocampal memory circuit (Cenquizca and Swanson, 2007). The CA1 has also been proposed to play a major role in novelty detection, input comparison, and enrichment of hippocampal output (Stuchlik et al. 2022).

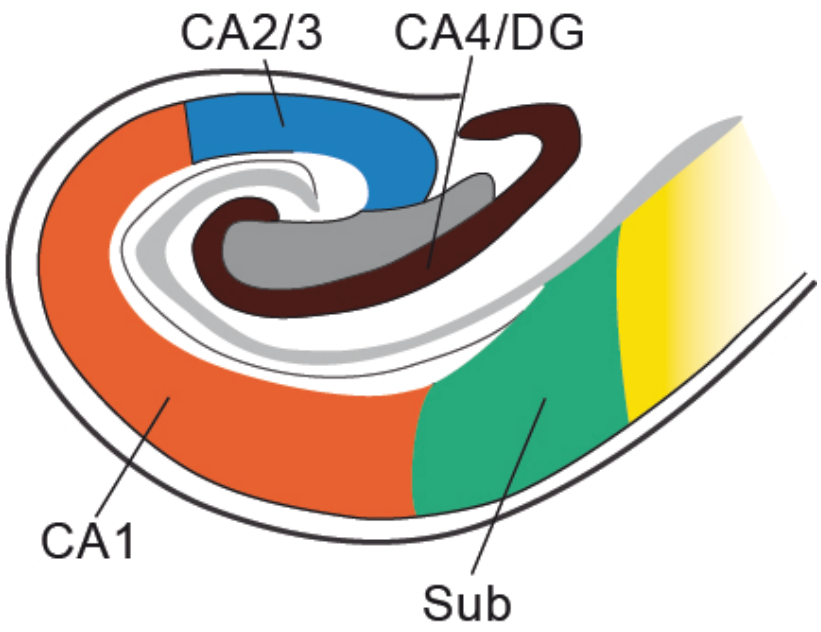

Fig 1: coloured hippocampal subfields in schematic illustration of the hippocampus in coronal view. Picture courtesy of Prof. Bartsch.

The entorhinal cortex (EC) projects to the CA3, CA1 and the DG. The CA3 is involved in a feedback loop to the DG via the excitatory mossy cells of the dentate hilus (Stuchlik et al., 2022). Lavenex also notes projections to CA2 (Lavenex, 2012).

The CA2 has recently been linked to its own functions, such as social recognition memory (Tzakis and Holahan, 2018), instead of being a relay unit/transition zone. Similarly to the CA3, the CA2 region is interconnected but also receives projections from EC, as well as projections from the posterior hypothalamus (Lavenex, 2012).

The **subiculum** consists of two layers: the molecular layer (receiving EC projections) pyramidal cell layer, (receiving CA1 projections). The subiculum in turn projects back to the EC as well as the presubiculum and the parasubiculum the lateral septal nucleus, the nucleus accumbens, and the mammillary nuclei. These connections constitute critical pathways for memory (Lavenex, 2012).

The **Presubiculum** has a cell-free superficial layer, as well as a second layer composed of small pyramidal cells. The presubiculum receives prominent inputs from the subiculum, as well as a direct projection from the anterior thalamic nuclei. Several other subcortical areas, including the

septum, supra mammillary nucleus, raphe nuclei, and locus coeruleus project to the presubiculum. The subiculum projects to the EC, contralateral caudal entorhinal cortex, thalamus and DG. It is interconnected with the retrosplenial cortex and is intrinsically connected (Lavenex, 2012).

1.1.2 metabolic influences on the hippocampus, hippocampal vulnerability

It has been well established, that the hippocampus has an increased vulnerability to external factors (Kempermann et al., 2015; Bartsch et al., 2015).

Those neurons, that have high energy needs are especially vulnerable to diseases such as Alzheimer's. These cells can be found in the CA1 region and the EC. To generate energy, typically aerobic metabolism and oxidative phosphorylation are relied upon. Those mechanisms can be influenced by external factors, for example, oxidative phosphorylation has been observed to be inhibited by smoking (Yang, 2007; Durazzo et al., 2014).

Some brain areas use aerobic glycolysis especially when high synaptic activity is needed (Goyal et al., 2014; Vaishnavi et al., 2010; Magistretti, 2018). In all cases, impairment or changes to energy production can negatively impact synaptic transmission and therefore neuron health as well as cognition (Michaelis, 2012).

Modifiable external factors can have a considerable effect on neuronal health. One example of this is smoking. Smoking Cigarettes has been observed to correlate with hippocampal atrophy (Debette et al. 2011) and has been proposed to be a risk factor in developing Alzheimer’s disease. Estimates of risk vary, depending on the type of study and the affiliation (Cataldo et al., 2010). Ott et al. estimate in their population-based study, that smoking led to a doubling of the risk of dementia and Alzheimer's disease. As to the cause of this effect a possible lead compound in cigarettes was named (Wallin et al, 2018) as well as cerebral oxidative stress (Durazzo et al., 2014). Oxidative stress can be induced by other factors such as high cholesterol as well (Stranahan et al., 2011).
Another important modifiable factor is diet. Maintaining a healthy weight comes with neurological benefits. Obesity in turn has been shown to negatively influence cognitive function (Cournot et al., 2006; Lee & Yau, 2020; Mattson, 2019). Obesity comes with metabolic alterations, such as hypertension, high inflammatory markers, high blood lipids or increased glucose and fasting insulin levels. Glucocorticoid receptor activation and impaired insulin and leptin signalling have been in turn linked to cognitive decline (Stranahan et al., 2008; Stranahan and Mattson, 2011), as well as obesity-induced neuroinflammation (Yang and Song, 2013; Erion et al., 2014).

A bidirectional influence has been assumed, a lifestyle associated with obesity can lead to reduced adaptive cellular stress responses. This in turn can lead to oxidative stress and inflammatory pathways, that negatively impact neurogenesis and lead to an increase in neurodegeneration (Fontan-Lozano et al., 2007; Stranahan, 2015, Erion et al.,2014).

Obesity has been observed to reduce brain-derived neurotrophic factor (Han et al., 2013). BDNF is a protein, that plays a central role in brain development, physiology, and pathology (Binder and Scharfman, 2004). In mice with type 2 diabetes, obesity in combination with insulin resistance leads to decreased BNDF in the Hippocampus (Dinel et al., 2011; Stranahan et al., 2009). This could be because of Increased synthesis of neurotrophic factors in obese individuals (Stranahan et al., 2009). Rodent studies have provided data on brain volume in overfed sedentary rodents to be reduced in volume, observable neurogenesis and synaptic density. Excessively eating mice showed impairment in spatial learning and recall (Strahanan et al., 2008).

Lifestyle changes can have a widely positive impact: Caloric restriction and exercise have been shown to positively impact neuroprotection, synaptic plasticity and neurogenesis by inducing adaptive cellular stress responses (Stranahan & Mattson, 2011). The switching from liver-derived glucose to ketogenic states stimulates neural signalling, which in turn positively affects cognition. In ketogenic states, fatty acids from adipose cells as well as ketones are used as energy supply for muscle cells and neurons (Mattson, 2018). Such switching can be initiated for example by intermittent fasting or running (Martin et al., 2006). Intermitted fasting in particular has been observed to increase neuroplasticity and cognitive function, as well as correlating with increased regional grey matter volumes (Mattson, 2019) while abdominal obesity in individuals with type 2 diabetes has been associated with lower total grey matter volume (Climie et.al, 2015).

Another marker derived from blood serum, that is of special interest for this study is Lipoprotein (a). Lipoprotein (a) (Lp(a)) is a macromolecular complex, that consists of polypeptides and lipids. It is made up of one low-density lipoprotein (LDL) bound to the glycoprotein apolipoprotein (a) (Kritharides et al., 2017). Importantly, lipoprotein (a) is not considered an external factor, since it is genetically determined and is not modifiable by lifestyle changes (Urakami et al. 2000, Ugovšek and Šebeštjen, 2021, Orsó and Schmitz, 2017; Mooser et al., 2000; Kritharides et al., 2017; Li et al., 2021; Pasławska and Tomasik, 2023, Röhr et al., 2020; Moriarty et al., 2016).

Lp (a) is involved in wound healing and promotes tissue repair as well as vascular remodelling (Pasławska and Tomasik, 2023; Orsó and Schmitz, 2017; Ugovšek and Šebeštjen, 2021). However, it is considered pro-atherosclerotic, pro-inflammatory, and pro-thrombotic. This is due to the fact that Lipoprotein (a) can build up in the arterial intima, leading to atherosclerotic plaque formation, making it proatherogenic (Pasławska and Tomasik, 2023; Orsó and Schmitz, 2017; Ugovšek and Šebeštjen, 2021; Scanu et al., 1991). The pro-inflammatory effect is linked to the susceptibility of Lipoprotein (a) to oxidative modifications. Its thrombogenic properties are due to its homology with plasminogen, which is partly responsible for its procoagulant properties (Hajjar et al. 1989). This can lead to intravascular thrombosis. (Ugovšek and Šebeštjen, 2021) Lipoprotein (a) is most commonly associated with cerebrovascular peripheral artery and cerebrovascular diseases (Urakami et al. 2000; Kunutsor et al., 2016; Sarti et al. 2001; Solfrizzi et al., 2002). Additionally, Lipoprotein (a) has been proposed as a risk factor for vascular dementia.

Lipoprotein (a) is of special interest, since an interplay of apoE and Lipoprotein (a) can be assumed. Some Apolipoprotein E (apoE) forms (namely ε4) have been identified as the main genetic determinant for developing Alzheimer disease (Liu et al. , 2013; Raulin et al, 2022; Corder et al. 1993). ApoE is primarily produced and secreted by the liver, brain, skin and macrophages (kunutsor et al., 2016). It is a polymorphic glycoprotein that plays an important role in the clearance of lipoproteins at the Low-density lipoprotein receptors as well as protein-1 (LRP1) and syndecan-1 (SDC1) (Moriarty et al. 2016). There are three isoforms of apoE ε2, ε3 and ε4. These differ in binding affinity for low-density lipoprotein receptors LRP1 and SDC1. The different types can be distinguished by their difference in single amino acid substitutions.

Lipoprotein (a) is proposed to have different effects and is potentially influenced by apoE polymorphic alleles. Lipoprotein concentrations are reported to be generally lower in those individuals with ε2 genotypes compared to ε4 genotypes (Moriarty et al., 2016; Kritharides et al. 2017).

1.1.3 The hippocampus in memory learning, cognition, emotion

The hippocampus has functional importance in multiple processes and functions linked to cognition. Such as attention and novelty (Bartsch, 2012), emotion (Stuchlik et al. 2022; Papez, 1937; Bigbee, 2011), spatial learning (O'Keefe and Nadel, 1978; Maguire et al., 2000), navigation (Maguire et al., 2000; Redish and Touretztky, 1998), learning (McClelland et al.,1995), memory (Bartsch, 2012; Bigbee, 2011), sensory information processing (Stuchlik et al., 2022), and motor function (Burman, 2019, Mukamel et al., 2010)

It is part of the Papez circuit, a circuitry that connects limbic structures involving the hippocampus, the Fornix, Mammillary bodies, the anterior thalamus, the cingulum and the parahippocampal gyrus (Bigbee, 2011; Bartsch, 2012; Papez, 1937).

Based on the Papez circuit, Maclean introduced a model of the visceral brain. The visceral brain includes the limbic lobe, as well as its projections to the septum, amygdala and hypothalamus. Both the Papez circuit and the visceral brain are concepts employed to understand emotion, emotion-based actions and experience (Bartsch, 2012; MacLean, 1952).

1.1.3.1 Memory

“Memory, my dear Cecily, is the diary that we all carry about with us.“
-Oscar Wilde (Wilde,1895)

As early as John Locke, philosophers have been aware of the importance of memory for self-identity (Locke, 1689/1997). Locke hypothesized that to form an identity one has to rely on continuity, which is dependent on memory. While those ideas have been critiqued and expanded ever since their postulation, their existence shows that humans have had an interest in memory for centuries.

Nowadays, Dementia has been identified as the seventh leading cause of death, as well as a leading cause of disability and dependency among older people globally by the WHO (WHO, 2023). This has long made its way to the mainstream: movies like “Honig im Kopf” (eng. Head Full of Honey) by German actor and director Til Schweiger tried to tackle the topic of Alzheimer’s disease and achieved a revenue of US$63 million in Germany alone (Blaney, 2015).

Other examples include games for supposed “brain training” focusing among others on improving memory function, selling up to 19.01 million copies (Nintendo, 2023). The game: “Brain Age: Train Your Brain in Minutes a Day!“, known as “Dr. Kawashima's Brain Training: How Old Is Your Brain?”, made it to the fourth best-selling game by Nintendo in the company’s history.

But what constitutes memory? What kinds of memory are there, and how is memory formed?

The understanding of memory has been subject to changes. While the storage bias largely influenced the discourse until the 1960s, the understanding of memory has changed to equally emphasise both storage and retrieval functions (Tulving, 1992). Memory relies on different circuits, with different tasks, and the activation of modules that each have their neural basis, as well as different properties and dynamics (Ferbinteanu, 2019). Key to this discovery were dissociation studies, such as the prominent case of patient H.M. (Scoville & Milner, 1957). Studying cases, where damage was confined to single brain areas, led to the observation that the nature of memory impairment corresponds to specific sites. In an attempt to provide schemas for understanding memory processing, Piefke and Fink defined 5 stages of information processing. First, registration, followed by encoding, third consolidation, saving and retrieval (Piefke & Fink, 2013).

Sensory pathways provide episodic and semantic information, that in the first step are registered (Piefke & Markowitsch, 2007). Both kinds of information might preliminarily be saved online in cortical association areas. The information is then transferred to the limbic system, where encoding and consolidation take place, which involves the hippocampus. While the areas involved in the

basolateral limbic circuitry are involved in affective and emotional information processing, the hippocampus, as part of the papez-circuitry, is more involved in cognitive processing.

The step of encoding encapsulates the activation of internal representations in cortical systems. Depending on the activated representations, representations in higher-order contextual systems (such as the Hippocampus) are activated. Their spatial and contextual attributes are encoded and indexed so that the entities that made up the event can be retrieved in the future (Nadel et al., 2012).

The term consolidation is used to refer to two different concepts. There is consolidation on a cellular/synaptic level „synaptic consolidation“ and „systems consolidation“. The former refers to those mechanisms that stabilize synaptic plasticity minutes to hours after learning (Dudai, 2004). Systems consolidation describes changes occurring during long-term memory in brain systems to accommodate reorganization over months or years (Squire and Alvarez 1995; Bolhuis, 2000; Dudai, 2012; Squire et al., 2015).

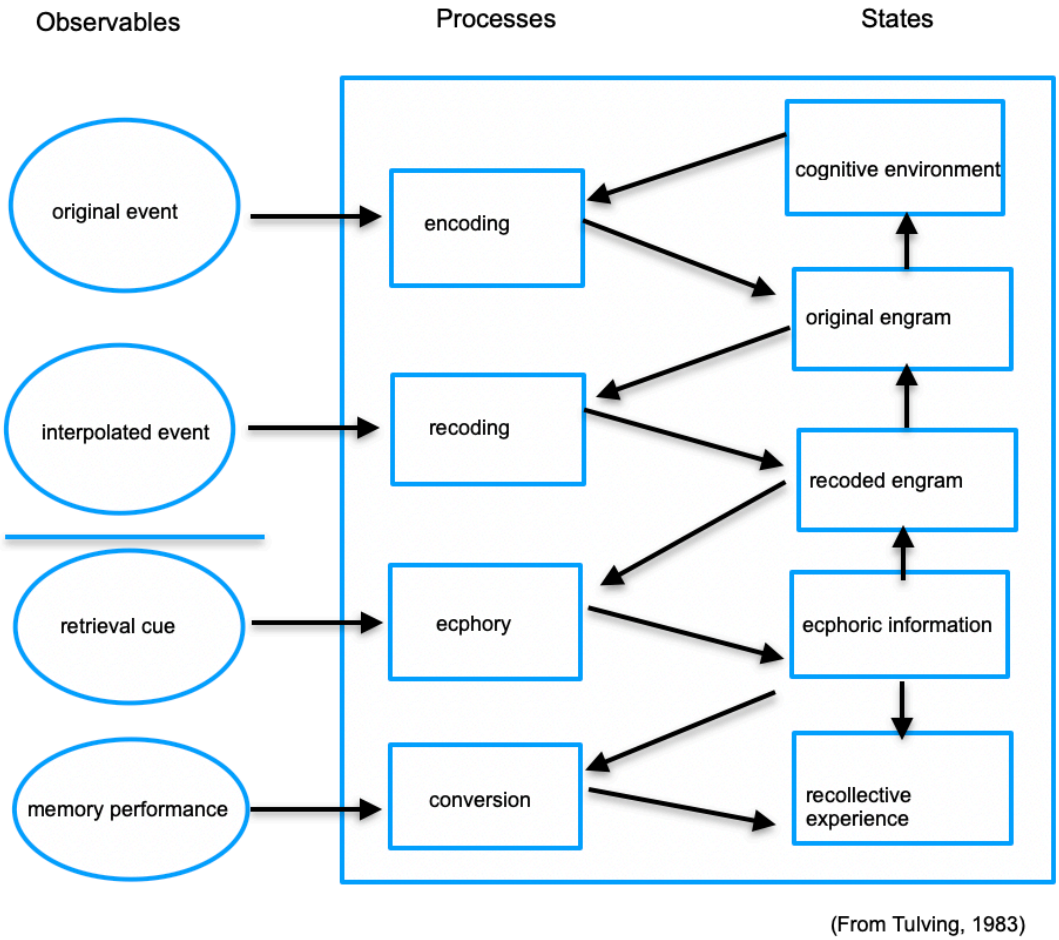

Fig. 2: schematic figure of GAPS as described by Tulving, 1992, showing the relationship betweenn different processes and stages as well as observables.

Expanding on the stages of encoding, storage and retrieval, Tulving presents the concepts of General abstract processing systems (GAPS) (Fig. 2) that show the processes and interrelations between the stages and the observables that can be discerned in tests. For that, hypothetical processes and hypothetical states (products of processes) are assumed. The previously

introduced concept of encoding is complemented with engram, ecphory and ecphoric information. The internal states or representations are called engrams in this system. Ecphory refers to the process that converts the engram, combining it with the retrieval cue to get ecphoric information (Tulving, 1992). Importantly, GAPS points out, that study/test paradigms can only capture observable states, neglecting the fact, that internal states as well as non-observable processes can pose a source for change, errors or factors that lead to discrepancies in input information and memory. Omitting these factors oversimplifies memory and, as Tulving puts it: “necessarily result[s] in an incomplete understanding of memory“ (Tulving, 1992). Tulving aimed to make tangible, the factors and variables that were known to determine memory and its manifestations in cognition and behaviour (Tulving,1983).

To achieve this, multiple different memory systems as well as categories have been proposed in the past. Categories overlap, lines are blurred and the overall benefits of such divisions are debated, critics are pointing out that a focus on classification could shift the attention from the delicate interplay of different systems that constitute forms of memory (Ferbinteanu, 2019). What classifies as memory is also up for debate since it can be hard to distinguish between learning and memorizing, particularly in sensitization, habituation and priming contexts. Instead of pairwise classifications of memory such as short and long-term memory, Tulving proposes five broad systems: procedural memory, perceptual priming, short-term memory, semantic memory and

	System	Related functions
1	Procedural memory	Skills; simple conditioning
2	Perceptual representation system	Perceptual priming of identification of objects
3	Short term memory	Highly accessible information from recent cognitive inputs
4	Semantic memory	General knowlege oft he world
5	Episodic memory	Conscious recollection oft he personal past

Table 1: overview of human memory systems as decribed by Tulving (Tulving, 1992)

episodic memory. An overview of these human memory systems by 2 is given in Table 1 (Tulving, 1992). Tulving notes, that memory forms listed in this table (Table 1), can depend on each other, with procedural memory for example, forming the basis for episodic memory, while not being dependent on episodic memory itself (Tulving 1992). Tulving’s terminology as well as the hierarchy lays a foundation to understand how information is processed over time and how different forms of memory interact.

Another model by Atkinson and Shiffrin differentiates between long- and short-term storage. In short-term storage, sensory information is stored for a few hundred milliseconds. Only if attention is attributed to the sensory information, does it move to short-term memory. Again, information

(five to 9 items) is stored there for up to 30 seconds and progresses to long-term memory storage, after being filtered again (Atkinson & Shiffrin 1968; Piefke & Fink 2013).

This model was expanded by Baddeley and Hitch (2000), who assumed the working memory to be an active manipulator of information. Working memory function can impact the following behaviour by influencing logical thinking, problem-solving, and integration of visuospatial information. Key to this are the phonological loop, the visuospatial sketchbook, the episodic buffer, and the central executive. These are known as the 4 components that make up working memory (Baddeley and Hitch, 2000) (Fig 3 & Fig. 4).

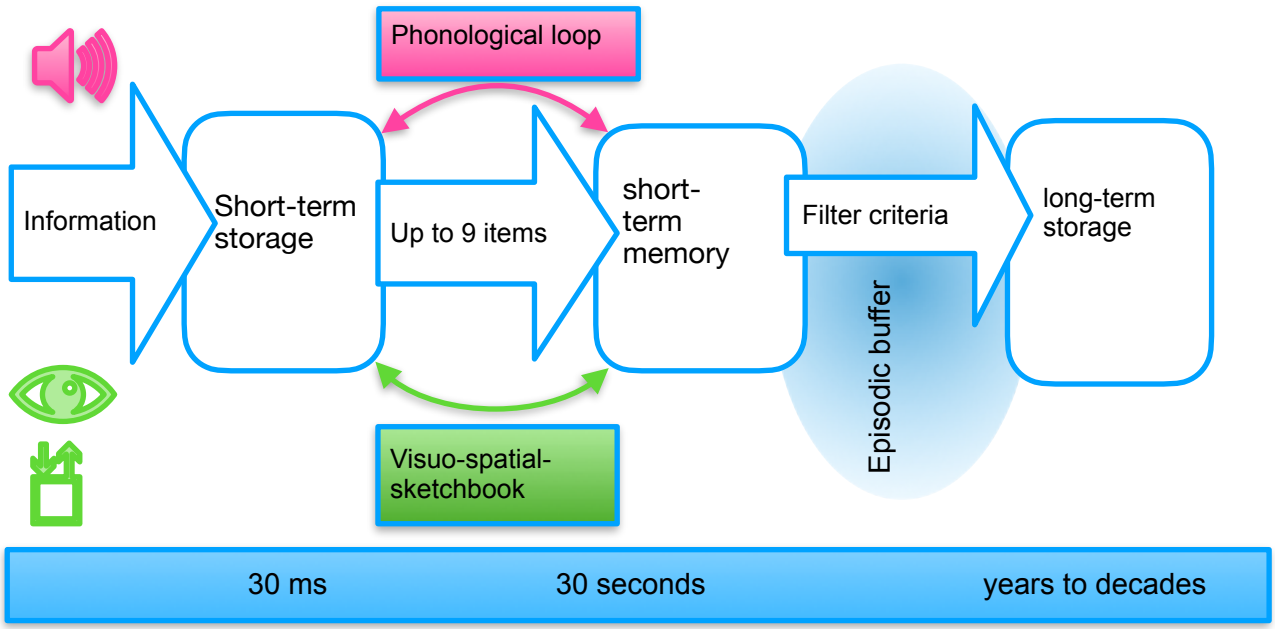

Fig.3: model of memory modified after Baddeley and Hitch (2000) as well as Atkinson and Schiffrin, 1968, incorporating time frames, phonological loop, visuospatial sketchbook and the episodic buffer.

The phonological loop works by first saving auditive information for a short time and repeating this information out loud. During the articulation, the information reenters the loop, so that the information can be stored longer (due to reentering) than usual. The visuospatial sketchbook is the visual pendant to this. The episodic buffer allows for information from the loops and long-term memory to be integrated. The central executive monitors attention and supervises and supports the other components of working memory (Fig. 3).

Additionally, to a time-dependent classification, different memory domains can be distinguished. The different domains oftentimes correspond to different parts of the brain. For example, priming and perceptual learning are dependent on the primary and associative neocortex (Piefke u. Fink 2013). Not only working memory but also long-term memory possesses multiple subdivisions: firstly, it can be subdivided into declarative and implicit memory. The first one being accessible and the second one not being accessible to conscious recollection. Implicit memory covers procedural memory, priming and perceptual learning (Fig. 4).

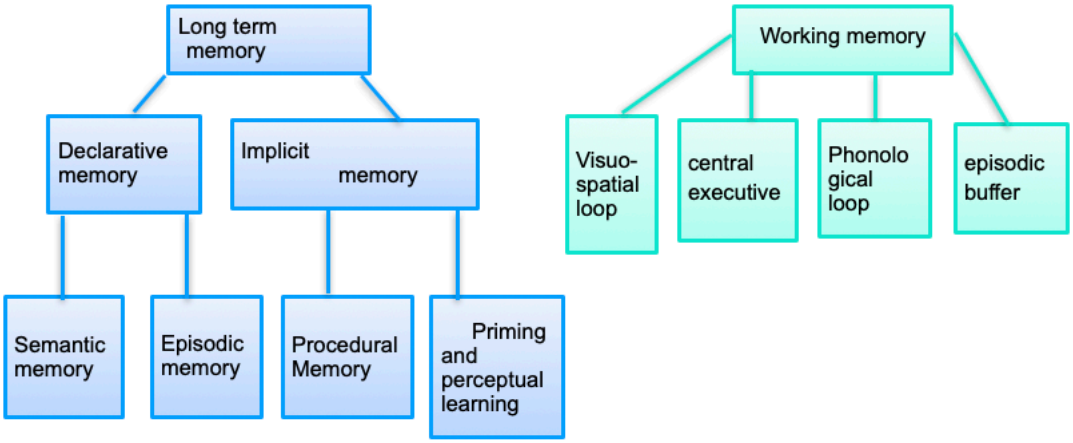

Fig.4: Schematic figure illustrating organisation of memory, differenciating working and long term meory as well as sub-categories

skills and habits constitute a part of procedural memory, examples would be: riding a bike or playing an instrument. These functions can be observed in the striatum, cerebellum and motor cortex. (Markovitsch & Staniloiu, 2015; Eichenbaum, 2002; Ferbiteanu, 2019)

Priming and perceptual memory are key to forming a sense of familiarity between objects and remembering key features These functions are related to the primary and association neocortex (Ferbiteanu, 2019)). Complementing implicit memory is declarative memory.

Declarative memory is conscious. It can be divided into semantic and episodic memory (Tulving, 1992) but also entrails autobiographical memory (Fig.3) (Ferbiteanu, 2019). Semantic memory is localised in the lateral and anterior temporal cortex and prefrontal cortex (Ferbiteanu, 2019). It entrails all kinds of rules and systems that help to understand how the world around the individual works.

Episodic memory covers explicit events in the past, such as one's first job, or last birthday party. It is at the intersection of subjective time, autonoetic consciousness and the self experiencing the self. The **hippocampus,** medial temporal lobe and neocortex make up the site where episodic memory functions can be localised (Piefke u. Fink 2013).

Focusing on the hippocampus, one can observe its key involvement in anterograde and partial involvement in retrograde memory.

For retrograde, memory retrieval functions are vital. Depending on the model of memory consolidation, the hippocampus is given varying importance in this.

The classical model postulates, that the hippocampus is only temporarily involved when declarative memory is consoled and information is transferred to neocortical areas (Piefke & Fink, 2013). After information is transferred to neocortical areas, the hippocampus is no longer involved when this information is retrieved. This explains why earlier episodic memory is oftentimes spared when damage to the hippocampus occurs (McClelland, 1995).

The multiple trace theory (Nadel, Moscovitch, 1997) however, sees the reason for that in cerebral representations that form for years and decades between the medial temporal lobe and the neocortex. The hippocampus would still be involved in the retrieval of episodic memory.

Importantly, the hippocampus is not set on episodic memories alone but is vital in the transferal of information from short- to long-term memory. The integration of new memories into cognitive schemata, as well as the transferal described above, called memory consolidation (McClelland, 1995).

1.1.3.2 Learning

Learning is the acquisition of knowledge and skills. Those properties can be of a social, mental or physical nature and are observable in an individual's behaviour. Learning can be tied to tedious and time-intensive endeavours, but can also happen unconsciously (implicit) (Bartsch, Falkai, 2013).

Learning is closely related to memory, and lines are blurred since testing often equates memory performance with learning success. One can roughly distinguish between learning as a process and memory as a result of learning providing knowledge. The classification of learning compared to memorising is often linked to labour and time, which has been associated with the acquisition of knowledge (Bartsch, Falkai, 2013).

Learning ability gives a name to the capability of an individual to register, integrate and save new information. Learning ability is influenced by age and other variable factors such as motivation or exhaustion. Part of the reason why learning ability is reduced in older individuals is found in neural plasticity, which decreases with age. Neural plasticity describes changes, on a neural level, that reflect changes during learning.

A prominent mechanism describing those changes is Hebbian learning. Often summarised as “what fires together, wires together“ (Gluck, Meyers, 1997) it states that if a presynaptic neuron repeatedly excites a postsynaptic neuron, the synapse is modified in a way, that the presynaptic neuron becomes more likely to excite the postsynaptic neuron (Morris, 1999). Hebbs’ rule can be summarised in a formula that gives a synapse a weight (wij) between presynaptic neuron j and postsynaptic neuron i. Activity is given the variable y (yi for the postsynaptic neuron; yj for the presynaptic neuron) and α as a constant term, with an undetermined function (Sejnowski, Tesauro, 1989). The general formula for Hebbian learning can be given as follows: (Gluck, Meyers, 1997).

Hebbian learning is closely related to long-term potentiation (LTP) and depression (LTD) (Levy et al. 1983). LTP is the process of strengthening synapses, leading to permanently improved signals between two neurons. Especially in the mammalian hippocampus, LTP that follows Hebbian rules can be observed (Sejnowski, Tesauro, 1989, Levy et al., 1983.). There are subforms of LTP such as spike-timing-dependent plasticity (STDP). STDP describes the effect that the timing of weak

and strong synaptic impulses, results in the modification of synaptic weight. These modifications can take the form of potentiation, or reduction (Gallistel, Matzel, 2013).

$$\Delta w_{ij} = \varepsilon (y_i y_j)$$

Hebbian learning can be observed when forming associations. In static associations this will result in an associative memory, (Anderson, 1970) in temporal associations (such as in classical conditioning) the individual learns to predict one stimulus to follow the other.

In classical conditioning, an individual is repeatedly presented with a neutral (later conditioned) stimulus (CS) and an unconditioned stimulus (US). In the prominent example of the Little Albert experiment, a child (11 months old) was presented with different objects, including a white rat (CS). The unconditioned stimulus was a loud sound produced by a hammer on a metal rod (US). Initially, the child showed no negative reaction to the rat (CS) but a fearful reaction to the sound (US). After presenting the rat multiple times followed by the unpleasant sound, the child reacted fearfully to the rat and other stimuli that resembled the rat (such as a rabbit) (Watson & Rayner, 1920) (see Fig. 5).

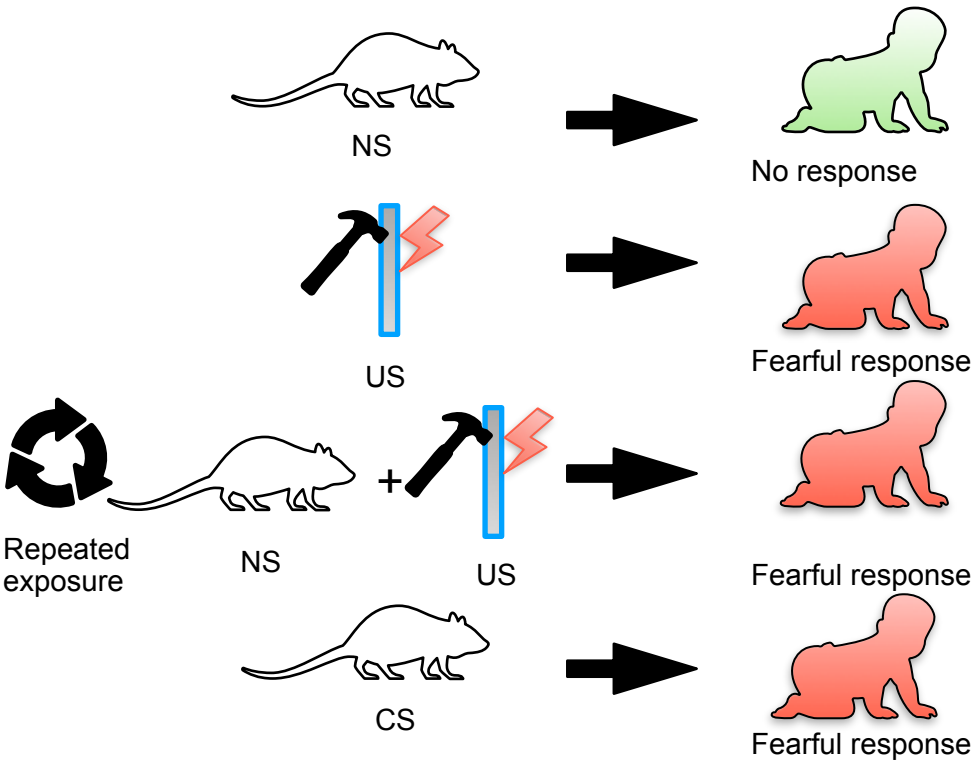

Fig. 5: Classical conditioning in little Albert experiment, with conditioned and unconditioned stimulus as well as response. (Watson & Rayner, 1920)

The example of Little Albert makes a tangible example, that the Hebbian learning model has to be modified to apply in some cases. If one were to model a simplified network of three neurons: a sensory neuron for the CS, a sensory neuron for the US, and a motor neuron, R. The weight of the US to R is high from the beginning, but the weight of CS to R would be weak. In this model, the synaptic weight of CS and US would increase no matter which one is shown first. This does not correspond to the behaviour that is observable during classical conditioning, since the temporal

order is crucial in these settings (Sejnowski, Tesauro, 1989). Transferring this to the example of little Albert would mean hitting the metal rod (eliciting a fear response) and afterwards showing the rat to the child.

Another problem noted by Sejnowski and Tesauro is, that if the synapse of CS and R gains so much weight that it can be activated without US, the weight would continue to increase, which again does not comply with observations made in animal studies. Presenting the CS without US leads to a weakening of the association (Sejnowski, Tesauro, 1989). One has to keep in mind, that weakening or zero learning is neglected in the basic Hebbian rule (Sejnowski, Tesauro, 1989).

Tackling this inaccuracy is sequence learning. It has been argued that the hippocampus can detect input patterns. Based on pattern completion, a network can retrieve a predicted next state. The CA3 region was proposed as a sequence predictor by Levy (1996) who also argued that the sequence prediction paradigm could involve other functions that are associated with the hippocampus such as contextual sensitivity, configuration, and cognitive mapping (Levy et al, 1995; Gluck, Meyers, 1997)

The CA1 has been proposed as a site of LTP activity. taking timing into account, the level of potentiation is influenced by afferent activity reaching a specific target neuron (Granger et al., 1996). Brief temporal sequences can be stored using this temporally dependent LTP form. Liaw & Berger (1996) propose that, due to different inhibitory and contributory hippocampal mechanisms interfering with each other, temporal chunking might result. In the proposed model, the synapses adapt to respond to subpatterns that are then combined in the postsynaptic neuron. Temporal patterns might also be made recognizable due to dynamic synapses learning to respond to one subtype of pattern. The postsynaptic neuron then combines these sub-patterns. (Liaw & Berger, 1996; Gluck, Meyers, 1997)

Lisman and Grace propose the joint activity of the hippocampus and the midbrain, involving the neurons of the ventral tegmental area (VTA). The VTA is of great importance to the mesocorticolimbic dopamine system. Newly arrived information can be detected by the hippocampus, and a resulting novelty signal might reach the VTA via the subiculum, accumbens, and ventral pallidum to the VTA. There novelty-dependent fiering could be initiated, resulting in the release of dopamine in the hippocampus. This could in turn affect LTP and learning (Lisman and Grace, 2005). Interestingly, the highest neural plasticity can be observed right after being born, while the highest cognitive ability is observed in adolescents. This could be due to the fact, that a high degree of neuroplasticity is needed right from birth to adapt to life outside the womb (e.g. to learn to speak). Once these frameworks are established, neuroplasticity decreases, fewer new skills are formed and more energy is invested in improving already existing skills (Bartsch, Falkai, 2013; Feldmann, 2009).

1.1.3.4 Spatial learning

One of the best-known functions of the hippocampus is spatial cognition (Ito and Lee, 2016). Observation of one of the most prominent cases of memory research, H.M (Scoville and Millner, 1957) laid the foundation for the widely accepted notion, that the hippocampus is vital to spacial learning. After his bilateral medial temporal lobe resection, pronounced deficits in spatial learning were observed, although spatial information processing was not impacted per se. Another milestone in understanding the hippocampus' role in spatial learning and navigation, has been the identification of "place cells" by O'Keefe and Nadel in rodents (O'Keefe and Nadel, 1978). It was, however, another study by Maguire et al. that brought public attention to this domain, by highlighting differences between taxi drivers' hippocampi and a control group. They showed, that the time spent as a taxi driver correlated with hippocampal volume (positively in the posterior and negatively in the anterior hippocampus) (Maguire et al., 2000).

Place cell systems allow for an individual to form abstract representations of layout and experienced space in an environment. Place cell systems involve different types of cells that have evolved to fire in specific instances that relate to an individual's location, such as place cells, border cells, grid cells, head direction cells, or boundary-vector cells (Long and Zhang, 2021, Gallistel und Matzel, 2013; Mattson, 2019). These cells are functionally specialized, in rodents place and grid cells have been discovered. Those cells, for example, have evolved to anchor their firing fields to the boundaries of an environment (Jefferey, 2024). Once encoded, the cognitive map and firing of place cells are not dependent on sensory input. The place cells fire when an individual is in a certain location in a familiar environment, if the environment changes, firing ceases or the location of activity changes (Gallistel and Matzel, 2013). An individual forms a cognitive map based on the inputs of different cells, representing locations (Gluck and Myers, 1997; Gallistel and Matzel, 2013). Place cells are not exclusively found in the hippocampus but are also found in the subicular complex and the entorhinal cortex. Anatomically the place cells' firing fields increase in size from dorsal to ventral in the hippocampus (Gallistel und Matzel, 2013).

1.1.3.5 Cognition

The field referred to as cognition is connected to numerous different processes. Following, some exemplary cognitive features, that particularly involve the hippocampus, will be introduced.

Contextual Memory:

Linked to the hippocampal role in memory is **contextual memory**. Contextual memory allows for environmental cues and contexts of past events to be remembered (Maren and Holt, 2000; Wiltgen et al., 2010)

In rodents, the dorsal hippocampus was activated when contextual fear memories were retrieved (Fanselow, 2000; Wiltgen et al., 2010). Depending upon whether the memory was generalised or not, mice experienced memory loss when the hippocampus was inactivated. Generalised memory could be recalled without the involvement of the hippocampus, while retrieval of contextual memories required hippocampal activity (Wiltgen et al., 2010). Similar reports have been made by Maren and Holt (2000). In rats, the hippocampus is not only involved in the retrieval of contextual memory but the projections from the subiculum to the nucleus accumbens have been observed to play a paramount role in regulating the exploration of an environment, which is vital to gathering contextual information (Fanselow, 2000). The CA1 and CA3 in particular are proposed to play an important role in the formation of contextual memory. The CA3 would function in the rapid elaboration of the joint context representation, while the CA1 area is active in the consolidation processes (Daumas et al., 2005).

Decision-Making:

To decide between options, choices have to be assigned values. Oftentimes, past experiences provide information about the values. Representations of past events are supported by the hippocampus. This could give the hippocampus a detrimental role in decision-making in situations of disambiguation, uncertainty and conflict (Palombo et al.,2015; Yu and Frank, 2015).
The hippocampus supports flexible representations via three mechanisms: updating, generalisation, and construction (Palombo et al.,2015).
In approach-avoidance conflict tests stimuli are presented that are associated with both reward and punishment. In their review paper, Ito and Lee conclude that the ventral (in rodents)/anterior (in humans) parts of the hippocampus contribute to decisions in the presented approach-avoidance models (Ito and Lee, 2016).

In an auditive adaption of the Stroop task, Oehrn et al. report a regionally specific activation of the hippocampus in the assessment of disambiguous stimuli. The study used a combined approach with fMRI and iEEG methods. The iEEG results point to theta oscillations being of importance for successfully solving response conflicts (Oehrn et al., 2015)

Imagination and Creativity:

Imagination can be defined as a function generating information or future predictions without relying on information from past events or external stimuli, that refer to the present or combine diverse kinds of information in novel ways (Thakral et al., 2020; Comrie et al., 2022).
Compared to other domains, these functions have only recently been investigated.
For imagination, functions like episodic memory retrieval, visualization, mental simulation and spatial navigation are recruited (Comrie et al., 2022; Jung et al. 2016). Some studies produced results that point to the potential ability of the hippocampus in combination with the „core network“ to play a role in generating episodic details in imagining future events, as well as the number of creative ideas produced (Thakral et al., 2020).

Thakral et al. used transcranial stimulation to interfere with baseline hippocampal function and subsequently observed participants to perform worse in divergent thinking tasks. They proposed that the hippocampus is critical for episodic simulation and divergent thinking.
Jung et al. administered a test for imagination (HIQ) and correlated the findings of 80 participants with volumetric data. They observed increased volumes in bilateral hippocampi, lingual gyrus, and caudal/rostral middle frontal lobe, and on the other hand, decreased volumes within the nucleus accumbens and regions within the default mode network. In an fMRI study, Beaty et al. observed activation of the bilateral hippocampus as well as the „core network“ during episodic retrieval and future simulation (Beaty et al., 2018).
Comparing these studies, which used different approaches, one may conclude a particular importance of the „core network“ (Jung et al. 2016; Thakral et al., 2020; Beaty et al., 2018) in particular the angular gyrus (AG) (Jung et al., 2016) as well as the **medial temporal lobe**, lateral, medial parietal cortex, and medial prefrontal cortex (among others).
Some of these structures overlap with the default mode network (medial prefrontal cortex, angular gyrus) that aids in imagining future events (Jung et al., 2016). Some reports state, that decreased activity or volumes in the default mode network had positive effects on creativity measures (Thakral et al., 2020; Jung et al., 2016).
However, it is hard to pinpoint one region in the activation pattern and assign it a certain function in such complex concepts like imagination or creativity.
Furthermore, is hard to differentiate the generation of truly new information from the recombining of aspects of previously made memories (Jung et al., 2016; Thakral et al., 2020).
This makes it a difficult task to conclude the functionality of the hippocampus alone, however, the evidence seems to point to an involvement of the hippocampus (possibly due to its function in memory retrieval) in creative and imagination tasks.
Ultimately, methodological problems of inconsistent definitions of creativity and imagination as well as non-uniform testing for these concepts, are factors that further complicate the scientific exploration of the already complex interaction of different networks involving the hippocampus.

1.1.3.6 Emotion

When assessing emotion the valence-arousal model is often consulted. It states that emotions vary in valence (positive or negative dimension) and arousal (intensity) (Russel, 1980; Atkins & Reuter-Lorenz, 2008). This makes it easier to quantify emotion in a questionnaire, however, its limits are reached in experiments that rely on observing emotion, instead of self reports.

Complicating the matter is the fact, that emotional learning and emotional memory, for example, fear conditioning (see little Albert experiment), are not tied to awareness, but are part of implicit learning (and are therefore not conscious in nature). In this, the hippocampus is critically involved.

What is known, is that during learning, the amygdala influences both encoding and storage, this is due to the amygdala’s influence on perception and attention (Phelps, 2004). During consolidation, newly formed memories are held in the hippocampus, before being transferred to neocortical areas

(Piefke, Fink, 2013). During this time, hormonal changes due to emotional activation might change the way information is stored. Remembering the information linked to emotional responses might increase survival, this is termed the modulation hypothesis (Phelps, 2004, Benjamin et al., 2008; McGaugh and Roozendaal, 2002; Atkins and Reuter-Lorenz, 2008). Additionally, Atkins and Reuter Lorenz propose the emotional richness of recollective experience to serve as a motivational factor in surviving (“inspiration to survive“) (Atkins and Reuter-Lorenz, 2008). The importance of remembering emotional events might explain the observation, that emotionally charged memories are usually better remembered than neutral ones (Anderson et al., 2005; Anderson et al., 2006, LaBar & Cabeza, 2006). Those brain areas that are active in fear conditioning, have been observed to be of particular importance in other forms of emotional learning and memory processes (Atkins and Reuter-Lorenz, 2008).

Not only in consolidation processes has the amygdala been observed to influence memory processing, but also in retrieval. Proposed is a bidirectional influence of the hippocampus and amygdala. While the hippocampus forms representations of emotional valence and arousal as well as significance, those representations lead to activation patterns during retrieval that influence the amygdala in emotional response when emotionally charged stimuli are encountered (Phelps, 2004). Both the amygdala and hippocampus have been observed to be increasingly activated during retrieval of emotionally charged memories (LaBar & Cabeza, 2006). These findings suggest an active role of the amygdala and related structures in hippocampal encoding and retrieval functions (Atkins and Reuter-Lorenz, 2008).

This is not only important for conditioned emotional reactions but is also key to acting empathetically. Empathy is a function that has been connected to the hippocampus (Moscovic et al. 2016) This could be due to the comparison of current events to past events, that critically rely on encoding and retrieval. The act of imagining oneself in another person is described as mentalising, this act is dependent on the auto-assessment of past autobiographical memories (Perry et al. 2010)

Lesion studies found that the extent of left amygdala pathology correlated with worse memory of emotional information and less activity in the hippocampus. Left hippocampal pathology correlated with less activity in the left amygdala, as well as more activity in the right amygdala. This could point to a joint functional importance in remembering emotional events (Richardson et al, 2004).

Bechara et al. observed that hippocampal damage in patients exhibiting retrograde amnesia did not impact their ability to evolve conditioned fear responses (Bechara et al., 1995). The contextual triggering of fear responses however is impacted by damage to the hippocampus, encoding and associating context with an emotional response is therefore probable to rely on hippocampal function (Phillips & LeDoux, 1992, Atkins and Reuter-Lorenz, 2008). Hippocampal damage also interferes with contextual reinstatement of conditioned fear responses, indicating the importance of this structure for encoding and associating the contextual cues with the learned fear response (Phillips & LeDoux, 1992; Atkins and Reuter-Lorenz, 2008)

Prospective possible intervention based on the emotional role of the hippocampus can be imagined in Improving the connectivity of the hippocampus and amygdala. This could prove fruitful in particular regarding improving emotional regulation. Experiments using neurofeedback in training observed increased connectivity of the amygdala and hippocampus after training to positively regulate emotions (Zhu et al, 2019)

In the special case of musical enjoyment, emotion and entertainment, elements of surprise and uncertainty, predictions and associations have been proposed to play a vital role (Jourdain, 1997; Salimpoor et al., 2015; Cheung et al., 2019) This has been well established in musicological research in the last years. Emotional involvement context, structure and previous experience play a pivotal role (Scherer, K. R. & Zentner, 2001). Functional MRI studies suggest, that the hippocampus might be involved due to its memory function (Koelsch, 2010) but interestingly it could also play a role in facilitating enjoyment via the decoding of rhythmic features (Toiviainen et al., 2014) or might be tied to expectations (Cheung et al., 2019).

However, there are numerous unanswered questions, evoked by cases such as Clive Wearing who despite extensive damage to the hippocampus, is still able to play and conduct music (and presumably enjoys doing so) (Wilson et al., 1995).

1.1.4 Neural substrates of pattern separation and completion in the hippocampus

Pattern recognition is of great importance when it comes to learning, at the same time it is a prime example of cognitive tasks the hippocampus takes on. In pattern recognition, presented information is compared and differentiated from previously presented information (McClelland et al., 1995; Knieriem, 2015).

One can differentiate pattern completion and pattern separation that roughly correspond to the dentate gyrus (DG) and CA3 for pattern separation and CA3 for pattern completion respectively (Knierim & Neunuebel, 2016; Yassa & Stark, 2011, Aimone et al., 2011).

Pattern separation allows for distinct representations of otherwise similar experiences. This prevents interference in the recall and storage of memories. While Marr originally proposed pattern separation to be performed by the CA3 (Marr, 1971) it was later demonstrated that the CA3 network was fed uncorrelated inputs. The DG has unique mossy fibre projections to the CA3 that were long neglected since they are sparse. It is now assumed that the few synapses formed from the DG might kick off CA3 targets to establish decorrelated patterns in the CA3 (O'Reilly and McClelland, Aimone et al, 2011; Yassa and Stark, 2011). To solidify this theory, patch-clamp studies were performed. These studies showed mossy fibre terminals (the synapses from the DG to the CA3) to be powerful enough to excite a CA3 neuron (Henze et al., 2002; Aimone et al., 2011). Other studies showed that Granule Cells were mostly inactive (Jung and McNaughton, 1993; Aimone et al., 2011).

The **DG** is observed to be particularly involved in the encoding process (Aimone et al., 2011). Studies in rodents do support these findings (Gilbert et al., 2001; McHugh et al., 2007, Leutgeb et al, 2007). As a site of adult neurogenesis studies on rodents have investigated the role of neurogenesis in pattern separation and found significant evidence for neurogenesis to impact pattern separation (Yassa & stark, 2011).

While some studies do report similar findings pointing to the particular involvement of the DG in encoding processes in humans (Hanert et al., 2019a; Berron et al. 2016, Bakker et al., 2008, Sahay et al, 2011), it has to be noted that the CA1 might play a more important role in human pattern separation (Hanert et al, 2019b) compared to rodents (Gilbert et al., 2001).

Pattern separation takes place as soon as a stimulus makes its way to be stored (Knieriem, 2015; Bakker et al., 2008). It influences how information is stored. For pattern separation, overlappings are reduced and differences are expanded to minimise interference (O'Reilly and McClelland, 1994; Neunuebel and Knierim, 2015; Bakker et al., 2008).

Pattern completion, on the other hand, refers to the action of retrieving a complete pattern from memory after an incomplete or noisy pattern is presented (Hanert et al., 2019; Knierim and Neunuebel, 2016; O'Reilly and McClelland, 1994). This could be the case for example with words missing a letter. Pattern recognition influences how information is retrieved. Neunuebel and Knierim propose a particular involvement of the CA3 region in retrieving coherent representations from incomplete input (Neunebel and Knierim, 2013).

1.2 Obesity

Obesity is a disease classified as a global epidemic by the World Health Organization in 2021 (WHO, 2021) and is defined as an increase in fat mass affecting health (O'Brien et al., 2017, ICD-11 Code 5B81). Each year, it is estimated that at least 2.8 billion people die as a result of being overweight or obese (WHO, 2021).

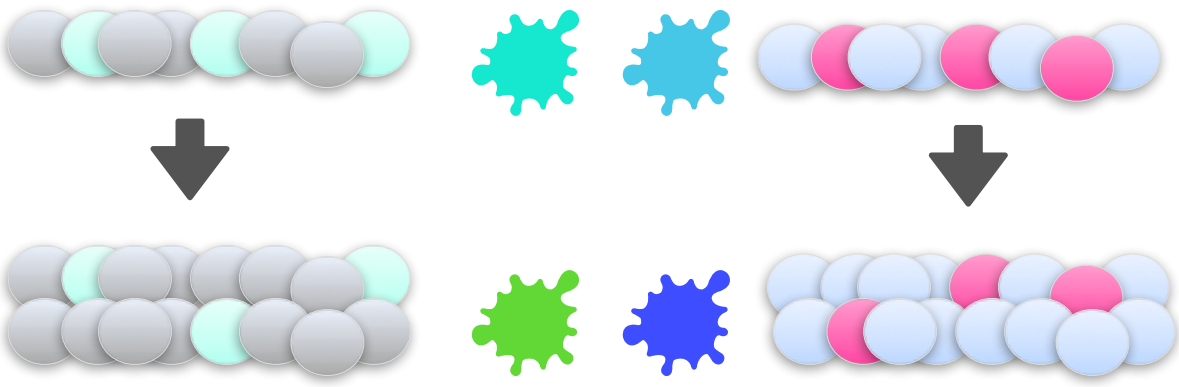

Fig.6: Pattren separation Modified from Knieriem and Neunebel (2015) with schematic visualisation of reduced overlappings for minimised interferance.

Obesity is a complex multifactorial disease, that poses a serious public health challenge globally and has been identified as a major determinant of disability and death in the WHO European Region (WHO 2021). In Austria the prevalence of obesity is reported to be rising, obesity rates from 2006 increased from 13.7% to 20% in men and from 15.2% to 17.8% in women in the year 2014/ 2019 (Dorner et al., 2022)

In Germany, 19% of adults are obese. obesity prevalence has continued to increase since 2012 for both women (+2.5%) and men (+2.1%). nearly 13 million adults in Germany are obese (Schienkiewitz et al., 2022). Those Numbers are expected to rise after the COVID-19 pandemic, which has impacted people's dietary choices while decreasing physical activity around the world since the end of 2019 (Dorner et al., 2022).

The World Health Organisation identifies obesity as a risk factor for a whole array of diseases such as: cardiovascular diseases, metabolic diseases, musculoskeletal diseases and mental disorders (WHO, 2021). The focus of this thesis is the neurological aspects of obesity since there have been findings that suggest obesity to be related to various regional brain volumes, including thr hippocampus (Climie et al., 2015; Favieri et al., 2019; Lee and Yau, 2020; Raji et al, 2010; Debette et al. 2011). Additionally, the combination of heightened BMI and WHR has been identified as an important risk factor for grey matter atrophy (Hamer & Batty, 2019).

1.2.1 metabolic effects of obesity

Individuals with obesity have an increased risk of developing (among others) insulin resistance, type 2 diabetes, and cardiovascular diseases (Braddon et al., 1986). All of these have been suggested to negatively impact neurocognitive function. Obesity has a significant negative influence on executive functions (Favieri et al., 2019).

Diabetes has been linked to a higher risk of memory or learning disorders, as well as depression and dementia (Vafaei-Nezhad et al., 2022). This could be due to the negative impact of diabetes on neurogenesis, dendritic remodelling, and increased apoptosis (Ho et al., 2013; Vafaei-Nezhad et al., 2022, Sadeghi et al., 2016; Strahanan, 2008). Adding to that high insulin levels, oftentimes associated with a high BMI, have been linked to hippocampal atrophy as well as other degenerative effects on other brain regions (Raji et al, 2010; Debette et al. 2011). Particularly the CA1 has been reported to be affected due to a decrease of long-term potentiation. In rodent studies diabetes has been observed to decrease synaptic plasticity in the DG (Vafaei-Nezhad et al., 2022). This could be negatively reflected in pattern separation tasks.

In their longitudinal cohort study, Arvanitakis et al. reported participants with **Diabetes** to have a 65% increased risk of developing AD. (Arvanitakis et al., 2004). The DG and CA3 regions would be among the first regions to suffer from related changes since they are especially vulnerable to neurodegenerative processes (Bartsch et al., 2015).

Stranahan et al propose, that cognitive deficits in individuals with diabetes are related to glucocorticoid-mediated deficits in neurogenesis and synaptic plasticity (Stranahan et al., 2008).

Specifically impaired cognitive domains are listed such as spatial learning, memory, and general cognition (Sadeghi et al., 2016).

In large-scale studies, **hypertension** has been linked to reduced hippocampal connectivity as well as impaired memory function (Feng et al., 2020). In studies specifically focussing on hippocampal volume, systolic blood pressure correlated significantly with decreasing hippocampal volumes in participants who exhibited early mild cognitive impairment (Ngwa et al., 2018).

obesity is oftentimes linked to increased **glucose levels** in the blood, these increased levels have in turn been associated with increased and premature cerebral atrophy (Cherbuim, 2012). Newer studies have associated high glucose levels with poorer performance in verbal learning tests (Kerti et al., 2013).

Interleukin-6 as a major inflammatory mediator that is often observed in obese patients, who are affected by a subclinical inflammatory state, is also of interest when talking about obesity-induced changes in hippocampal regions. Eder et al. propose IL-6 to be a systemic regulator of body weight and lipid metabolism (Eder et al., 2009). IL-6 is known to play a role in neurogenesis, both in glial cells and neurons, and is also reported to be increased in Alzheimer's patients (Erta et al., 2012)

Interleukin-6, CRP and triglycerides are known to influence eachother**: IL-6** has pro- and anti-inflammatory effects, and spikes during inflammatory states as part of the acute phase response (Eder et al., 2009). It is known to stimulate the production of **C-reactive protein (CRP)** (Ramírez-López et al., 2013), both IL-6 and CRP are investigated in this study, as they have been observed to be elevated in obese patients (Aronson et al., 2004; Ramírez-López et al., 2013). This could be due to the fact that Lipocytes are known to increase IL-6, as they can produce up to 30% of the cytokines in obese patients. This can have negative effects on the activity of lipoprotein lipase, inhibiting the hydrolyzation of **triglycerides** in **lipoproteins**. Furthermore, the oxidation of glucose and fatty acids as well as glucagon and cortisol liberation is simulated by high levels of IL-6 (Mohamed-Ali et al., 1998). IL-6 has also been shown to reduce insulin-dependent hepatic glycogen synthesis (Eder et al., 2009; Klover et al., 2003). IL-6 injections in mice have been shown to kick off mechanisms that lead to an inhibition of hepatic insulin-dependent receptor autophosphorylation and IRS-1 tyrosine phosphorylation (Klover et al., 2003). Both IL-6 As well as CRP have been recognised to be predictors of the development of type 2 diabetes (Wang et al., 2013). **Triglycerides** have been observed to cross the blood-brain barrier and induce leptin and insulin receptor resistance, again with possible detrimental effects on cognition (Banks et al.,2018). **Insulin** resistance can be associated with metabolic syndrome, not solely diabetes type II (Buchmann et al., 2022; Eder et al., 2009). Metabolic syndrome is highly prevalent in Germany (Buchmann et al., 2022) and is associated among others with high-glucose levels, High triglycerides, hypertension and hyperlipidemia. Metabolic syndrome has been associated with an increased risk for dementia and cognitive decline in a population-based study of individuals aged 85 and older (van den Berg et al., 2007). Generally, metabolic syndrome is associated with

cognitive dysfunction (Yates et al., 2012). High levels of **fasting insulin** are associated with both obesity and insulin resistance (Parakash, 2021) Newer studies have linked obesity to changes in the intestinal microbiome (Liu et al., 2021). Rodent studies showed that specific diets with high contents of saturated fatty acid and sugar can impair hippocampal-dependent functions (Beilharz et al., 2016).

Lipoprotein (a) is an independent risk factor for cerebrovascular peripheral artery and cerebrovascular diseases (Urakami et al. 2000; Kunutsor et al., 2016; Sarti et al. 2001; Solfrizzi et al., 2002) as well as Alzheimer's disease (Mooser et al., 2000; Kunutsor et al., 2016; Blanchard et al., 2019; Raulin et al, 2022). It is not directly correlated with weight and interacts with apoE, depending on phenotype (Mooser et al., 2000; Kunutsor et al., 2016; Blanchard et al., 2019; Raulin et al, 2022; Kritharides et al. 2017). It is generally non-modifiable and genetically determined (Urakami et al. 2000, Ugovšek and Šebeštjen, 2021, Orsó and Schmitz, 2017; Mooser et al., 2000; Kritharides et al., 2017; Li et al., 2021; Pasławska and Tomasik, 2023, Röhr et al., 2020; Moriarty et al., 2016). It is not linked to obesity but plays a role in comorbidities that have been observed in obese patients (Pasławska and Tomasik, 2023; Orsó and Schmitz, 2017; Ugovšek and Šebeštjen, 2021; Scanu et al., 1991).

1.2.2 classification of obesity

To measure the grade of obesity and distinguish between different grades of overweight, the Body Mass Index (BMI) is commonly used (World Health Organization, 2022)

The BMI is calculated by dividing a person's weight by their height and given in kg/m2 (ICD-11 Code 5B81). An increased BMI is linked to ill health, however, it does not distinguish between adiposity and other tissue and is therefore not a direct measure of adiposity and its conclusiveness regarding fat mass is influenced by age, sex and race of the measured individual (World Health Organization, 2022)

The WHO does speak in favour of using the BMI as a reasonable proxy when used for large numbers of people since correlations between BMI and total body fat, as well as total abdominal adipose tissue, have been found (World Health Organization, 2022). From those parameters, abdominal adipose tissue is assumed to have a particularly negative health impact, especially when found viscerally or intra-abdominally. To gather data on this type of fat, the waist-to-hip ratio (WHR) is used as a proxy (Hamer & Batty, 2019; World Health Organization, 2022).

The ICD-11 (WHO, 2019/2021) distinguishes several BMI categories, three of them referring to obesity classes of different severity:

- Underweight BMI Below 18.5
- Normal weight BMI 18.5–24.9
- Pre-obesity BMI 25.0–29.9

- Obesity class I BMI 30.0–34.9
- Obesity class II BMI 35.0–39.9
- Obesity class III BMI greater than or equal to 40

2 Study

In this study effects of metabolic and inflammatory biomarkers related to obesity and their effect on hippocampal sub-volumes are investigated. For this, volumetric MRI data and bioloical as well as demographic data was gathered.

2.1 introduction

To study obesity related effects, two groups were compared, obese and nonobese paarticipants. For this thesis, data from the Cohort study FoCus as well as Cognifast were used. Following, both studies are briefly described.

2.1.1 introduction to the Cohort-study FoCus and Cognifast

The FoCus cohort was launched in 2011 and had its first follow-up in 2020. Participants were recruited at the Outpatient Centre of the University Medical Center Schleswig–Holstein (UKSH) and via residents' registration offices. The cohort aims to be representative of the Northern German population of the Kiel region. In total, 1795 individuals were analyzed at baseline. Baseline data collection took place between 2011 and 2014. Follow-up for the assessment of disease progression (such as diabetes mellitus), as well as the onset of new diseases with changes in the individuals's phenotype, diet or lifestyle factors is planned every 5 years. The first follow-up period was finished in 2020 and included 820 individuals.

Collected data included: phenomics, microbiomics, metabolomics, genomics, and metagenomics as well as nutrition profiling, taste perception phenotyping social network analysis, and for some MRI data. Data on 71 participants from the FoCus cohort (23 overweight and 48 normal weight) was revisited, depending on the availability of MRI data and the quality of the Data gathered. To increase statistical power, supplementary data of 23 obese patients from the study Cognifast was added. Cognifast is an intervention study that uses the Optifast®-52 Programme to reach lasting weight reduction in obese patients, Noticeably, the program is designed to be effective in patients with a BMI >40 kg/m2. To reach weight loss, multiple approaches are combined, taking into account necessary modifications of nutritional, behavioural, and social aspects as well as offering psychological and physiotherapeutic treatment (about 4 hours a Week). In total, the program lasts 12 months, including a starting period of 12 weeks. In the starting period, caloric intake is restricted to about 800 kcal per day, as a very-low-calorie-diet (VLCD) with a formula diet.

Cognifast is the overarching study that tests cognitive ability and gathers MRI data of patients who enrol in the Optifast®-52 Programme at the University Clinic Schleswig-Holstein, Campus Kiel. The Cognifast study has yet to be evaluated and published (as of January 2024).

The study was approved by the Ethics Committee of the Medical Faculty of Kiel Christian Albrechts University (A156-03/Date 2011/07/28) and was conducted following the Declaration of Helsinki revised in 2013 by the 64th General Assembly of the World Medical Association in Fortaleza (Brazil), which was first adopted in June 1964. The study was registered under the clinical trial number DRKS00005285 at the German Clinical Trials Register in Cologne. The participants were informed about all steps of the study procedure, including all examinations, as well as data handling. Participants had time to consider their participation and were informed about the possibility of withdrawing from the study at any time, without giving reasons. In case of withdrawal, all data was deleted from the database. Only those participants who gave written consent are included in the FoCus and Cognifast study. All participants voluntarily agreed to participate after informed consent and signed an informed consent form. Participants were also asked for their consent to be recontacted in the future.

2.2 Materials and Procedure

For this study different materials and procedures have employed, that are specified in the following sections on biological parameters as well as MRi data and demographic data.

2.2.1 biological parameters

All physical examinations were performed by trained medical staff and each measurement was repeated twice by the same staff member. For data analyses, mean values were calculated. For the FOCUS study, different biological parameters were collected, of these parameters, the following were selected to be further investigated in this study: systolic blood pressure, Glucose mg/dl, Triglycerides mg/dl, CRP mg/l, Interleukin 6 pg/ml, Lipoprotein(a) mg/l, Insulin µU/ml, previous diabetes diagnosis.

Blood pressure was measured by trained professionals in the participants who took part in the FOCUS study. For the statistical evaluation, the systolic blood pressure in Hg/mm is considered. For measuring a sphygmomanometer with weight adopted blood pressure cuffs (BOSCH + SOHN GmbH u. Co. KG, Jungingen, Germany) as well as a stethoscope were used. Blood pressure was measured after a 5-10 min sitting position (Geisler et al., 2022).

Systolic blood pressure was chosen as a measure to observe possible hypertension in the participants. The other parameters (Glucose mg/dl, Triglycerides mg/dl, CRP mg/l, Interleukin 6 pg/ml, Lipoprotein(a) mg/l, Insulin µU/ml) were gathered from fasting blood samples collected from the participants via venopuncture after an overnight fast (average fasting time 10.75 ± 5.3 h) (Geisler et al., 2022).

Both Cognifast and FoCus participant's height was measured and BMI was calculated (BMI = weight (kg)/ height (m)2). BMI classes were defined, with any BMI over 25 as overweight and any

BMI below 25 and over 18 as normal weight. To get accurate Data, participants were weighed wearing light clothes and no shoes using digital scales (Tanita BC-418 MA, Tanita Europe BV, Amsterdam, Netherlands). Data on weight was determined to the nearest 0.1 kg, and height was measured to the nearest 1 cm using a stadiometer (seca GmbH&Co.KG, Hamburg, Germany).

For both Cognifast and FOCUS participants, data was gathered using the same questionnaire, that was originally used for FoCus participants in 2011 (version 1.1 from July 18, 2011).

The questionnaire relies on self-reports. Questions include participants' medical history, sociodemographic (e.g. school graduation, type of household, children), socioeconomic (e.g. employment status) and lifestyle (e.g. satisfaction with life, smoking or history of smoking) aspects (Geisler et al., 2022) The questionnaire was divided into sections focusing on diverse medical conditions. For some questions, answers rely on previous diagnoses. For example, it was not possible to measure the insulin levels of participants from the Cognifast cohort or to diagnose them with diabetes using only the questionnaire. Therefore, the question for diabetes asked if diabetes was previously diagnosed. It is theoretically possible that participants were included that have not yet been diagnosed with diabetes, albeit presenting with high levels of insulin. From this questionnaire, data on cigarettes smoked per day (n) as well as previous diabetes diagnoses were of particular interest for the statistical analysis.

2.2.2 laboratory analysis of the biological parameters

Biological parameters, that needed laboratory analysis, were exclusively gathered from blood. These parameters include:

C-reactive protein (CRP), interleukin-6 (IL-6), fasting glucose, fasting insulin, triglycerides and Lipoprotein (a). Blood samples were analysed the same day, they were collected. Samples were stored at 4°C until they were transported to be analysed in the central laboratory of the UKSH Kiel. There samples were centrifuged, separated and aliquoted. Samples were then stored at -80°C. Importantly, the lower detection limit for Lipoprotein 8a) levels is 93.1 mg/l.

2.2.3 Acquisition of MRI-Data

All examinations were performed on 3T MRI scanners. For the participants in the FoCus study, the model Phillips Achiva with a 32-channel head coil (Dual coil) was used (Achieva; Phillips Medical Systems, Eindhoven, the Netherlands). The scans for the Cognifast study were done on the Phillips Ingenia CX using multi-coil.

Detailed data on the MRI protocol can be retrieved from Table 2.

	Voxel size in mm³	Repetition Time in sec	Echo time in sec	Flip °
FoCus T1 images	1,0 x 1,0 x 1,0	≈ 7.591	≈ 3.48	8
FoCus T2 images	≈ 0.429 x ≈ 0.429 x 2.0	3000.0	80.0	90
Cognifast T1 images	≈ 0.929 x ≈ 0.929 x 1.0	≈ 8.198	≈ 3.757	8.0
Cognifast T2 images	≈ 0.491 x ≈ 0.491 x1.0	≈ 3665.262	100.0	90

Table 2: MRI imaging resolution, RT, Echo Time and Flip-angle.

2.2.4 Processing of MRI-Raw Data generating the volumetric data

Raw data was processed using Freesurfer (freesurfer for linux-ubuntu version 7.2.0). Freesurfer provides Segmentation of hippocampal subfields and nuclei of the amygdala. The labels are for the head, body and tail of: the presubiculum, subiculum, CA1, CA3, CA4, GC-ML-DG, Molecular_layer, _Hp-head. Additionally, it provides volumes for the parasubiculum, HATA, fimbria, hippocampal tail, and hippocampal fissure (Augustinack et al., 2015).

For the statistical analysis head, body and tail were added together. HATA, Fimbria, hippocampal tail, hippocampal fissure and molecular layer were not considered in the statistical analysis.

To control segmentations for accuracy, all segmentations were reviewed using ITK Snap (ITK-SNAP 4.0.2. September 25, 2023). In ITK Snap segmentations were displayed on The T1 scan of the brain. Via Segmentation -> open segmentation. Labels were imported via segmentation-> import label descriptions from a text document used at UKSH to label hippocampal subfields (Fig. 7). After confirming the segmentation results visually, the volumetric data in a separate table was accepted. Men are typically reported to have larger volumes on both left and right hippocampi (Tan et al., 2015; Ruigrok et al., 2014) however it has been reported that such differences are less dependent on sex and are mostly affected by the total intracranial volume (Pintzka et al., 2015)

To correct for headsize and age data processed with a GLM using data on age and estimated total intracranial volume (eTIV) a measurement generated by Freesurfer giving the estimated total volume of all intracranial structures,

To then perform statistical analyses JASP (Version 0.18.3 for Intel) IBM (formerly known as SPSS) version 28.0.1.0 as well as Excel from Microsoft Office Standart 2013 (version 15.0.4569.1506) were used. All three were used to create diagrams. Additionally, Pages Version 12.1 (7034.0.86) , JASP (Version 0.18.3 for Intel) and python (version 3.12.2 for macOs) with Pandas (version. 2.2.1, the pandas team, 2020) and Matplotlib (Hunter, 2007) were used to create diagrams, tables and graphics.

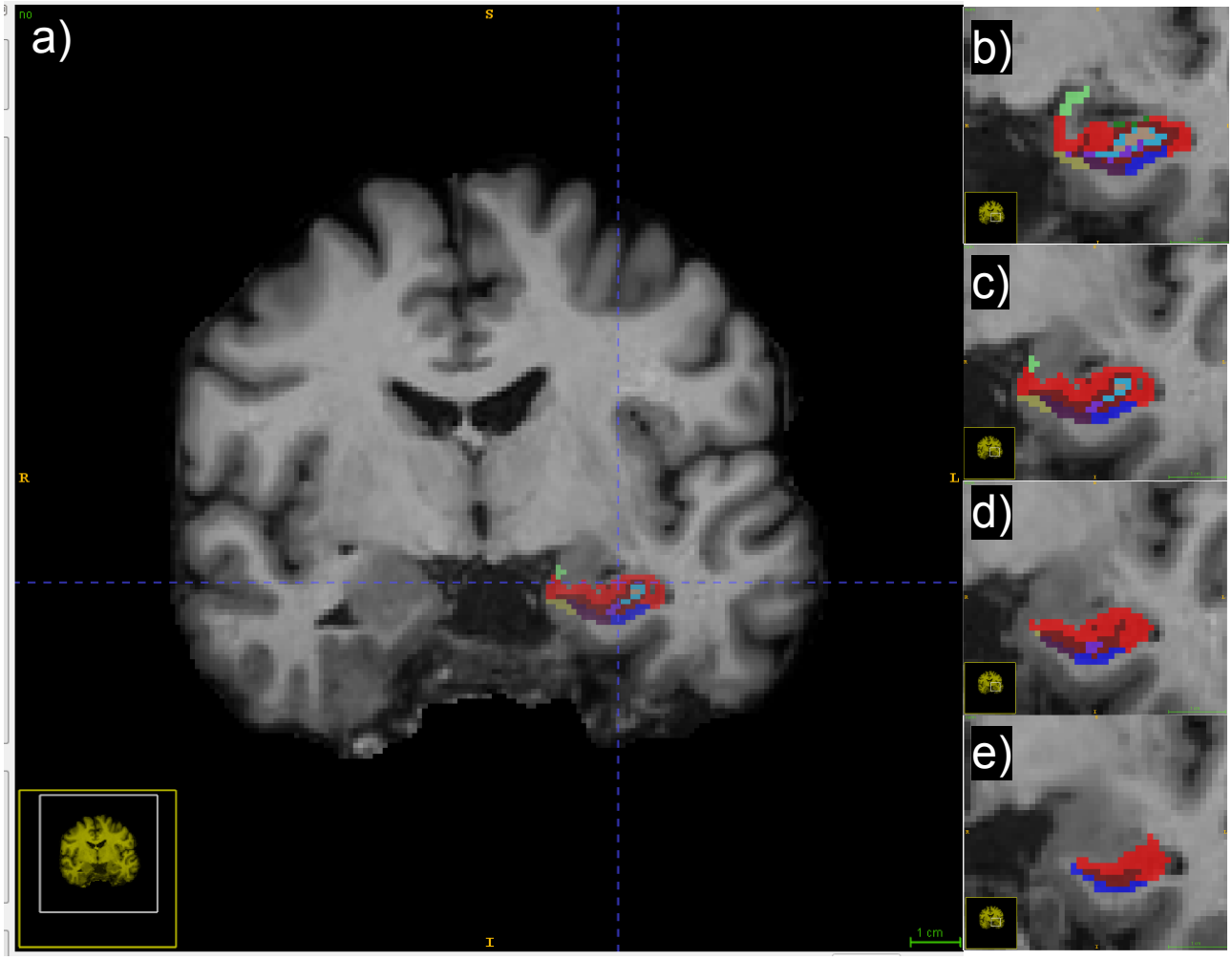

Fig. 7: Screenshot of segmentation from freesurfer opened in ITKSnap, slice 126 (b), slice 128 ((a&c)big), slice 130 (d) and slice 132 (e).

2.3 Participants

Participants of the FOCUS study were recruited from the inpatient clinic (at the University Clinic Schleswig-Holstein, Campus Kiel).The supplementary participants from the Cognifast Cohort were recontacted after their initial participation in the Cognifast study, via phone calls. Participants were former patients who were selected from a pool of participants of the Optifast®-52 Programme that is offered at the university hospital Schleswig-Holstein Campus Kiel. These patients had previously consented to be contacted in the future. Participants filled out the same questionnaire, which was given to the FOCUS cohort. Out of 23 supplementary participants who were selected for their BMI

	Number (n)	Number in %
Obese (BMI>25)	47	50
Normal weight (BMI<25)	47	50
Obese male (BMI>25)	6	12.77
Normal weight male (BMI<25)	5	10.64
Obese female (BMI>25)	41	89.36
Normal weight female (BMI<25)	42	87.23

Table 3: Group variables on sex for men and whomen in both groups.

and MRI data, 20 were successfully contacted. 9 questionnaires were sent back and data was

	Mean	Standart deviation	Range	Shapiro-Wilk test
Age	43.800	10.995	18.88-70.37	0.177
BMI	33.840	12.102	18.1-60.243	<0.001
Diabetes, n (%)	9 (9.57%)			<0.001
Cigarretes per day (n)	5.444	626	0.000-60.000	<0.001
Reported history of smoking (n, %)	37 (39,36%)			<0.001

Table 4: demographic data for both groups, including Shapiro-Wilk test for nornal distribution.

subsequently added to the FOCUS data. Already existing MRI data was added from all 23 selected participants.

2.3.1 demographic data

In this study, a total number of 94 participants (11 male (11.7%), and 83 female (88.3%)) were evaluated (Table 3).

The mean age was 43.8 years (IQR: 14.8) minimum age was 18.88 years and the oldest participant was 70.37 years old (Table 4).

Category according to ICD-11(2018)	Count (n)/male(n)/ female (n)	Percent (%) / male (%) /female (%)
Underweight	2/0/2	2.13/0/2.13
Normal	45/5/40	47.87/5.32/42.55
Pre-obesity	1/0/1	1.06/0/1.06
Obesity class I	0/0/0	0/0/0
Obesity class II	3/2/1	3.19/2.13/1.06
Obesity class III	43/4/39	45.74/4.26/41.49

When classified according to ICD-11 (WHO, 2019/2021), 2 (2.1%) participants met the criteria for being underweight, 45 (47.8%) met the criteria for being normal weight, while one of the participants met the criteria for pre-obesity (1%) but none for obesity class I. 3 (3.2%) participants were classified as class II obese, and 43 (45.7%) met the criteria for class III obesity (Table 5 and figure 9).

	BMI <25 (n=47)				BMI > 25 (n=47)				BF_{10}
	Mean	Range	SD	Shapiro Wilk-test	Mean	Range	SD	Shapiro Wilk-test	
Age	43.98	18.88 – 70.37	10.368	0.004	43.61	20.27-62.9	11.698	0.185	0.221
BMI	22.41	18.01 - 24.85	1.630	0.023	45.27	26.57–60.24	5.158	0.017	328975.169
Diabetes, n (%)	4 (8.51%)			<0.001	5 (10.64%)			<0.001	0.302
Cigarretes per day	10.67	1- 21	8.153	<0.001	16.58	2- 60	11.016	<0.001	0.377
Reported history of smoking (n, %)	23 (48,93 %)			<0.001	14 (29,78%)			<0.001	0.528

Table 6: in group demographic data on age, BMI, diabetes, and smoking for control and obese groups

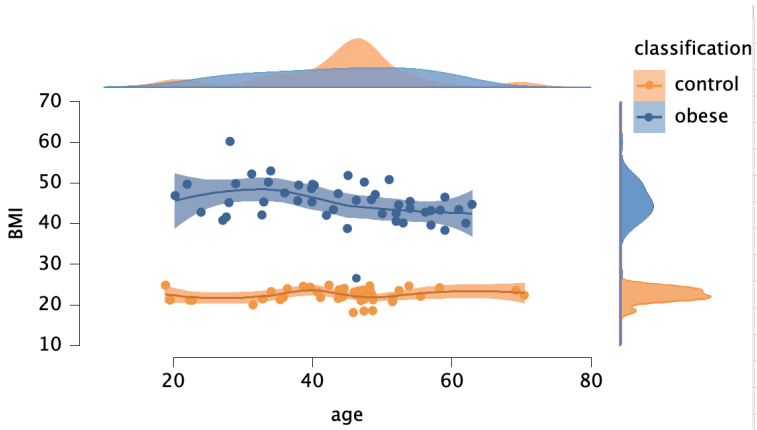

Fig. 8 a: BMI and age in control and obese group as a raincloud plot showing age (x axis) and BMI (y-axis)

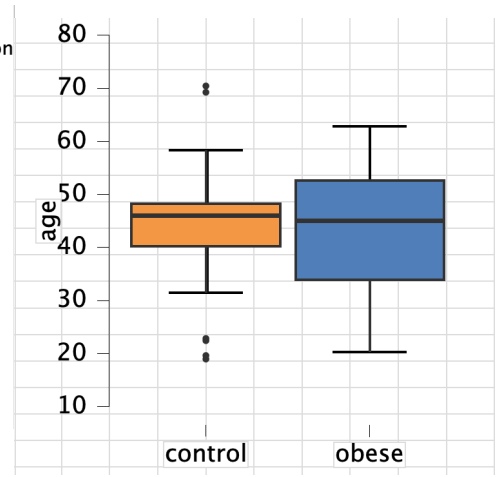

Fig. 8 b: Boxplots BMI and age in control and obese group

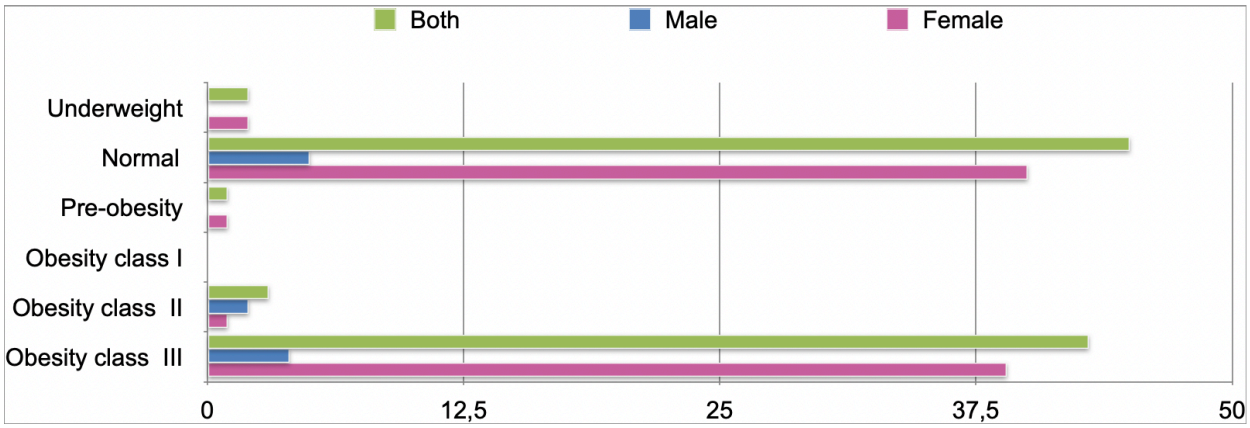

Fig. 9: participants and respective weight class according to ICD-11 (WHO, 2019/2021) in a bar chart for male and female participants as well as all genders

47 participants (50%) had normal weight, 47 (50%) met the criteria for obesity. Age was normally distributed globally (Shapiro-Wilk test: p=0.177) And did not correlate with BMI category (BF_{10}= -0.221) (Figure 8a and b). Age was normally distributed in obese patients (Shapiro-Wilk test: p=0.185). However, there was no normal distribution in participants in the category “normal weight“ (Shapiro-Wilk test: p=0.004) (Figure 8a and b). BMI was not normally distributed in neither the control (p= 0.023) nor obese group (p=0.017) nor globally (p<0.001). In the control group, 5 were male (10.64%) and 42 were female (89.36%) (Table 3). In the obese group, 6 were male (12.77%) and 41 were female (87.23%) (Table 3). Median BMI was 33.8 kg/m² ranging from 18.1 to 60.2 kg/m2 (Table 6).

In the control group, the median age was 43.98 years (min 18.88 years, max 70.37) years, standard deviation was 10.37): the median BMI was 22.41 kg/m² (min 18.11 kg/m² max 24.85 kg/m² standard deviation was 1.63 kg/m²). In the Obese group, the median age was 43.61 years (min 20.27 years, max 62.89 years, standard deviation was 11.69): the median BMI was 45.27 kg/m² (min 26.57 kg/m² max 60.24 kg/m² standard deviation was 5.158 kg/m²) (Table 6). Demographic data of both groups was compared using a two-sample Bayesian Whitney-Mann U test. No significant effect was observed except for the expected effect of BMI, which functions as the main criterion to determine the assignment to either the obese or control group.

3 Results

Following, the results of correlations for volumetries (in both groups and globally) and possible influencing factors as well as group comparisons for obese and normal-weight participants will be presented.

3.1 Results Biological parameters

Biological data such as levels of Glucose and CRP is presented first, before investigating the influence on hippocampal volumetric data.

3.1.1data distribution and group comparison

The Shapiro-Wilk test was conducted to test for normal distribution of biological parameters. Results showed all biological parameters (CRP, Glucose, Insulin, Lipoprotein a, Triglycerin, Systolic blood pressure, IL-6) to not be normally distributed ($p<0.001$). Biological data could not be generated for all participants since supplementary participants, who were recruited from the Cognifast study did not give blood samples. Additionally, not all blood parameters could be determined for participants of the FoCus study, most noticeably in the parameter Lipoprotein a, with data being available on 49 out of 94 participants (Table 7). The minimum, maximum, mean, standard deviation and the p-value of the Kolmogorov-Smirnov test for normal distribution are listed in Table 7. For the two observed groups (BMI>25 and BMI<25), descriptive statistics on biological parameters (table 8) can be obtained from table 8.

	n=	Min	Max	Mean	SD	P Shapiro-Wilk test
CRP	71	0.9	33.6	4.63	6.16	<0.001
Glucose	71	65	262	96.887	24.808	<0.001
Insulin	71	1.6	106.2	15.19	16.884	<0.001
Lipoprotein a	49	93	800	197.327	160.73	<0.001
Triglycerin	71	45	305	106.09	54.34	<0.001
Systolic bloodpressure	71	105	150	123.85	10.98	<0.001
IL-6	71	1.5	14.4	3.19	2.29	<0.001

Table 7: data on biological parameters for both obese and control groups, giving maximum, minimum, mean,

	BMI <25 (n=47)			BMI > 25 (n=47)		
	Mean	Range	P value Shapiro-Wilk test	Mean	Range	P value Shapiro-Wilk test
CRP mg/l	3.84	0.9 – 29.6	<0.001	6.18	0.9-33.6	<0.001
Glucose mg/dl	94.32	76- 147	<0.001	101.92	65- 262	<0.001
Insulin µU/ml	13.202	1.6 – 80.9	<0.001	19.092	4– 106.2	<0.001
Lipoprotein(a) mg/l	189.121	93 - 800	<0.001	214.250	93- 621	0.003
Triglycerides mg/dl	98.532	45-238	<0.001	142.04	49- 679	<0.001
Systolic blood pressure Hg mm	121.915	105 - 145	<0.001	126.58	110 - 150	<0.001
Interleukin 6 pg/ml	2.99	1.5 – 10.6	<0.001	3.6	2 – 14.4	<0.001

Table 8: biological parameters in the control and obese group giving mean, range as well as p-values of the Shapiro-Wilk test

3.2.MRI-Data (volumetry)

The following sections evaluate the results for volumetric data generated using MRI.

3.2.1 Data Distribution and Group Comparison

Shapiro-Wilk test showed data on subfields not to be normally distributed in the right and bilateral subiculum; left GC_ML_DG; left and bilateral CA4; right, left CA1 and bilateral CA1; right, left and bilateral whole hippocampus. The data for left subiculum, right and bilateral GC_ML_DG, right CA4, right, left and bilateral CA3 were normally distributed. Data on eTIV was not normally distributed according to the Shapiro-Wilk test (p=0.019).

subfield	Range in mm3	Mean in mm3	SD	Control Range in mm3	Control mean in mm3	Control SD	Obese range in mm3	Obese mean in mm3	Obese SD	BF_{10}
right subiculum	270.843 - 550.246	400.932	45.505	270.843-550.246	392.516	48.594	337.707-542.809	409.349	40.992	1.415
Left subiculum	279.303 -604.656	408.760	50.930	279.303-518.935	396.920	51.473	327.285-604.656	420.601	48.043	1.680
Bilateral subiculum	550.146-1147.465	809.693	92.007	550.146-1069.181	789.436	95.533	664.992-1147.465	829.950	84.554	2.421
Right GC_ML_DG_	234.146 - 378.284	291.779	30.750	240.504-357.188	289.351	28.445	240.504-357.188	289.351	28.445	0.244
left GC_ML_DG_	230.212 - 379.972	285.565	27.491	244.217-361.858	285.191	27.217	230.212-379.972	285.940	28.051	0.224
Bialteral GC_ML_DG	464.358 - 758.256	577.344	55.792	489.219-709.440	574.542	53.144	464.358-758.256	580.147	58.761	0.235
Right CA4	192.179 - 309.894	242.271	25.531	198.966-292.923	239.874	23.756	192.179-309.894	244.669	27.234	0.292
left CA4	191.611-319.947	235.023	22.647	198.583-290.325	234.088	21.832	191.611-319.947	235.957	23.634	0.218
Bialteral CA4	393.208-629.841	477.294	45.472	401.724-574.827	473.961	43.517	393.208-629.841	480.626	47.581	0.265
Right CA3	160.633-316.380	241.993	31.819	193.069-316.380	240.225	29.038	160.636-304.788	243.761	34.602	0.234
Left CA3	162.226-295.204	224.320	29.286	163.218-279.122	224.819	27.627	162.226-295.204	223.821	31.149	0.218
Bialteral CA3	357.365-591.180	466.313	54.744	372.499-575.099	465.044	51.471	357.365-591.180	467.582	58.365	0.217
Right CA1	490.630-967.960	639.891	78.951	501.375-827.218	622.611	68.240	490.630-976.960	657.172	85.646	1.414
Left CA1	454.956-924.585	613.257	76.603	454.956-765.992	601.042	75.956	495.890-924.585	625.472	76.089	0.728
Bialteral CA1	968.660-1892.545	1253.148	149.529	968.660-1593.210	1223.652	140.383	986.520-1892.545	1282.643	154.008	1.363
Right whole hippocamous	2817.087-5684.099	4010.432	490.192	3128.989-5694.009	4032.179	512.759	2817.087-5268.671	3988.685	471.076	0.230

subfield	Range in mm3	Mean in mm3	SD	Control Range in mm3	Control mean in mm3	Control SD	Obese range in mm3	Obese mean in mm3	Obese SD	BF_{10}
Left whole hippocamous	3226.191-5748.745	3983.767	471.255	3226.191-5748.745	4011.003	549.269	3226.191-5748.745	4011.003	549.269	0.223
Bialteral whole hippocampus	6355.180-11068.420	7994.199	885.076	6355.180-11068.420	8043.181	981.239	6403.833-10780.983	7945.216	784.867	0.226
eTIV	96461.647-174782.719	129971.18399	20457.119392	984387.617-1748000	1342000	212262.667	964616.474-1670000	1260000	186878.891	1.549

Table 9: Distribution of volumetric data globally and in both groups including BF10 for two sample Mann-Whitney U test.

For the control group, Shapiro-Wilk test (p= 0.087) showed eTIV to be normally distributed. right and left subiculum, left GC_ML_DG right CA1, right and bilateral whole hippocampal volumes were not normally distributed according to the Shapiro-Wilk test. Shapiro Wilk-Test showed data for the

	BMI <25 (n=47)		BMI > 25 (n=47)		BF_{10}
	Mean	Range	Mean	Range	
Age	43.98	18.88 – 70.37	43.61	4	0.215
BMI	22.4	18.01 - 24.85	45.27	23	1.783x 10^+ 44
Diabetes, n (%)	4 (8.51%)		5 (10.63%)		0.287
Systolic blood pressure Hg mm	121.915	105 - 145	126.58	110 - 150	0.642
Glucose mg/dl	94.32	76- 147	101.92	65- 262	0.293
Triglycerides mg/dl	98.532	45-238	142.04	49- 679	0.522
CRP mg/l	3.84	0.9 – 29.6	6.18	0.9-33.6	0.596
Interleukin 6 pg/ml	2.99	1.5 – 10.6	3.6	2 – 14.4	0.331
Lipoprotein(a) mg/l	189.121	93 - 800	214.250	93- 621	0.331
Insulin µU/ml	13.202	1.6 – 80.9	19.092	4– 106.2	0.714
Cigarretes per day	10.67	1- 21	16.58	2- 60	0.357
Reported history of smoking (n, %)	23 (48,93 %)		14 (29,78%)		0.527

Table 10: correlation for demographic data and biological data in both groups.

left, right and bilateral subiculum, right, left and bilateral CA1, left and bilateral hippocampus in the obese group to not be normally distributed. Data on the other subfields was normally distributed in the obese group. A two-sample Bayesian Mann-Whitney U test showed no evidence that

suggested an influence of weight category (obese/control) on hippocampal and hippocampal sub-volumes (Table 9).

A two-sample Bayesian Mann- Whitney U Test showed no evidence for a correlation between obesity-class (control and obese) biological parameters demographic data or data about previous diabetes diagnoses or smoking history, given in cigarettes (n) smoked per day, for current and previously smoking participants (Table 10).

3.3 Statistical evaluation

Because testing for data distribution showed data not to be normally distributed, Mann-Whitney U tests were used because of the robustness against non-normal distribution.

	Bayes Factor (BF_{10})
Extreme evidence for H1	>100
Very strong evidence for H1	30-100
Strong evidence for H1	10-30
Moderate evidence for H1	3-10
Anecdotal evidence for H1	1-3
No evidence	1
Anecdotal evidence for H0	0.333 (1/3)
Moderate evidence for H0	0.1 (1/10)
strong evidence for H0	0.03 (1/30)
Very strong evidence for H0	0.01 (1/100)
Extreme evidence for H0	<0.01 (<1/100)

Table 11:Significance thresholds for BF_{10} (Lee and Wagenmakers, 2013)

To avoid false positives due to multiple testing, bayesian t-tests and Bayesian correlation were used (Kubsch et al., 2021). Significance thresholds for Bayes Factor 10 (BF_{10}) were adopted from Lee and Wagenmakers (Lee and Wagenmakers, 2013) as follows:

3. 3.1 Correlations

Correlatrions are listed and elaborated according to the subfield and following in the groups obese/control.

Whole Hippocampus:

For the whole hippocampus, bayesian correlation showed no significant correlation of any biological parameter on bilateral, left or right hippocampal volumes (Table 12).

whole hippocampus	Left	Right	Bilateral	n=
BMI	0.178	0.154	0.172	94
Age	0.129	0.129	0.129	94
CRP	0.149	0.152	0.149	71
IL-6	0.198	0.241	0.233	71
Insulin	0.148	0.241	0.172	71
Lipoprotein a	0.207	0.195	0.203	49
Val-syst	0.271	0.157	0.200	71
Glucose	0.155	0.148	0.151	71
Triglyc	0.185	0.180	0.190	71
Diabetes	0.185	0.166	0.177	94
Smoke cig	0.136	0.235	0.173	90

Table 12: correlations for whole hippocampal volume for all participants.

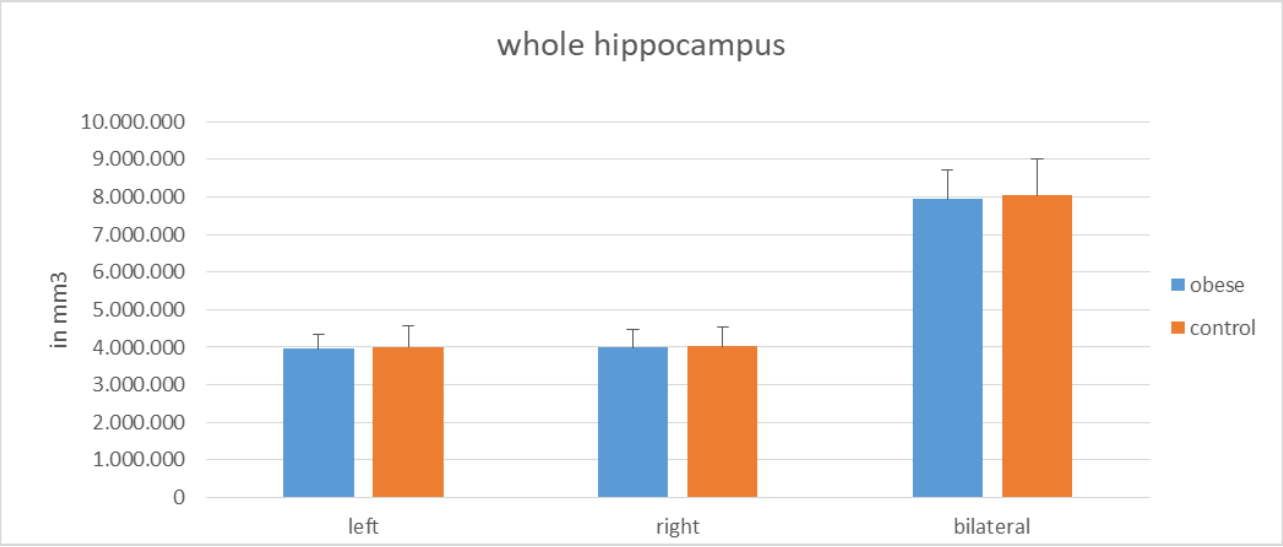

Fig. 10: group comparison of left, right and bilateral hippocampal volumes for obese and control groups.

A two-sample Bayesian Mann-Whitney U Test showed no significant difference in obese and healthy-weight participants in neither left (BF_{10}=0.223) or right (BF_{10}=0.230) hippocampal volumes. No significant difference was observed in total bilateral hippocampal volumes in the obese and control group (BF_{10}=0.226) (Fig.10).

No significant correlations were observed in in-group testing for neither the control (Table. 13) nor obese group (Table 14). In the control group, anecdotal evidence suggests an influence of glucose on the right (BF_{10}=1.073) and bilateral hippocampal volumes (BF_{10}=1.094). Testing also produced anecdotal evidence for an influence of glucose on bilateral hippocampal volumes as well as an influence of previously diagnosed diabetes on right hippocampal volume. This however remained non-significant.

whole hippo (control)	Left	Right	Bilateral	n=
BMI	0.211	0.184	0.187	47
Age	0.182	0.229	0.191	47
CRP	0.182	0.182	0.182	47
IL-6	0.218	0.705	0.370	47
Insulin	0.206	0.182	0.189	47
Lipoprotein a	0.309	0.312	0.320	33
Val-syst	0.182	0.215	0.188	47
Glucose	0.871	1.073	1.094	47
Triglyc	0.756	0.968	1.119	47
Diabetes	0.277	1.105	0.563	47
Smoke cig	0.183	0.190	0.186	47

Table 13: correlation for whole hippocampus in the control group

whole hippo (obese)	Left	Right	Bilateral	n=
BMI	0.269	0.232	0.261	47
Age	0.182	0.227	0.194	47
CRP	0.305	0.253	0.265	24
IL-6	0.390	0.254	0.281	24
Insulin	0.267	0.454	0.359	24
Lipoprotein a	0.390	0.436	0.448	16
Val-syst	1.581	0.373	0.704	24
Glucose	0.899	0.365	0.569	24
Triglyc	0.259	0.257	0.259	24
Diabetes	0.226	0.587	0.370	47
Smoke cig	0.220	0.773	0.423	47

Table 14: correlation for whole hippocampus in the obese group

CA1

Bayesian correlation showed very strong evidence for an influence of lipoprotein (a) on bilateral CA1 volumes (BF_{10}=61.873) (Fig.11c, Table 15). Extreme evidence was observed for an influence of lipoprotein (a) on left volumes of the CA1 (BF_{10}=192.409) (Fig. 11d). Bayesian correlation plots

CA1	Left	Right	Bilateral	n=
BMI	0.341	0.545	0.473	94
Age	0.129	0.129	0.129	94
CRP	5.583	5.377	7.399	71
IL-6	2.249	2.568	3.013	71
Insulin	0.198	0.415	0.218	71
Lipoprotein a	192.409	7.695	61.873	49
Val-syst	0.180	0.151	0.163	71
Glucose	0.174	0.186	0.182	71
Triglyc	0.167	0.172	0.171	71
Diabetes	0.335	0.458	0.420	94
Smoke cig	0.132	0.134	0.132	90

Table 15: correlations for CA1 volumes for all participants

showed a flooring effect at 100 mg/l. This is due to the lower detection-limit of the employed Lp(a) measurement. After a pass-through filter was applied at mg/l=100, to control for this effect, BF_{10} remained at 37.717 for bilateral volumes (Fig. 11a) and at BF_{10}= 53.049 for the left CA1 (Fig. 11b).

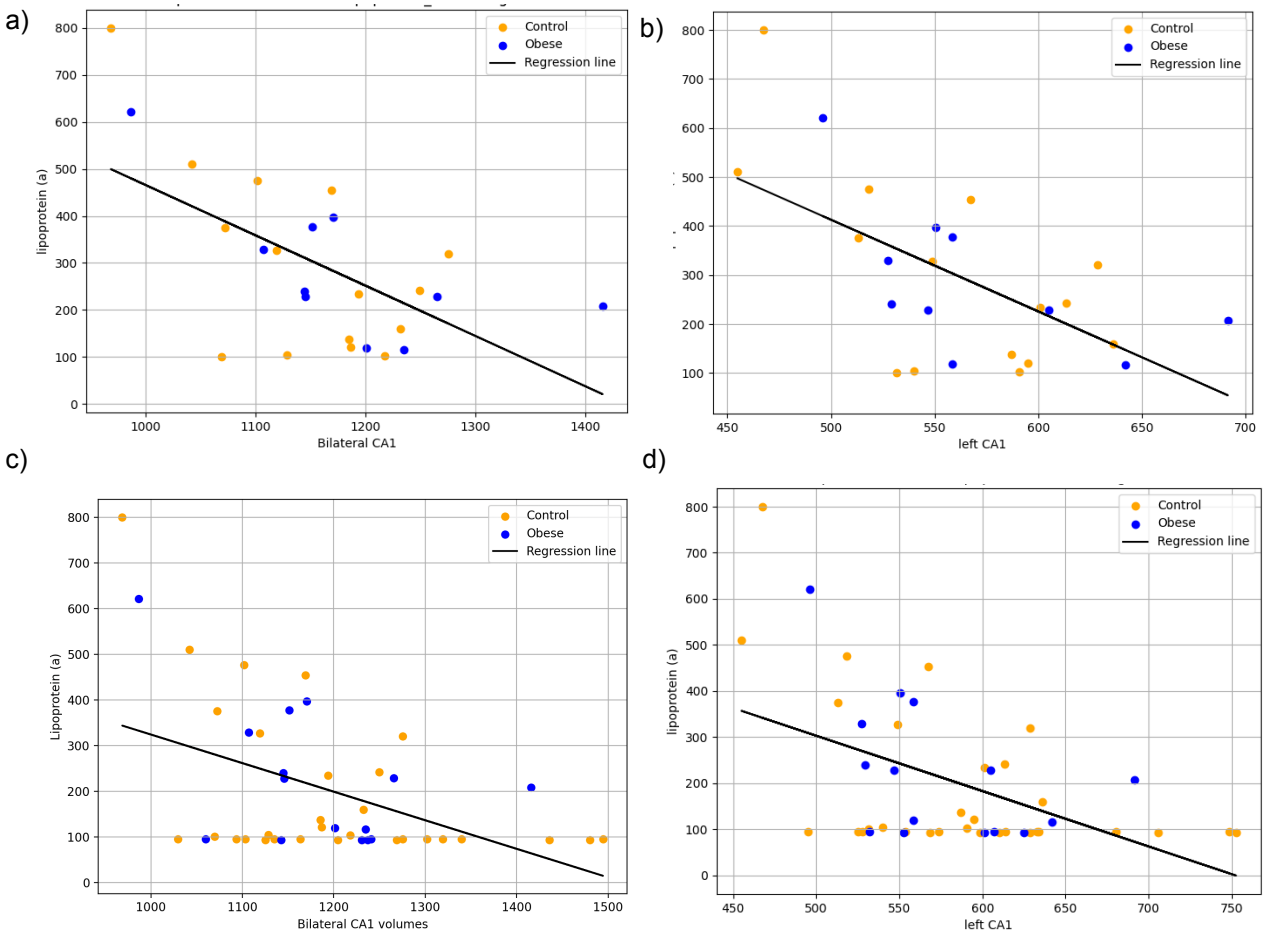

Fig. 11: bayesian correlation plots for bilateral CA1 volumes (a &c), and left CA1 volumes (b&d) with (a&b) and without (c&d) a pass-through filter at 100mg/l.

For right CA1 evidence for an influence of Lipoprotein (a) remained moderate (BF_{10}=7.695) and therefore non-significant. Moderate evidence was found to suggest an influence of CRP on left (BF_{10}=5.583), right (BF_{10}=5.377) and bilateral CA1 volumes (BF_{10}=7.399). Anecdotal and moderate evidence points to an influence of Interleukin-6 on left (BF_{10}=2.249), right (BF_{10}=2.568) and bilateral CA1 volumes (BF_{10}=3.013). This however remains non-significant.

A two-sample Bayesian Mann-Whitney U test showed no significant difference in left and right CA1 volumes in obese and healthy-weight participants. For the left CA1 the test showed evidence of BF_{10}=0.728. On the right, evidence for a difference was BF_{10}=1.414. For bilaterally added volume

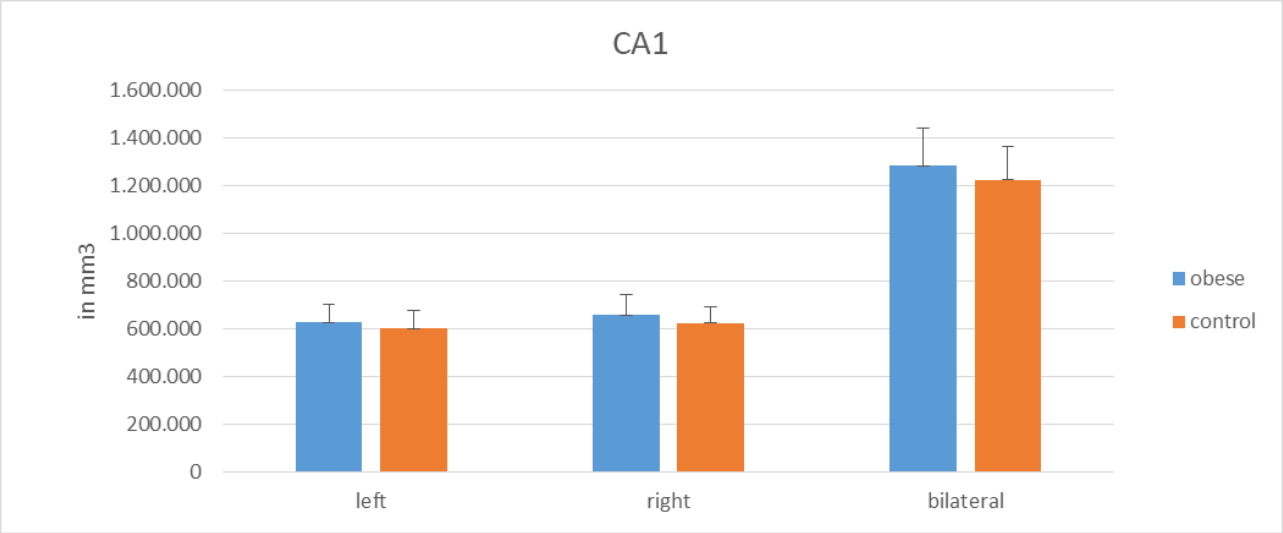

Fig. 12: group comparison of left, right and bilateral CA1 volumes in both groups

there was no evidence of a significant correlation (BF_{10}=1.363).

CA1 in control:

CA1 (control)	Left	Right	Bilateral	n=
BMI	0.201	0.189	0.195	47
Age	0.196	0.496	0.271	47
CRP	4.519	3.450	4.768	47
IL-6	1.237	1.843	1.678	47
Insulin	0.248	0.437	0.322	47
Lipoprotein a	20.518	3.120	10.387	33
Val-syst	0.294	0.324	0.317	47
Glucose	0.231	0.329	0.273	47
Triglyc	0.191	0.197	0.194	47
Diabetes	0.376	0.642	0.501	47
Smoke cig	0.199	0.182	0.185	47

Table 16: correlations for CA1 in the control group

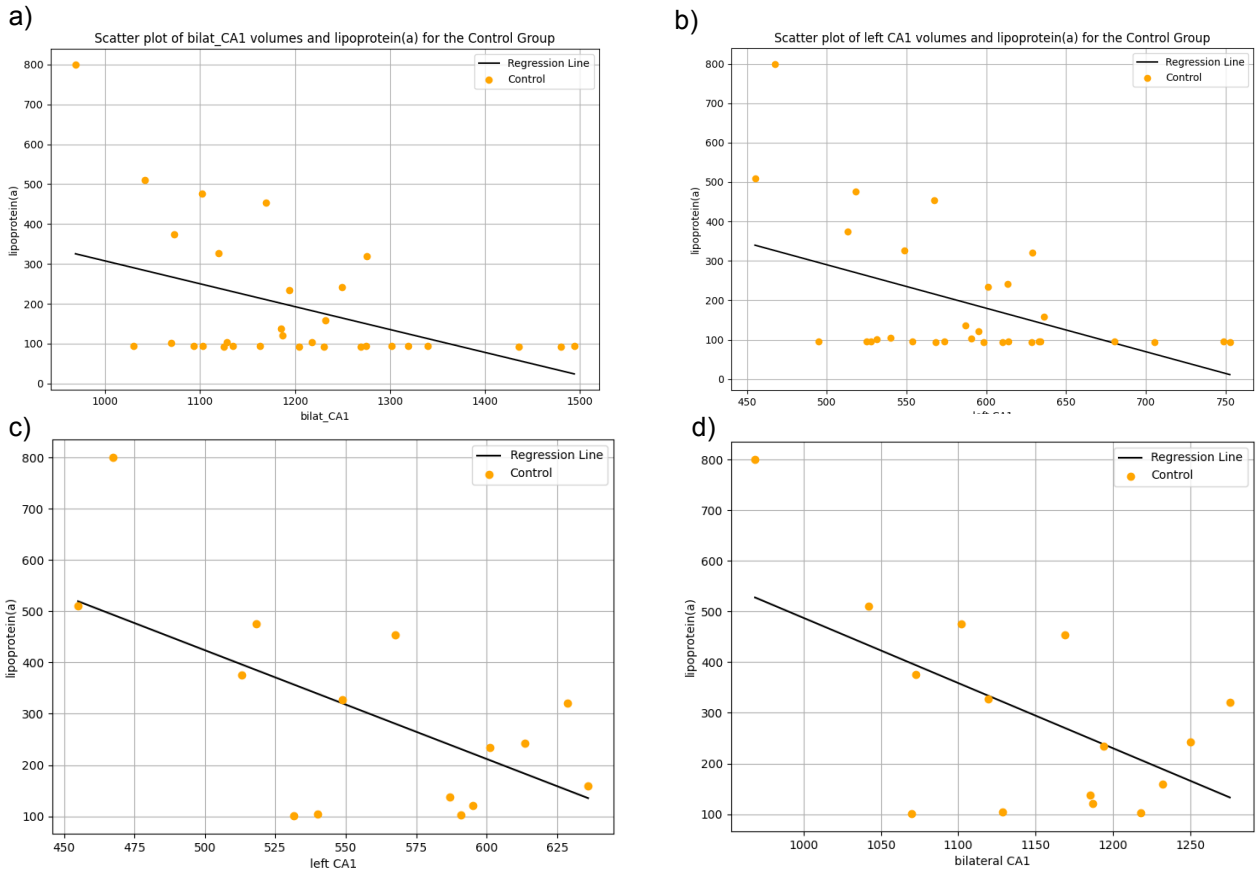

Fig. 13: Scatterplots of bilateral CA1 volumes with (d) and without filter (a) at <100 mg/l for lipoprotein (a), as well as for left CA1 volumes (b &c) in the control group

Bayesian correlation showed strong evidence for an influence of lipoprotein (a) on the left (BF_{10}= 20.518) and bilateral volumes (BF_{10}=10.387) of the CA1 (Table 16). Moderate evidence was observed for an influence of CRP on left (BF_{10}= 4.519) right (BF_{10}= 3.450) and bilateral CA1 volumes (BF_{10}=4.768). After applying the passthrough filter for Lp(a) BF_{10} for left CA1 remained at 8.589 (figure 13a), and for bilateral volumes BF_{10}= 5.217 (figure 13b)

CA1 in obese participants

CA1 (obese)	Left	Right	Bilateral	n=
BMI	0.182	0.258	0.205	47
Age	0.192	0.294	0.234	47
CRP	0.413	0.547	0.519	24
IL-6	0.580	0.513	0.605	24
Insulin	0.255	0.319	0.279	24
Lipoprotein a	1.982	0.660	1.308	16
Val-syst	0.254	0.441	0.307	24
Glucose	0.256	0.256	0.256	24
Triglyc	0.310	0.346	0.340	24
Diabetes	0.257	0.249	0.257	47
Smoke cig	0.192	0.191	0.191	47

Table 17: correlations for CA1 in the obese group

For the obese group, none of the biological parameters reached significance in Bayesian correlation testing. The highest Bayesian factors were observed in lipoprotein (a) influence on the left (BF_{10}= 1.982) and bilateral (BF_{10}= 1.307) volumes. However, these provide at most anecdotal evidence (table 17).

CA3:

CA3	Left	Right	Bilateral	n=
BMI	0.136	0.131	0.129	94
Age	0.129	0.129	0.129	94
CRP	0.605	0.173	0.309	71
IL-6	0.415	0.201	0.308	71
Insulin	0.245	0.154	0.189	71
Lipoprotein a	2.331	0.358	1.058	49
Val-syst	0.149	0.189	0.162	71
Glucose	0.161	0.165	0.148	71
Triglyc	0.280	0.286	0.323	71
Diabetes	0.143	0.718	0.215	94
Smoke cig	0.135	0.546	0.241	90

Table 18: correlations for CA3 volumes for all participants

In the CA3 none of the biological parameters correlated significantly with volumes of the left, right and bilateral CA3. An influence of lipoprotein a was observed, however, it remained non-significant and provided only anecdotal evidence (Table 18).

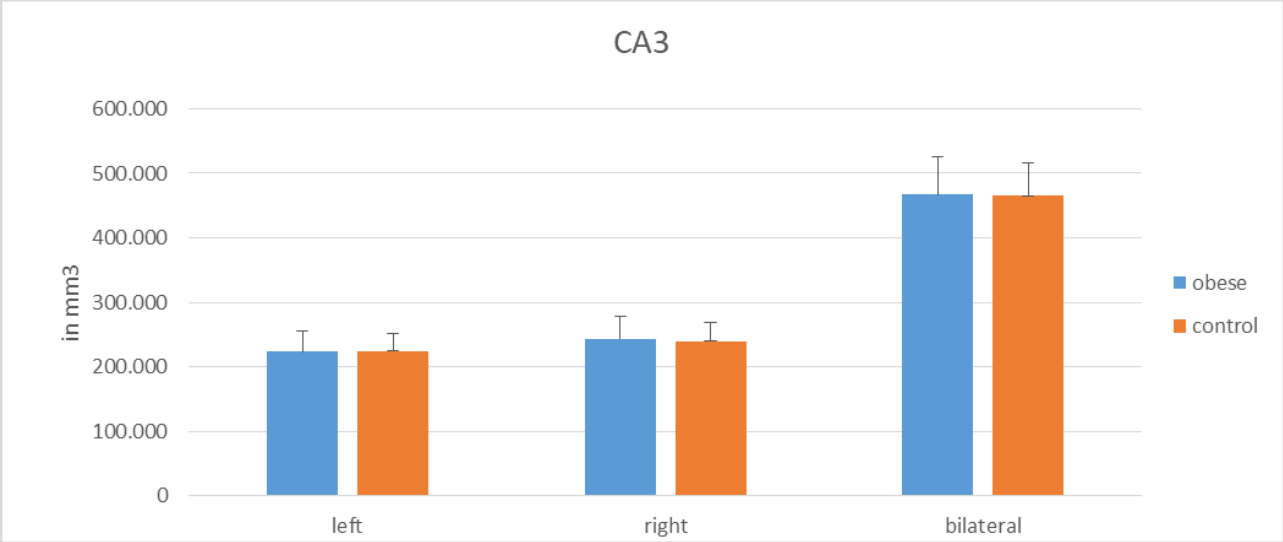

Figure 14: group comparison of left, right and bilateral CA3 volumes in both groups

A Mann-Whitney U test showed no evidence for a difference in left CA3 volumes in obese and healthy-weight participants (BF_{10}=0.218). For the right CA3, the test showed no evidence for a significant difference (BF_{10}=0.234). For bilateral volumes, there was no evidence for an influence of weight group on CA3 volumes (BF_{10}=0.217) (Fig. 14).

in the control group:

CA3 (control)	Left	Right	Bilateral	n=
BMI	0.234	0.498	0.365	47
Age	0.186	0.340	0.240	47
CRP	0.834	0.266	0.504	47
IL-6	0.405	0.287	0.382	47
Insulin	0.202	0.204	0.208	47
Lipoprotein a	8.487	0.374	1.712	33
Val-syst	0.225	0.207	0.223	47
Glucose	0.386	0.201	0.197	47
Triglyc	0.220	0.201	0.215	47
Diabetes	0.257	0.258	0.182	47
Smoke cig	0.215	0.183	0.188	47

Table 19: correlations for CA3 volumes in the control group

In the control group, no significant correlation between biological parameters and left, right or bilateral CA3 volumes was observed (Table 19). There is moderate evidence for an influence of lipoprotein (a) levels on left CA3 volumes (BF_{10}=8.487) in the control group. There was no correlation between the biological parameters and the left CA3, for bilateral volumes correlation only amounts to anecdotal evidence (BF_{10}= 1.712).

CA3 in the obese group :

CA3 (obese)	Left	Right	Bilateral	n=
BMI	0.193	0.217	0.210	47
Age	0.186	0.255	0.218	47
CRP	0.272	0.260	0.254	24
IL-6	0.301	0.254	0.272	24
Insulin	0.313	0.256	0.263	24
Lipoprotein a	0.309	0.338	0.314	16
Val-syst	0.289	0.794	0.457	24
Glucose	0.253	0.258	0.254	24
Triglyc	0.509	0.594	0.635	24
Diabetes	0.253	0.786	0.441	47
Smoke cig	0.243	1.169	0.610	47

Table 20: correlations for CA3 volumes in the obese group

In the obese group, no significant correlations were observed for bilateral CA3 volumes and biological parameters. Anecdotal evidence suggests an influence of the number of smoked cigarettes on the right CA3, this correlation remains non-significant (Table 20).

CA4:

CA4	Left	Right	Bilateral	n=
BMI	0.130	0.155	0.141	94
Age	0.129	0.129	0.129	94
CRP	0.980	0.614	0.918	71
IL-6	2.225	0.747	1.549	71
Insulin	0.676	0.235	0.399	71
Lipoprotein a	15.936	0.816	4.116	49
Val-syst	0.222	0.204	0.220	71
Glucose	0.187	0.226	0.212	71
Triglyc	0.264	0.460	0.378	71
Diabetes	0.218	0.861	0.456	94
Smoke cig	0.135	0.165	0.148	90

Table 21: correlations for CA4 volumes for all participants

For the left CA4, bayesian correlation showed strong evidence for an influence of Lipoprotein on left CA4 volumes (BF_{10}=15.936). Bilaterally a Bayes factor of 4.116 showed moderate evidence for an influence of lipoprotein (a) on CA4 volumes. There is anecdotal evidence pointing to an involvement of IL-6 values in CA4 volumes on the left (BF_{10}=2.225) and bilaterally (BF_{10}=1.549). This however remains non-significant (Table 21). For the correlation with lipoprotein a, the initial effect of BF_{10}=15.936 (fig. 15a) remained relatively unaffected by applying the filter at 100mg/l at BF_{10}= 12.570 (fig. 15b).

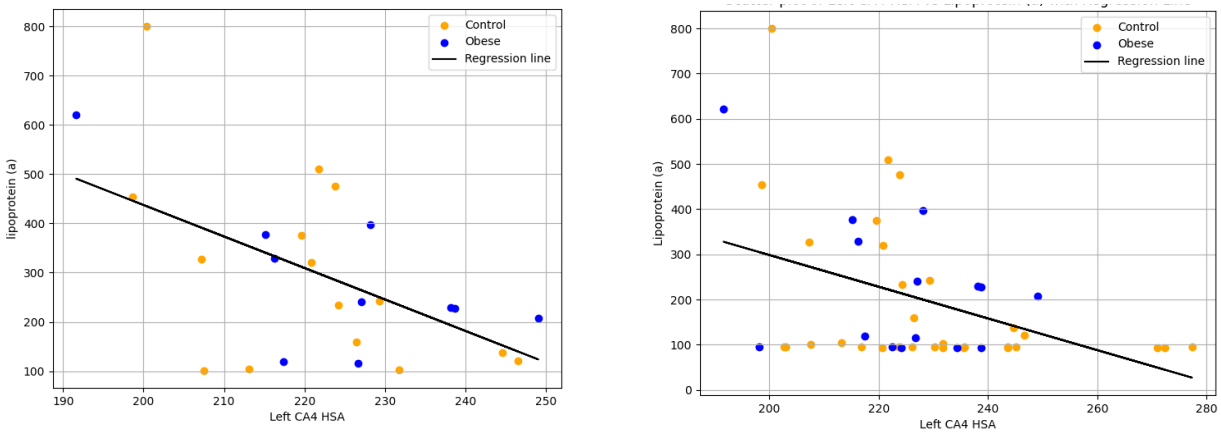

Fig. 15: bayesian correlation plots for left CA4 with (a) and without (b) a pass-through filter at 100mg/l

A two-sample bayesian Mann-Whitney U test showed no significant difference in right CA4 volumes in obese and healthy-weight participants (BF_{10}=0.0.292) (Fig.16). For the left CA4 t-test showed no significant difference (BF_{10}=0.218). Bilaterally no significant correlation (BF_{10}= 0.265) can be observed.

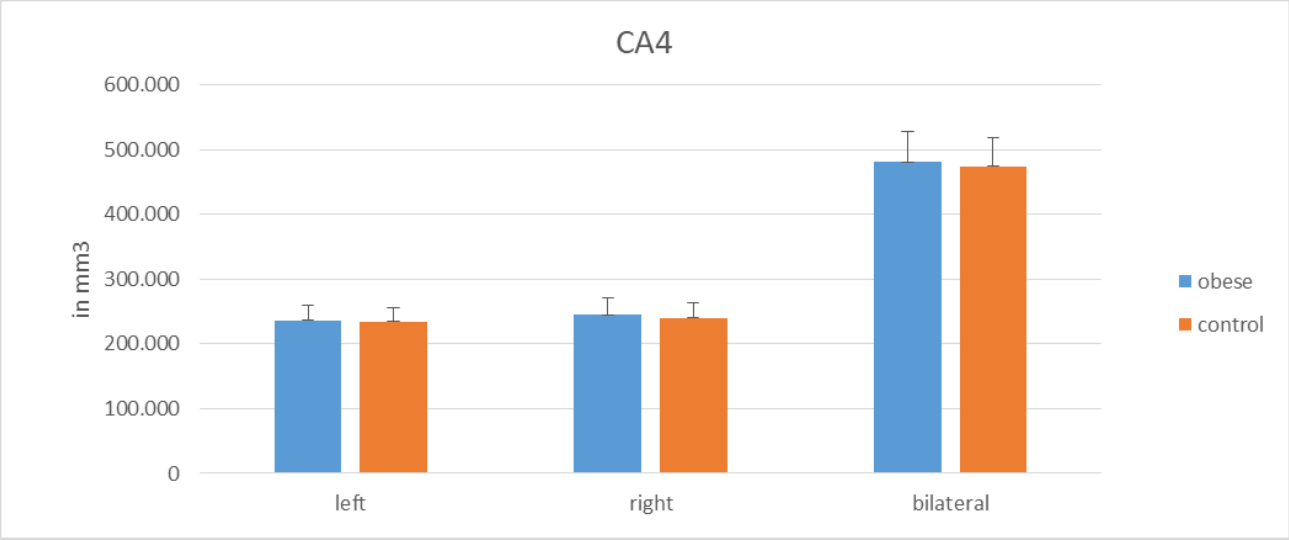

Fig. 16: group comparison of left, right and bilateral CA4 volumes in both groups

CA4 control

CA4 (control)	Left	Right	Bilateral	n=
BMI	0.206	0.182	0.188	47
Age	0.201	0.285	0.239	47
CRP	2.061	1.255	1.973	47
IL-6	4.428	0.593	1.660	47
Insulin	0.473	0.409	0.478	47
Lipoprotein a	5.139	0.675	2.006	33
Val-syst	0.182	0.193	0.187	47
Glucose	0.242	0.312	0.284	47
Triglyc	0.187	0.182	0.182	47
Diabetes	0.197	0.317	0.246	47
Smoke cig	0.190	0.182	0.184	47

Table 22: correations for CA4 volumes in the control group

Bayesian correlation showed moderate evidence for a correlation between lipoprotein (a) and left CA4 volumes (BF_{10}= 5.139), bilaterally the Bayes factor showed at most anecdotal evidence (BF_{10}=2.006). Furthermore, moderate evidence for an influence of interleukin-6 for the left (BF_{10}=4.428) and anecdotal evidence for the influence of interleukin-6 bilaterally (BF_{10}=1.660) have been observed. Anecdotal evidence suggests an influence of CRP levels on left (BF_{10}=2.061), right (BF_{10}=1.255) and bilateral (BF_{10}=1.973) CA4 volumes. None of the given correlations reached a level of significance (Table 22).

CA4 obese

CA4 (obese)	Left	Right	Bilateral	n=
BMI	0.211	0.242	0.233	47
Age	0.195	0.237	0.218	47
CRP	0.259	0.259	0.260	24
IL-6	0.312	0.373	0.355	24
Insulin	0.357	0.253	0.278	24
Lipoprotein a	0.726	0.375	0.537	16
Val-syst	0.497	0.818	0.723	24
Glucose	0.258	0.272	0.265	24
Triglyc	0.342	0.893	0.570	24
Diabetes	0.333	0.748	0.555	47
Smoke cig	0.190	0.250	0.209	47

Table 23: correlations for CA4 volumes in the obese group

The Bayesian correlation did not produce any evidence for a correlation of biological parameters and CA4 volumes for the obese group (Table 23).

GC_ML_DG

GC_ML_DG	Left	Right	Bilateral	n=
BMI	0.129	0.144	0.133	94
Age	0.129	0.129	0.129	94
CRP	0.932	1.043	1.200	71
IL-6	2.578	1.103	2.087	71
Insulin	1.285	0.266	0.564	71
Lipoprotein a	14.329	1.507	6.492	49
Val-syst	0.228	0.193	0.215	71
Glucose	0.194	0.207	0.207	71
Triglyc	0.296	0.406	0.377	71
Diabetes	0.484	0.979	0.797	94
Smoke cig	0.132	0.136	0.133	90

Table 24: correlations for GC_ML_DG volumes for all participants

For the left GC_ML_DG, Bayesian correlation showed strong evidence for a correlation of Lipoprotein (a) with the left GC_ML_DG (BF_{10}=14.329) (Figure 17a, Table 24). With a filter at 100mg/l, the evidence remained at BF_{10}= 7.843 (Figure 17b). Bilaterally moderate evidence suggests an involvement of Lipoprotein (a) (BF_{10}=6.492).

There is anecdotal evidence pointing to a correlation between Interleukin-6 levels and left (BF_{10}=2.578), right (BF_{10}=1.103) and bilateral (BF_{10}=2.087) GC_ML_DG volumes. Furthermore, there is anecdotal evidence hinting at a possible correlation between fasting insulin levels and GC_ML_DG volumes (BF_{10}=1.285). These did not reach significant levels (Table 24).

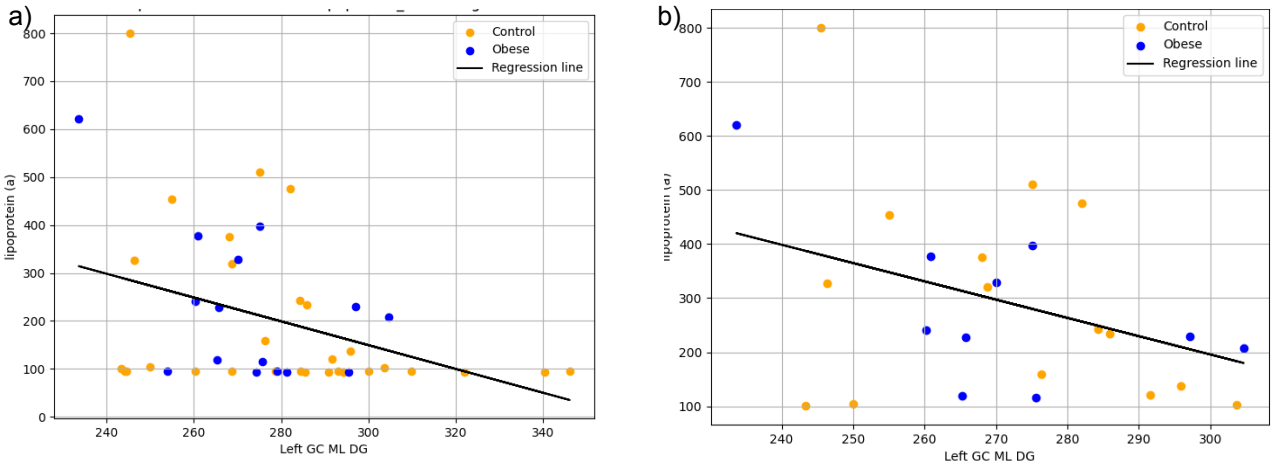

Fig. 17: bayesian correlation plots for lipoprotein (a) and left GC_ML_SG with (b) and without filter (a)

A bayesian two sample Mann-Whitney U test showed no significant difference in right GC_ML_DG volumes in obese and healthy-weight participants (BF_{10}=0.244). For the left GC_ML_DG, the test showed no significant difference (BF_{10}=0.224) as well as for bilateral volumes (BF_{10}=0.235) (Fig. 18).

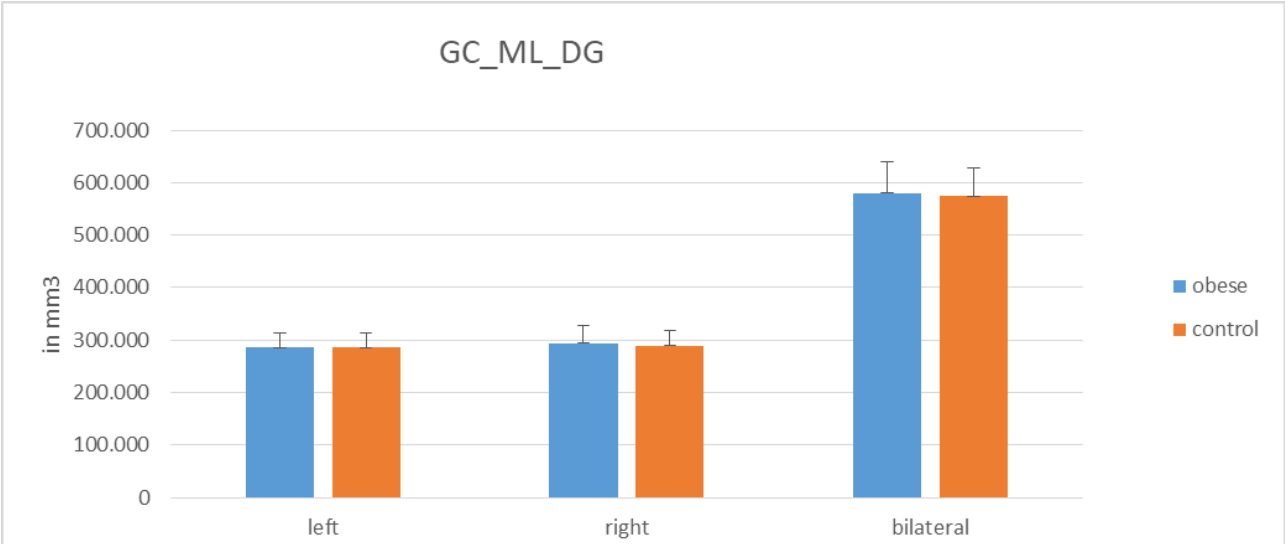

Fig. 18: group comparison of left, right and bilateral GC_ML_DG volumes in both groups

GC_ML_DG in the control group

In the control group, the Bayesian correlation produced moderate evidence for an influence of Lipoprotein (a) on the left (BF_{10}=5.506) and right GC_ML_DG volumes (BF_{10}=3.017). Anecdotal evidence suggests a correlation between CRP and left (BF_{10}=1.628), right (BF_{10}=1.255) and bilateral volumes (BF_{10}=1.332). Anecdotal evidence links Interleukin-6 levels to left (BF_{10}=2.375) and bilateral (BF_{10}=1.332) GC_ML_DG volumes. All these correlations remain non-significant (Table 25).

GC-ML-DG (control)	Left	Right	Bilateral	n=
BMI	0.184	0.182	0.182	47
Age	0.236	0.285	0.261	47
CRP	1.628	1.255	2.210	47
IL-6	2.375	0.593	1.332	47
Insulin	0.480	0.409	0.576	47
Lipoprotein a	5.506	0.675	3.017	33
Val-syst	0.186	0.193	0.200	47
Glucose	0.296	0.312	0.379	47
Triglyc	0.182	0.182	0.182	47
Diabetes	0.280	0.317	0.394	47
Smoke cig	0.182	0.182	0.182	47

Table 25: correlations for GC_ML_DG in the control group

GC_ML_DG in obese

In the obese group, bayesian correlation showed anecdotal evidence of systolic blood pressure affecting the right (BF_{10}=1.097) and bilateral GC_ML_DG volumes (BF_{10}=1.047). This however remained a non-significant effect (Table 26).

GC-ML-DG (obese)	Left	Right	Bilateral	n=
BMI	0.206	0.241	0.226	47
Age	0.223	0.229	0.230	47
CRP	0.257	0.270	0.264	24
IL-6	0.386	0.463	0.448	24
Insulin	0.580	0.254	0.298	24
Lipoprotein a	0.618	0.429	0.547	16
Val-syst	0.739	1.097	1.047	24
Glucose	0.254	0.254	0.254	24
Triglyc	0.421	0.745	0.606	24
Diabetes	0.496	0.484	0.522	47
Smoke cig	0.191	0.194	0.191	47

Table 26: correlations for GC_ML_DG in the obese group

Subiculum:

For the left subiculum, bayesian correlation showed anecdotal and moderate evidence for an influence of Lipoprotein (a) on the left (BF_{10}=1.071), right (BF_{10}=3.299) and bilateral subiculum volumes (BF_{10}=2.356). Anecdotal and moderate evidence for an influence was also found for Interleukin-6 levels for the left (2.307), right (2.555) and bilateral subiculum volumes (BF_{10}=3.403). Furthermore, moderate and anecdotal evidence of an influence of biological parameters was observed for CRP and left (BF_{10}=2.109), right (BF_{10}=5.961) and bilateral subiculum volumes (BF_{10}=5.043) (Table 27).

subiculum	Left	Right	Bilateral	n=
BMI	0.944	0.434	0.749	94
Age	0.129	0.129	0.129	94
CRP	2.109	5.961	5.034	71
IL-6	2.307	2.555	3.403	71
Insulin	0.251	0.215	0.244	71
Lipoprotein a	1.071	3.299	2.356	49
Val-svst	0.160	0.149	0.150	71
Glucose	0.581	0.242	0.395	71
Triglyc	0.160	0.155	0.158	71
Diabetes	0.201	0.188	0.201	94
Smoke cig	0.132	0.181	0.142	90

Table 27: correlations for subiculum volumes for all participants

A two-sample bayesian Mann-Whitney U test showed no significant difference in left subiculum volumes in obese and healthy-weight participants (BF_{10}=1.680). For the right subiculum, the test showed no evidence of a significant difference (BF_{10}=1.415). For total bilateral subiculum, the Bayes factor was BF_{10}= 2.421 (anecdotal evidence) was calculated (Fig.19).

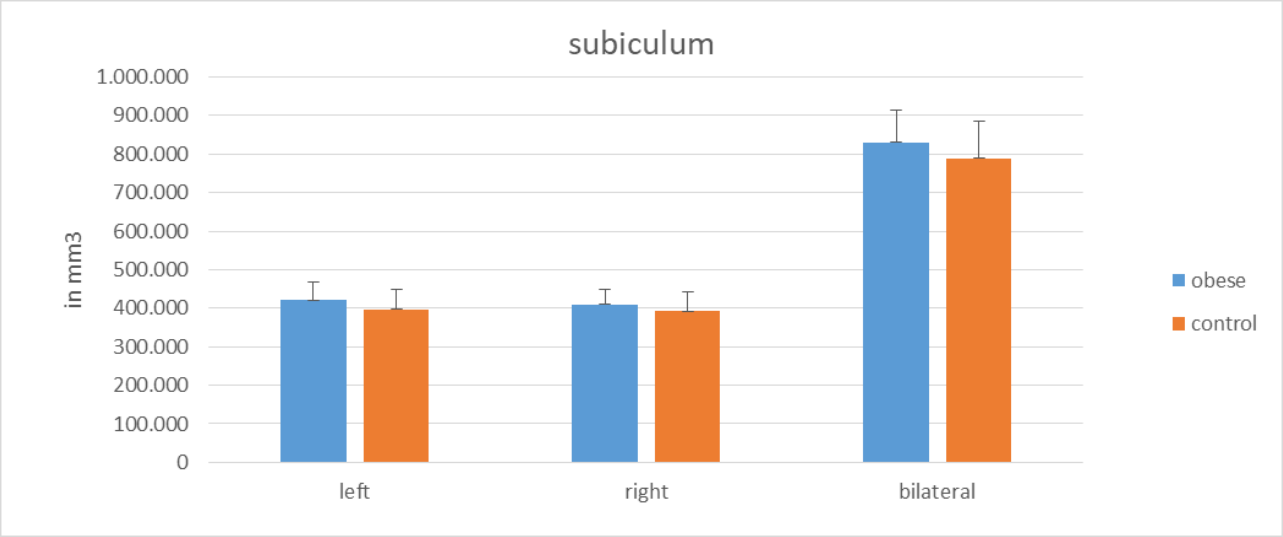

Fig.19: group comparison of left right and bilateralsubiculum volumes in both groups

Subiculum in the control group

Moderate and anecdotal effects were observed for CRP and left (BF_{10}=2.663), right (BF_{10}=9.476) and bilateral subiculum volumes (BF_{10}=6.658). For interleukin-6 and left (BF_{10}=7.590), right (BF_{10}=4.042) and bilateral subiculum volumes (BF_{10}=7.960) moderate effects were observed. For

Lipoprotein (a) anecdotal evidence suggests an effect on the right (BF_{10}=2.679) and bilateral subiculum volumes (BF_{10}=1.324). None of these effects reached a level of significance (Table 28).

subiculum (control)	Left	Right	Bilateral	n=
BMI	0.209	0.207	0.182	47
Age	0.204	0.196	0.201	47
CRP	2.633	9.476	6.658	47
IL-6	7.590	4.042	7.960	47
Insulin	0.400	0.314	0.378	47
Lipoprotein a	0.589	2.679	1.324	33
Val-syst	0.298	0.184	0.219	47
Glucose	0.497	0.261	0.371	47
Triglyc	0.198	0.194	0.198	47
Diabetes	0.464	0.332	0.421	47
Smoke cig	0.186	0.202	0.193	47

Table 28: correlations for subiculum volumes in the control group

Subiculum in obese

Bayesian correlation showed no significant effects of biological parameters on subiculum volumes in the obese group (Table 29).

subiculum (obese)	Left	Right	Bilateral	n=
BMI	0.189	0.226	0.204	47
Age	0.199	0.199	0.201	47
CRP	0.346	0.407	0.406	24
IL-6	0.288	0.405	0.355	24
Insulin	0.255	0.260	0.258	24
Lipoprotein a	0.739	0.422	0.600	16
Val-syst	0.427	0.308	0.377	24
Glucose	0.698	0.358	0.535	24
Triglyc	0.259	0.260	0.261	24
Diabetes	0.239	0.226	0.234	47
Smoke cig	0.191	0.261	0.202	47

Table 29: correlations for subiculum volumes in obese group

4. Summary of data:

The data showed a significant influence of lipoprotein on the left and bilateral CA1 volumes.

For the left this extreme effect had a Bayes Factor of BF_{10}= 192.409. Bilaterally the very strong effect was: BF_{10}= 61.873. When conducting in-group testing the main effects were observable in the control group, while BF_{10} remained less pronounced in the obese group. In the control group, a Bayes factor of 20.518 indicates Strong evidence for an influence of Lipoprotein a on left CA1 volumes as well as bilateral volumes (BF_{10} = 10.387). The effect was most pronounced globally in the left CA1 (BF_{10}= 192.409).

There was also strong evidence for an influence on GC_ML_DG volumes on the left side (BF_{10}= 14.329) and the CA4 on the left side (BF_{10}= 15.936). The global effect in these was stronger than in-group effects, with effects in both groups not reaching significant levels.

For those Subvolumes that were impacted by Lp(a) levels, other influences have been recorded, that failed to reach a significant level. For the CA1 those were CRP and Interleukin-6 levels.
CRP levels influenced left (BF_{10}=5.583), right (BF_{10}=5.377) and bilateral CA1 volumes globally, and reached moderate influence in controls for left (BF_{10}= 4.519), right (BF_{10}= 3.450) and bilateral CA1 volumes (BF_{10}=4.768).
For IL-6, anecdotal and moderate evidence points to an influence of Interleukin-6 on left (BF_{10}=2.249), right (BF_{10}=2.568) and bilateral CA1 volumes (BF_{10}=3.013).
The CA4, that was significantly impacted by Lp(a) levels, was influenced by CRP and IL-6 as well, In controls, CRP levels had an impact on left (BF_{10}=2.061), right (BF_{10}=1.255) and bilateral (BF_{10}=1.973) CA4 volumes. Globally, levels for the left reached BF_{10}=1.628, BF_{10}=1.255 for the right and BF_{10}=1.332 for bilateral volumes.Anecdotal evidence points to an influence of IL-6 on CA4 volumes on the left (BF_{10}=2.225) and bilaterally (BF_{10}=1.549). In controls, moderate evidence for an influence of interleukin-6 for the left (BF_{10}=4.428) and anecdotal evidence for the influence of interleukin-6 bilaterally (BF_{10}=1.660) have been observed.
Additionally to the significant influence of Lp(a) on the GC_ML_DG, anecdotal evidence links Interleukin-6 levels to left (BF_{10}=2.375) and bilateral (BF_{10}=1.332) volumes in the control group. In the obese group, bayesian correlation showed anecdotal evidence of systolic blood pressure affecting the right (BF_{10}=1.097) and bilateral GC_ML_DG volumes (BF_{10}=1.047).
There was also recorded influence of Lipoprotein (a) on the subiculum volumes, that failed to reach a significant level, similarly to the GC_ML_DG, the CA4 and CA1, CRP and IL-6 did also correlate with volumes. For the left subiculum, bayesian correlation showed

anecdotal and moderate evidence for an influence of Lipoprotein (a) on the left (BF_{10}=1.071), right (BF_{10}=3.299) and bilateral subiculum volumes (BF_{10}=2.356). Anecdotal and moderate evidence for an influence was also found for Interleukin-6 levels for the left (2.307), right (2.555) and bilateral subiculum volumes (BF_{10}=3.403). Furthermore, moderate and anecdotal evidence of an influence of biological parameters was observed for CRP and left (BF_{10}=2.109), right (BF_{10}=5.961) and bilateral subiculum volumes (BF_{10}=5.043). In the control group, anecdotal evidence suggests an effect of Lp(a) on the right (BF_{10}=2.679) and bilateral subiculum volumes (BF_{10}=1.324). Moderate and anecdotal effects were observed for CRP for the left (BF_{10}=2.663), right (BF_{10}=9.476) and bilateral subiculum volumes (BF_{10}=6.658). For interleukin-6 the effects were moderate and affected the left (BF_{10}=7.590), right (BF_{10}=4.042) and bilateral subiculum volumes (BF_{10}=7.960).
In regards to the question of how obesity affects the structural integrity of the hippocampus, strong and extreme evidence suggests a negative influence of lipoprotein on CA1 size most noticeably on the left side, with weaker evidence pointing to possible involvement of CRP and IL-6 as influence factors.

5. Discussion

The observed influence of lipoprotein (a) on the CA1, GC_ML_DG and CA4 present specific examples of genetically determined processes impacting hippocampal subvolumes. Higher Lipoprotein (a) levels correlated with lower CA1 volumes bilaterally and on the left, as well as lower volumes in the GC_ML_DG and the CA4.

The CA1 has been recognised as especially vulnerable to metabolic influences as well as being selectively affected, among others, by hippocampal ischemia and limbic encephalitis (Bartsch et al., 2015). Since CRP and IL-6 respond to infection and tissue injury, higher levels could be linked to injury resulting in CA1 damage. However, the effect of CRP and IL-6 remained low when compared to Lp (a). In this study, CA1 was by far the most affected area of the hippocampus, with extreme and strong evidence suggesting an influence of Lipoprotein (a) on left and bilateral CA1 volumes. These effects remained robust even when controlled for a flooring effect. A possible mechanism behind this observation could be linked to the fact, that higher levels of lipoprotein (a) have been proposed to be a risk factor for vascular dementia (Urakami et al. 2000), which in turn has been associated with a significant loss in CA1 volume (Kril et al., 2002). Additionally, Lp(a) has pro-inflammatory, thrombogenic procoagulant properties (Hajjar et al. 1989). The CA1 subfield is especially vulnerable to suffering the effects resulting in delayed neuronal death (Bartsch et al., 2015).

Other hippocampal sub-volumes that were negatively affected by Lp(a) levels include the GC_ML_DG and CA4. The DG is known to be a site of increased adult neurogenesis (Stuchlik et al., 2022; Clelland et al. 2009; Lavenex, 2012). A decrease in size could point to inhibited

neurogenesis as a result of inflammatory states (Chesnokova et al., 2016). As part of the immune response, IL-6 is released, which in turn stimulates CRP. The increase in both correlated, albeit not significantly, with lower GC_ML_DG volumes in this study. The CA4 area was similarly affected by CRP and Il-6 in the presented study. Since the CA4 is located at the hillus of the DG this might be due to its spatial relation to the GC_ML_DG (Taupin, 2007; Cauhan et al., 2021). Findings on the influence of lipoprotein (a) on neurogenesis are sparse, however, the apoE genotype ε4, which is associated with higher Lp(a) levels, has been linked to impaired hippocampal neurogenesis in mice (Li et al., 2009).

A possible mechanism for the effect of lipoprotein (a) on hippocampal volumes of the CA1, CA4 and GC_ML_DG could lie in the genetically determined concentration and molecular weight of Lipoprotein (a) as well as apoE genotype. There are different types of of Lp (a), distinguishable by their molecular masses of protein and sugar chain moieties (Urakami et al. 2000). Smaller types of lipoprotein (a) are generally associated with higher blood concentrations (Kritharides et al., 2017). High concentrations of LP(a) can have detrimental effects, since lipoprotein (a) can build up in the arterial intima, leading to atherosclerotic plaque formation, making it proatherogenic (Pasławska & Tomasik, 2023; Orsó & Schmitz, 2017; Ugovšek & Šebeštjen, 2021; Scanu et al., 1991). Additionally, lipoprotein (a) has been proposed as a risk factor for vascular dementia. The risk was especially high in those individuals whose lipoprotein (a) phenotype was of lower molecular weight (Urakami et al. 2000). Lower molecular weight in turn is associated with higher concentrations of Lp(a) (Kritharides et al., 2017). Since higher concentrations in lipoprotein (a) have been observed in this thesis study to be linked to lower volumes in CA1, GC_ML_DG and CA4, a potential influence of lipoprotein (a) phenotype linked to lower molecular weight might be of special relevance. It could be that those participants that had higher levels of Lipoprotein (a) did so because their Lipoprotein (a) was of lower molecular weight, which is associated with a higher risk for vascular dementia.

Importantly, there is an interplay of apoE and Lipoprotein (a). Lipoprotein concentrations are reported to be generally lower in those individuals with ε2 genotypes compared to ε3 and ε4 genotypes (Moriarty et al., 2016; Kritharides et al. 2017). It could be that the high lipoprotein (a) levels observed in this study correlate with an ε4 genotype in the participants. In that case, the observed correlation between lower CA1, GC_ML_DG and CA4 volumes could potentially show early degenerative effects suffered by carriers of the ε4 apoE allele, since ε4 is known to be the strongest genetic predictor for Alzheimer's disease (Raulin et al, 2022; Corder et al. 1993). Conversely, the apoE phenotype ε2, which is associated with lower lipoprotein (a) levels (Blanchard et al., 2019) is also proposed as a protective factor (compared to ε3 and ε4) in assessing the risk for Alzheimer's (Raulin et al, 2022).

For those individuals that carried the apoE ε4 allele, Mooser et al. proposed lipoprotein (a) as a risk factor for late-onset Alzheimer's. Contrasting this, Lp (a) had the opposite effect on those, who did not carry the ε4 allele. For them, it reduced the risk of late-onset Alzheimer's disease (Mooser et al., 2000).

Reduced risk for late-onset Alzheimer's in older patients with higher lipoprotein (a) levels was observed by Solfrizzi et al. (2002) as well as for middle-aged male Caucasian individuals (Kunutsor et al., 2016)

The described degenerative effects present different consequences for each affected subfield.

The CA1 has a major role in transferring excitatory information via the deep layers of the EC or subiculum, it is a key output node of the whole hippocampal memory circuit (Cenquizca and Swanson, 2007). Impact on the CA1 could possibly influence associated cognitive function. Degenerative effects on the CA1 have previously been observed and linked to Alzheimer's in mice (Shu et al. 2016; Yang et al., 2018) as well as in humans (Ray et al., 2013; Martins & Creegan, 2015; Schippling et al., 2000).

The DG is well connected to other subfields mainly the CA3, this, as well as the received projections from para- and presubiculum and subcortical areas (Lavenex, 2012) could be affected by DG atrophy.

Atrophy of the DG has been linked to impaired pattern separation in Patients with LGI1 Encephalitis (Hanert et al., 2019), as well as depression (Ho et al., 2013). In a study on the influence of blood lead levels on the hippocampus, atrophy of the DG and C4 region (which was also affected by lipoprotein in this study), resulted in lower scores in recall, orientation and executive function/visuospatial abilities (Shi et al, 2023).

5.1 Limitations

Limitations are listed for methods and participant studies.

5.1.1 Limitations of Methods

Relying on anatomical MRI scans does not give a measure of the functionality of subfields, their interconnection or neuron density. There was no cognitive testing, however, this is planned for at least one of the two studies that data was revisited from (Cognifast). In that study, cognitive testing will assess changes after caloric restriction.

5.1.2 Limitations of participant studies

In this study, the most striking limitation is the discrepancy between the number of women and men who took part. Out of 94 participants, only 11 were male (11.7%).

Another limitation is, that not all data was available for all participants, since they were selected from two previously conducted studies. Lipoprotein (a) data was most affected by this, with data being available for only 49 out of 94 participants. Generally, more data was available for the control group compared to the obese group. This was again most noticeable in Lipoprotein, with data for 16 obese and 33 normal-weight participants being available. The reason for this was, that blood parameters were only analysed for FOCUS participants and that lipoprotein levels were only

recorded above a concentration of 93.1 mg/l. The latter resulted in a flooring effect. Observed correlations remained robust even when controlling for this.

Additionally, those parameters assessed via a questionnaire, such as history of smoking/number of cigarettes smoked and previous diabetes diagnoses, were reliant on participants' truthful self-assessment. In the case of the measure for diabetes, this meant accepting the fact, that some participants might have diabetes, but have not yet been diagnosed. However, fasting insulin levels were also measured. Most participants in the obese group had a BMI over 40 and relied on their insurance to help with the costs of their treatment.

It is also unclear what dietary choices participants are making while taking part in the study, only the current BMI was assessed.

5.2 Outlook and Conclusion

The study provides reason to believe that levels of lipoprotein (a) can have a significant impact on neuronal health. In the future, volumetric studies would benefit from a more diverse cohort profile, especially equal gender distribution. Since the effect of lipoprotein (a) (kunutsor et al., 2016) as well as concentrations of lipoprotein(a) in blood (Kritharides et al. 2017, Moriarty et al., 2016) are greatly affected by apoE genotypes, genotyping would provide fruitful insights. Especially since the propensity to Alzheimer's disease can be linked to variations connected to lipoprotein (a) and apoE (Moriarty et al. 2016).

Furthermore, additional cognitive testing could provide supplementary data of special interest. Currently there exist different reports of cognitive performance linked to lipoprotein (a) levels. Röhr et al reported a trend of low Lp(a) concentrations and better cognitive performance, similar observations have been made by Li et al. (2021), while Sarti et al. reported no influence of lipoprotein (a) levels on cognitive performance (Sarti et al. 2001).

Since CA1, CA4 and GC_ML_DG were most affected in this study, cognitive testing in the domains of pattern separation and memory would be of special interest.

Circling back to the introduction, observing only the data that was statistically evaluated in this thesis, it cannot be determined from a neurocognitive/neuroscientific standpoint, if it would be advisable to follow Karl Nehammer's dietary advice. Although a correlation between obesity-related inflammatory markers and hippocampal subfield volumes was observed, this remained non-significant. From a broader standpoint and after considering the broad spectrum of neuroscientific literature on this topic, a high-caloric diet, based on fast food as a major source of nutrition, would bring obesity-related metabolic changes, that would be expected to impact neuronal health negatively. Since Nehammer explicitly mentioned children, further studies on younger participants could provide fruitful insights. The main observed effect of lioprotein (a) on CA1 is not mediated by external factors.

Lp (a) phenotype and levels are genetically determined (Urakami et al. 2000, Ugovšek and Šebeštjen, 2021, Orsó and Schmitz, 2017; Mooser et al., 2000; Kritharides et al., 2017; Li et al.,

2021; Pasławska and Tomasik, 2023, Röhr et al., 2020; Moriarty et al., 2016). Testing for apoE genotype as well as evaluating the type of lipoprotein (a) in the participants would be key to further understanding the mechanisms underlying the observed influence of lipoprotein (a) on hippocampal subfield volumetries.

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7. Appendix

7.1 List of figures

7.2 List of Tables

7.3 Abstract in English

The hippocampus plays a crucial role in an array of cognitive tasks such as: learning and memory, pattern separation and pattern completion, regulation of emotion, fear, anxiety, and stress (Scoville and Milner, 1957; Frankland & Bontempi, 2005; O'Reilly and McClelland, 1995; Bartsch &Wulff, 2015). The hippocampus is known to be a site of increased adult neurogenesis and neuroplasticity, making it especially vulnerable to external influences (Kempermann et al., 2015; Bartsch & Wulff, 2015), on of them being obesity-related changes in inflammation markers and metabolism. The damage to the hippocampus can be different to each subfield, thus presenting different cognitive consequences (Bartsch, 2015).

The effects of obesity-related inflammatory and metabolic changes on these subfields are the subject of investigation in this study. Anatomical MRI data, data on inflammation markers and metabolism, and data from a questionnaire are revisited for 94 participants. Ultimately, higher levels of lipoprotein(a) have been observed to correspond to lower volumes in the left and bilateral CA1. This could point to genetically determined processes impacting hippocampal subvolumes affecting brain structures crucial for long-term memory as well as related behaviour and spatial tasks. The CA1 has a major role in transferring excitatory information via the deep layers of the EC or subiculum, it is a key output node of the whole hippocampal memory circuit (Cenquizca and Swanson, 2007). Impact on the CA1 could possibly influence cognitive function related to memory and spatial tasks. Degenerative effects on the CA1 have been observed in mice and linked to Alzheimer's in humans as well (Yang et al., 2018; Ray et al., 2013; Martins and Creegan, 2015**;** Schippling et al., 2000). A direct influence of lipoprotein (a) has been observed in Vascular Alzheimer's disease (Ray et al., 2013; Moriarty et al. 2016; Urakami et al. 2000).

7.4 Kurzfassung

Der Hippocampus spielt eine entscheidende Rolle bei einer Reihe von kognitiven Aufgaben wie: Lernen und Gedächtnis, Mustertrennung und -vervollständigung, Emotionsregulation, Furcht, Angst und Stress (Scoville und Milner, 1957; Frankland & Bontempi, 2005; O'Reilly und McClelland, 1995; Bartsch & Wulff, 2015).

Der Hippocampus ist bekannt dafür, ein Ort erhöhter Neurogenese und Neuroplastizität im Erwachsenenalter zu sein, was ihn jedoch besonders anfällig für äußere Einflüsse macht (Kempermann et al., 2015; Bartsch & Wulff, 2015), zu denen auch adipositasbedingte Veränderungen von Entzündungsmarkern und Stoffwechsel gehören. Die Schädigung des Hippocampus kann für jedes subfield unterschiedlich ausfallen und somit unterschiedliche kognitive Folgen haben (Bartsch, 2015). Die Auswirkungen von fettleibigkeitsbedingten Entzündungs- und Stoffwechselveränderungen auf diese Teilbereiche sind Gegenstand der vorliegenden Studie.

Anatomische MRT-Daten, Daten zu Entzündungsmarkern und zum Stoffwechsel sowie Daten aus einem Fragebogen werden für 94 Teilnehmer erneut ausgewertet. Letztlich wurde beobachtet, dass höhere Lipoprotein(a) Werte mit geringeren Volumina im linken und bilateralen CA1 einhergehen. Dies könnte auf genetisch bedingte Prozesse hindeuten, die sich auf die Subvolumina des Hippocampus auswirken und Hirnstrukturen betreffen, die für das Langzeitgedächtnis sowie für damit zusammenhängende Verhaltensweisen und räumliche Aufgaben entscheidend sind. Der CA1 spielt eine wichtige Rolle bei der Übertragung erregender Informationen über die tiefen Schichten des EC oder Subiculum und ist ein wichtiger Ausgangsknoten des gesamten hippocampalen Gedächtniskreislaufs (Cenquizca und Swanson, 2007). Auswirkungen auf den CA1 könnten möglicherweise die kognitiven Funktionen im Zusammenhang mit dem Gedächtnis und räumlichen Aufgaben beeinflussen. Degenerative Auswirkungen auf den CA1 wurden bei Mäusen beobachtet und auch beim Menschen mit Alzheimer in Verbindung gebracht (Yang et al., 2018; Ray et al., 2013; Martins und Creegan, 2015; Schippling et al., 2000). Ein direkter Einfluss von Lipoprotein (a) wurde bei der der vaskulären Alzheimer-Krankheit beobachtet (Ray et al., 2013; Moriarty et al. 2016; Urakami et al. 2000).