A novel paradigm for testing the initial coding of hierarchical relationships within the medial temporal lobe in a circuit specific manner

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Abstract

The Medial Temporal Lobe (MTL) is central to spatial navigation and to the processing of conceptual associations, functions which can be implemented via the grid cell system. Evidence exists that also hierarchical processing - an integral part of cognitive capacities such as language, motor action and sequential planning - draws on the MTL. This raises the question of whether hierarchical processing shares the same cellular substrate with spatial navigation and concept association formation. Here we present two novel tasks (hierarchy and control) specifically designed to test (using fMRI) whether grid cells also support the representation of hierarchical relations. We present the first results of their behavioral validation with respect to specificity, and show that our hierarchical task, but not the control task, correlates well with other tasks that necessitate hierarchical processing (Tower of Hanoi and a Visual Recursion Task). Furthermore, we show that some of these effects remain even when removing the shared variance that can be explained by a range of unspecific factors. This gives reason to believe that our task is a valid method for probing the relationship between grid cells and hierarchical processing.

Significance Statement

The MTL is implicated in a variety of functions such as spatial navigation, the formation of associative and episodic memory and the extraction of schematic and hierarchical knowledge. Pinpointing part of the cellular substrate of any of these functions will give a clearer understanding of how these may be concurrently realized within the hippocampus. In this study we focus on the processing of hierarchies. In addition to that, knowledge about the cellular underpinnings would allow to link potential findings with highly detailed anatomical and invasive studies on the same circuits, predominantly conducted in rats and primates. The development and validation of an appropriate task is the first crucial step to allow rigorous empirical assessment of the cellular substrate underlying the involvement of MTL in hierarchical processing.

Structure

In this first section of this thesis, I will provide the broad context of research into which this thesis falls. This includes mainly research on rule processing in language and other cognitive domains, its evolutionary origin and its relation to canonical "memory" systems such as the hippocampus. As one of the major strengths of our approach is that it tries to establish a link to the underlying cellular substrate required for hierarchical processing, I will try to approach this level of granularity whenever possible by taking reference to data gained from animal models. In the second part, I will then present our novel tasks and their validation with respect to the cognitive construct – the capacity to process hierarchies – that I aim to probe. In the last part I will give an outlook to the planned subsequent fMRI study, foreseen necessary adjustments to the experimental design, potential analysis approaches and limitations.

Part I: Anatomical, developmental and evolutionary aspects of the neuroscience of hierarchical processing (a brief review)

Functional aspects of rule acquisition and processing

Studies on rule learning and application broadly implicate the medial prefrontal cortex in various processes relating to the acquisition and application of rules (Johnson et al., 2016). Despite considerable variation across species, the prefrontal cortex (PFC) can be consistently subdivided into orbital (OFC) and medial (mPFC) regions (Öngür and Price, 2000). Even though there is no clear cut and commonly agreed upon subdivision, the mPFC (ventromedial PFC in primates) can be described as encompassing parts of the (dorsal) anterior cingulate cortex (dACC; Broadman Area [BA] 32, BA33, BA24), prelimbic (BA32) and infralimbic cortices (BA25). Primates, in contrast to other mammalian clades, possess an additional lateral subdivision of the PFC (LPFC).

In humans, the left VLPFC (BA44, BA45, BA47/12) has been traditionally described as one of the most central language brain areas. Within the lateral subdivision of the PFC, the inferior frontal gyrus - more specifically a subfield corresponding to Broadman area 44 (BA44) - has been related to the processing hierarchies in language (Berwick et al., 2013; Friederici, 2011) but also across domains (Bianco et al., 2015; Fadiga et al., 2009; Fitch & Martins, 2014). These studies usually refer to the computational mechanism that enables the creation of linguistic hierarchies as merge (Zacarella et al., 2017). Important for the emergence of merge and the recruitment of BA44 for hierarchical processing more generally is supposedly is the expansion of connections from BA44 to superior temporal areas, which is especially strong in humans (Rilling et al., 2008). Theories about the specific function of BA44 diverge as to its specific contribution to hierarchical processing: Whereas some posit it as locus for hierarchical processing *per se* (Fadiga et al., 2009; Koechlin & Jubault, 2006), others hold a more nuanced view and see it rather as providing a set of computations that are necessary for the (automatized) processing of temporally ordered complex structures (Bornkessel-Schlesewsky et al., 2015; Dehaene et al., 2015; Martins & Villringer, 2016). In the latter view, the IFG might support online maintenance of previously acquired schemas and instantiate those in appropriate contexts.

In addition to the PFC, it is argued that the mediotemporal memory system - including hippocampus, subiculum, entorhinal, peri- and postrhinal cortices - may be additionally involved, especially for *de-novo* aquisition of hierarchical knowledge. Evidence for that can be found in studies that implicate the hippocampus in the generation of (minimal) hierarchies across domains (Berens and Bird, 2017; Martins et al. 2017; Theves et al., 2016), implicit motor sequence learning

(Schendan et al., 2003) and more generally in item-to-context binding (ICB; see Ranganath, 2010). ICB has furthermore been shown to be present in the hippocampus of rats - a species that does not possess a LPFC (McKensize et al., 2014).

These findings can be be backed by theoretical considerations: For the successful creation of hierarchical compounds, the substrate enabling this compounding needs to have/receive reference(s) to the respective items to be compounded/merged. These references can either refer to either single concepts or previously established compounds. Studies looking at the representation of concepts in the brain have provided evidence for a representation by distributed neural assemblies (Pulvermüller et al., 2014). References on a neural level to such assemblies can be realized through convergence within the cortex - i.e in association areas such as STS and BA45 - but also in the hippocampus, which similarly encompasses widespread connectivity and incidentally also takes a prominent part in associative memory consolidation closely linked to concept formation.

Evolution of cortex and higher cognitive functions

The ability to process hierarchies (including the computation of merge), is argued to be a human specific trait (Berwick et al., 2013; Fitch & Martins, 2014) and thus must have evolved during the human lineage evolution, spanning the last 7 million years of history (see Figure 1 for an overview of human brain evolution). In contrast to traditional viewpoints that imply emergence of merge in IFG in a discrete evolutionary step, others consider the possibility that it might have evolved in multiple stages (see for example Martins & Boeckx, 2019), possibly on the basis of precursors such as item-to-context binding (ICB). An intermediate non-linguistic proto-merge might have initially enabled assembly of more complex tools from simpler objects (Fujita, 2017). This gradual evolution may have tracked the expansion of the cortex (especially association areas) in close interplay/concert with connected subcortical areas, such as thalamus or hippocampus (Bruckner and Kriemen, 2013). This extends considerably the relevant evolutionary time frame during which additional permissive genomical changes might have occurred.

The cortex itself likely evolved prior to the appearance of the first amniotic species, as reptiles, birds and mammals have homologous areas (Figure 1). The cornia ammonis subfields of the hippocampus have been suggested to be an evolutionary antecedent to the layered structure of the cortex (Mercer and Thomson, 2017). This is in line with findings that show that variation on existing genetic motives can be the basis for evolutionary innovation (i.e. Carter, 2014; Fischer and O'Connell, 2017). More recent genomic innovation is mainly characterized by changes to the

regulatory regions of the genome. This includes the emergence of region-specific promoters during corticogenesis that likely have enabled areal-specialization, layering differences as well as specific neural differentiation and migration (Reilly et al., 2015). A viable source for this could be the action of Non-long terminal repeat (LTR) retrotransposons - such as L1 elements - whose proliferation has accompanied the past 80 million years of primate evolution and lead to one insertion of new genetic material into the germline for every 20-200 births through L1 action alone, which has lead to an expansion of the human genome by about 80% over the past past 150 million years of evolution (Cordeaux and Batzer, 2009). This concentration of genetic innovation to non-coding regions may be due to that fact that changes to coding regions have a stronger direct impact on the fitness of an individual and more often than not have proven fatal. As the coding capacity of the genome is inherently limited (Karmiloff-Smith, 2015), the genetic organization of the brain must follow broad principles. Some of these principles have already been discovered: The human cortex is hierarchically subdivided into modules as evidenced in regional distributions of transmitter receptors, cell types, and connectivity (Zilles and Amunts, 2012; Chen et al., 2012), potentially mediated by genetic gradients and distinct transcription factors (Arendt et al., 2016). Similarly the connectivity between cortical areas seems to follow closely the three (orthorgonal) principal axes of growth direction during brain development when projecting the folded cortical sheet onto a two-dimensional plane (Wedeen et al., 2012). This reduces the necessary signals for axonal guidance drastically and renders it efficient.
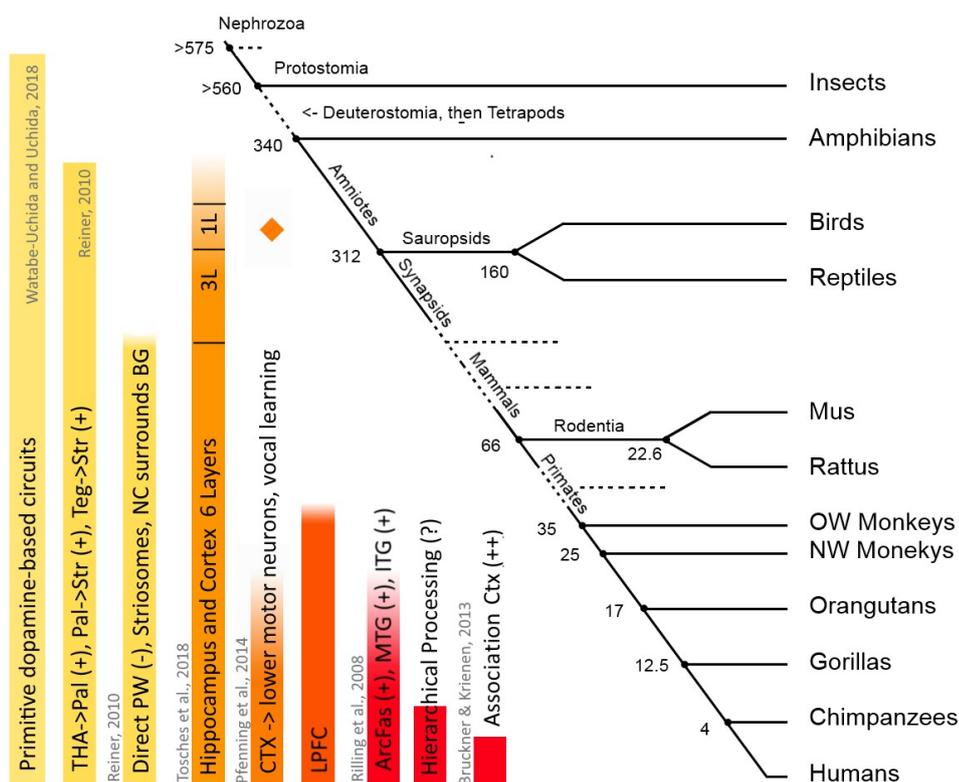

Figure 1: Evolution of the human brain. Numbers next to branches indicate the approximate number of million years ago when then branching happened. As this is mostly based on fossil data, branching times may be overestimated, see Kumar & Hedges (1998).The presence of vocal learning in some bird species (indicated by the orange diamond) points to convergent evolution.

Abbreviations: THA – Thalamus, Pal – Palladium (ProtoCortex), Str – Striatum, Teg - tegmental dopaminergic field, PW – Pathway, NC – NeoCortex, BG – Basal Ganglia, L – Layers, CTX – Cortex, LPFC – lateral Prefrontal Cortex, ArcFas – Arcuate Fasiculus. (-) decrease, (+) increase, (++) strong increase.

Vital behaviors, such as foraging, defense and aggression (Yamaguchi and Lin, 2018; Miller et al., 2019), urination (Yao et al., 2018), sleep and rest (Dibner et al., 2010; Zha and Xu, 2015) and mating and parenting (Wei et al., 2018; Kohl et al., 2018) are rooted in subcortical areas and have evolved over considerably larger evolutionary time frames. Similarly to cortical organization, also the structure of the subcortex seems to be modular (Xu, 2013). This may be a direct result from the fact that newer subcortical circuits - such as those underlying parental care and sociality - may have evolved through variation on and (minor) modification of evolutionary more ancient feeding-related peptides and circuits convergently across species (Carter, 2014; Fischer & O'Connell, 2017). Primitive dopamine-based circuits supporting such behaviors are found throughout the animal kingdom, including insects (Watabe-Uchida and Uchida, 2018). This dates their emergence prior to the division of the nephrozoa into chordata (superclade of vertebrates) and artropoda (superclase of insects) around 650 mya. Such dopamine based circuits were elaborated throughout evolution (Reiner et al., 1984) initially by establishment of the midbrain dopamine centers - Ventral Tegmental Area (VTA) and Substantia Nigra pars compacta (SNc) - followed by further diversification through gene duplication (Yamamoto et al., 2010).

The emergence of the cortex and its expansion throughout evolution also prompted the expansions of subcortical areas they receive the projections from. This includes the Thalamus (Bruckner and Kriemen, 2013) as well as the basal ganglia (Reiner, 2016). The hippocampus is another subcortical area that continuously interacts with and shapes the cortex. Its implication in hierarchical processing renders it a prime target for our current investigation.

The role of the hippocampus and grid cells

The hippocampus is key for memory acquisition, even beyond adolescence and the closure of sensitive periods of brain development. The fundamental organization of the hippocampus is consistent across species (Fanselow and Dong, 2010), yet surprisingly little is known about its evolutionary origin. Its primal role is speculated to lie in the realm of spatial navigation, but evidence for this remains outstanding. The hippocampus enables the incorporation of new memories in existing knowledge structures by a mechanism referred to as systems consolidation. For that the hippocampus has to readily acquire associations (i.e. between stimuli or context - stimulus pairs, or between events giving rise to what is referred to as "episodic memory") that are then consequently transferred to cortical areas through replay. Kitamura and colleges (2017)

showed that memory traces are created early on during learning in both hippocampus and cortical areas. In order to be able to replay the correct memory, the hippocampus has to hold a reference to the cortical memory trace. Dopamine activity likely plays a facilitatory and integrative role in the establishment both memory traces and references by providing a brain wide amplification signal during encoding (Feld and Born, 2020). This requires similar plasticity mechanisms to be at work in hippocampus and cortex. Karunakaran et al. (2016) show for example that dopamine receptor (DR) 1/5-mediated signaling onto parvalbumin-expressing (PV+) neurons supports LTP in both ventral hippocampus but also primary motor cortex in mice. This is also in line with research that shows that dopamine also directly influences sensory areas (Bao et al., 2001; Arsenault and Vanduffel, 2018) and that memory consolidation in humans may benefit from dopamine dependent amplification of neural pattern reactivation (Gerlicher et al., 2018), akin to hippocampal replay during sleep and wake. In turn, also multi-task learning realized using reinforcement algorithms modeled on dopamine function has been shown to benefit from an episodic memory-like contextual signal that gates information processing (Ritter et al., 2018). This could also be relevant for the acquisition of hierarchical knowledge, as the hippocampus might extract hierarchical dependencies akin to such a contextual signal.

The entorhinal cortex is a main input and output hub for the hippocampus. The entorinal cortex has a lateral (LEC) and a medial (MEC) subdivision in rats (corresponding to anterior later EC and posterior medial EC in humans, see Navarro Schröder et al., 2015). The MEC contains spatially selective neurons, whereas those are not present in LEC (Yoganarashima et al., 2011 [Rodents]). LEC instead has been linked to olfactory association learning (Li et al., 2017 [Mice]). LEC and MEC also differ in their layering and cellular composition, with LEC expressing a marked lack of PV+ interneurons (Witter et al., 2017 [Mice]).

Witter and colleges (2017) have extensively reviewed the inputs to the EC: Olfactory input arrives at superficial layers (LII and LIII) throughout the EC. Ventral OFC, postrhinal cortex, pre- and parasubiculum project to the superficial layers of the MEC, whereas afferents from OFC, insular and perirhinal cortex project to superficial LEC. Parietal cortex projects moderately to both superficial and deep layers (LV and LVI) of both EC subdivisions. MEC deeper layers receive visuocortical, pre- and parasubicular and almost exclusive retrosplenial input, whereas LEC deeper layers receive comparatively denser input by ACC. Principal neurons residing in the superficial layers project to different sub-fields of the hippocampus (Kitamura et al., 2015 [Mice]). Even though LII stellate cells have the most pronounced contribution to the perforant pathway (major

pathway going from EC to hippocampus), cells in all MEC layers contribute to the perforant pathway (Toader 2016 [Mice]). Superficial LEC and MEC project to partially different hippocampal subregions along the transverse axis of the CA1 field paralleled by a gradient in neuromodulator (dopamine, norepinephrine and acetycholine) receptor expression (Igarashi et al., 2014 [Rodents]). Output by the hippocampus arrives at the deep layers (LV) of the EC. MEC LVa neurons project widely throughout the cerebrum (Sürmeli et al., 2015 [Mice]). LIII neurons are furthermore the predominent receeipient of projections from deeper layer (predominantly from LVb). Deep layers of MEC, especially LVa, project to medial PFC, caudal ACC and retrosplenial cortex (Kitamura et al., 2017 [Mice]).

Grid cells are found throughout the layers of the MEC, their exact substrate still remains unclear. Grid cells are physically clustered into modules, wherein the firing fields of individual grid cells share a fixed spacing (Stensola et al., 2012 [Rodents]). This spacing differs between neighboring modules by a factor of around 1.5, which is thought to enable the most efficient coverage of the environment (Toader, 2016 [Mice]).

These modules are distributed along the dorso-ventral axis of the MEC with increasing spacing towards more ventral parts and is accompanied by a decrease in inhibitory inputs by PV+ interneurons to LII stellate cells (Beed et al., 2013 [Rodents]). This topographic organization along the dorso-ventral axis is paralleled in the hippocampus (corresponding to posterior-anterior axis in humans). Further studies show genetic and functional differences in the hippocampus along this axis (reviewed in Fanselow and Dong, 2010; Lee et al., 2019 [Humans]). For example neurons CA1 of the ventral hippocampus were found to transiently store social memory (Okuyama et al., 2016 [Mice]). It is still a matter of debate, how these two types of organization - gradient-like and distinct functional subregions - can be reconciled with each other. In the human hippocampus, coarse-to-detailed representations of space maps onto the same axis (Evensmoen et al., 2015). Collin and colleges showed that abstraction in episodic memory is also similarly represented (Collin et al., 2015). Posterior regions of the hippocampus held more transient about single events, whereas more anterior regions held a robust representation of complex multi-event episodes.

Our initial motivation for looking at the hippocampus was its apparent involvement in the processing of hierarchies. One important aspect therein is the extraction of structure and tracking of hierarchical level. Similarly to the extraction of abstract representation for space and episodic memory, this requires more elaboration and parallel tracking of information. More anterior regions

of the hippocampus (and ventral regions of the EC) could be particularly well equipped for that purpose. Furthermore, planning ahead could draw on a similar mechanism (Stachenfeld et al., 2017). Elaboration may happen though interaction with the EC and potentially also the cortex by recurrent processing in different loops. Whereas the recurrent loop between the EC and hippocampus (superficial EC -> hippocampus -> deep EC -> superficial EC) may be dispensable for simple fear association learning (Kitamura et al., 2017), it might sub-serve this more elaborate processing by i.e. iteratively extracting/building up hierarchical levels. Furthermore the emergence of loops and a potential posterio-ventral expansion of the hippocampus and of the EC may be readily achieved through evolutionary processes and facilitate comparably higher cognitive functions.

In the last paragraph I delineated the potential mechanisms by which grid cells and the hippocampus could sub-serve hierarchical processing. This leaves the question of what constitute the specific advantages bestowed by such an elaborate coding mechanism.

So far, I have only highlighted the properties of the grid system for the encoding of two dimensions. A restriction to two dimensions would constitute a strong limitation for its application, as in ecological valid scenarios, sensory information and task features are not only two dimensional, but inherently multi-dimensional. Thus in order to be useful across domains, the grid cell system has to be capable of representing more than just two dimensions. Even within in the canonical field of spatial navigation, two dimensions may not be sufficient for successful navigation of the environment, as certain species do not only have to take latitude and longitude, but also altitude into consideration. A study by Ginosar et al. (2019) specifically looked at characteristics of grid cell coding while bats freely explored a three dimensional cube. They discovered that the firing fields of a single grid cell indeed also span 3D-spaces, are roughly spherical and equidistant to their nearest neighbors, but do not to express a hexagonal lattice structure characteristic for grid cells in 2D environments. The absence of this hexagonal lattice structure is what limits current experimental designs to artificial feature spaces composed of only two dimensions, as it is presupposed by our analysis method (see Part III of this thesis). Hence it is reasonable to assume, that at least in principle grid cells could enable the flexible representation of higher-dimensional cognitive variables.

It is evident that a linear representation of sensory and cognitive variables is superior, as this helps to generalize across experiences and reduce information complexity. Complexity reduction would

also reduce the amount of coding space necessary to represent a specific concept. Theoretical and computational works have pointed out that grid cells may implement a sort of dimensionality reduction algorithm (Klukas et al, 2019; Stachenfeld et al., 2017), which enables this complexity reduction. This would also approximate the hypothesized compression algorithm necessary for pointers (a pointer holds a reference to the actual site of storage of a concept) to enable large-scale knowledge representation in the MTL (Crawford et al., 2015; Legenstein et al, 2018).

Taken together, I have shortly summarized the current literature on hierarchical rule processing in the brain and provided the evolutionary rationale and evidence supporting the contribution of the medial temporal lobe. Furthermore I detailed its circuit structure, the mechanisms it may use to sub-serve hierarchical cognition and potential advantages that may result from such a circuit architecture. This includes its re-entrant circuitry, its organization along an anatomical and functional gradient, its extensive inter-connectivity with the cortex and the fact that its modulated by contextual signals. In the following section, I will now present both the design and the validation of the experimental tasks that we have conceived of for testing the contribution of the MTL to hierarchical cognition.

Part II: Design and Validation of the Experimental Task

Introduction

Here we present a research project with which we aim to investigate the role of the medial temporal lobe (MTL) – hippocampus and its surrounding areas - in the generation of hierarchies. One of the best explored functions of the hippocampus is its role in spatial memory and navigation. Certain types of cells found in the MTL, including place, border and grid cells (GCs) - that fire at specific locations in a physical environment - are known to underlie this navigation ability (Moser et al., 2008) and seem to be evolutionarily conserved in a range of species (Rowland et al., 2016). In humans these cells have additionally been shown to enable the mapping of arbitrary pairs of stimulus features (Constantinescu et al., 2016; Bao et al., 2019), a process that likely assists in the formation of task-relevant stimuli categories which can then figure in the formation of associative memories.

Other strands of research have implicated the MTL in the generation of (minimal) hierarchies across domains (Berens and Bird, 2017; Martins et al. 2017; Theves et al., 2016; Opitz & Frederici, 2003). Crucially, gradients for both spatial as well as mnemonic coarsity have been reported along the longitudinal axis of the MTL (Strange et al., 2014; Collin et al., 2015) and thus could potentially also subserve the hierarchical organization of knowledge and hierarchical planning (Stachenfeld et al., 2016). Grid cells and place cells are similar in the fact that they fire for specific locations in a given environment. Place cells fire only at a single or very few locations (i.e. at one corner of a room). Grid cells encompass multiple firing fields that span the entire environment and are regularly distributed. Furthermore GCs, similarly to place cells, have been shown to change their firing pattern depending between environments (i.e. different boxes or rooms). Whereas an individual place cells may fire for one or very few locations in a given environment, it may not be active at all in another environment and if it is active, then the relative distribution of the firing fields of multiple place cells is usually not preserved. This change in firing characteristics is referred to as *global remapping*. The firing fields of GCs in turn are being rotated and shifted between environments, in accord with global place cell remapping (Fyhn et al., 2007). One underlying cause for this may be the fact that GCs align their firing fields according to external cues or environmental boundaries that differ in separate contexts (Stensola et al., 2012). Boundary anchored grid codes have also been reported in humans (Julian et al., 2018). In summary, GCs a

promising candidate substrate for hierarchical processing due to the following properties: They constitute a substantial part of the cellular population of the entorhinal cortex (which is strongly interconnected with the hippocampus), they remap depending on contextual and potentially state information and their grid spacing varies along an anterior-posterior gradient in grid spacing that mirrors functional gradients in other domains. Yet so far, no studies have explicitly looked at the contribution of the grid cell system to hierarchical processing.

In humans, GCs are predominantly studied non-invasively using functional magnetic resonance imaging (fMRI; Doeller et al., 2010). This is possible due to their stereotyped alignment of their firing fields to boundaries in the environment (Stensola et al., 2012) leading to similar firing properties in a substantial portion of GCs within a cortical patch. A single stimulus can thus trigger all these GCs at the same time, resulting in activity differences that can be picked up by fMRI. Specifically, GCs show differential firing for trajectories in the environment that are either aligned or misaligned with one of the tree main axes on which their firing fields are organized.

Here, we have developed a set of tasks that would enable us to investigate the relationship between MTL circuitry and the acquisition of hierarchical knowledge, making use of the principles described above. The first task - the hierarchical conceptual task (HCT) - directly targets the cognitive capacity associated with hierarchical processing and the second task - the iterative conceptual task (ICT) - provides an appropriate control condition.

In this behavioral study, we will assess if: i) the tasks can be successfully completed by the participants and ii) whether HCT specifically isolates cognitive resources utilized in hierarchical processing. These steps are crucial to interpret the results of future fMRI experiments. To externally validate our tasks, we will use the Tower of Hanoi (TOH), a task that requires recursive planning (Goel & Grafman, 1995), as well as both the Visual Recursion Task (VRT) and Embedded Iteration Task (EIT) that have been related to recursive hierarchical embedding and simple iterative abilities in the visual domain (Martins et al, 2016). We hypothesize that the HCT, but not the ICT, correlates well with tasks that necessitate hierarchical processing (TOH and VRT), and that this association remains even when controlling for a range of unspecific factors. Furthermore, we give an outlook about the next steps in conducting the fMRI experiment and discuss potential mechanisms for grid coding, which could be elucidated by it.

Methods

Participants

We tested 27 healthy individuals (f=19, mean age=24.59), recruited from the internal database of the institute. The following criteria were applied: Participants had to be between 18-50 years of age with normal or corrected to normal color vision without any (history of) neurological conditions or extensive use of pharmaceutics/drugs, that do not belong to a group of specially vulnerable people (i.e. pregnant or breastfeeding) and give written consent to all aspects of the procedure can take part in these two experiments. Participants were reimbursed for their time with a financial incentive (9 € per hour as is the institutes' standard for computer-assisted tests that do not involve MRI). The height of the reimbursement depended on the time spent at the institute for the purpose of solving the experimental tasks with a maximum duration of two hours and hence the maximal amount of reimbursement was 18€. Ethical approval was granted by the Ethics-Commission of the Medicine Faculty of Leipzig University bearing the reference 216/19-ek was granted prior to the commencement of the experiment.

Stimuli

In order to allow future analysis of GC in a fMRI setup, our visual stimuli were designed to vary along 2 dimensions (line thickness and form) which can be implicitly mapped onto a 2D conceptual space (Doeller et al. 2010). Such implicit mapping is a crucial feature of previous fMRI procedures able to detect GC activity in non-spatial tasks (Constantinescu et al., 2016; Bao et al., 2019). Here, the 2D space was divided in two halves (Fig. 1, upper part). Objects that fall into one half of this 2D space - with thick lines and a more square-like appearance - belong into one category ("big") and objects in the other half - more thin and pointed - belong to the other ("small"). Objects can take one of two colors (red or green). All four object classes are shown in the lower part of Figure 2. We assume that despite the presence of a third (yet binary) variable (color), the same underlying 2D object mapping within the EC is used.

Training – Acquisition of basic categories

Participants initially learned to categorize these objects into one out of four classes (Figure 2, upper row) in a forced-choice paradigm. Each trial included a target object that had to be classified by selecting one out of two objects that were chosen to be prototypes of their respective class (one of the correct class of the target object and the other of a different class). Overall, participants had to successfully complete 84 trials. If the participant did not identify the class of

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the target object correctly, the trial was pushed to the end of the queue. The training ended once all trials were successfully completed.
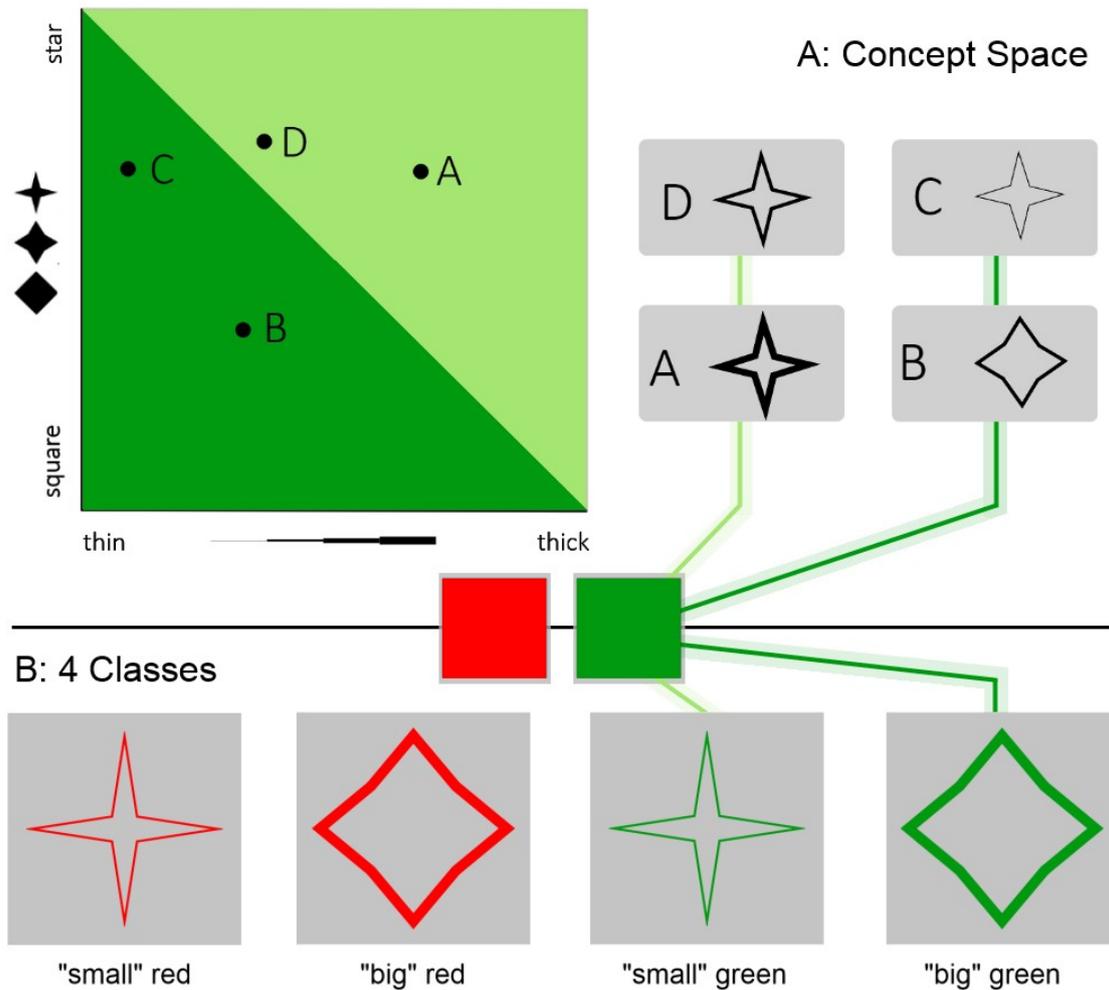

Figure 2: A: The underlying conceptual space divided in two halves. The same space is used for red colored objects. B: All four stimulus categories.

Iterative and Hierarchical Conceptual Tasks

The main task consisted in finding the association between a pair of visual classes and a specific integer value, for example, a big red object followed by a small green object may be associated with the value 'three'. In each trial (Figure 3, upper part), participants saw two objects (each of a certain class) appearing consecutively on the screen and were asked to attribute a correct value from the range of 1-4, after which they received feedback. The feedback screen also included a depiction of the object class pair-value associations of the three most recent trials to facilitate learning. Trials were entirely self-paced and participants would always proceed to the next screen by button press.

Two rules were used in the main task (hierarchical - HCT and iterative - ICT), each creating a different set of associations (Figure 3). HCT set of rules was: i) If the first object was of red color,

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then the potential outcome values for the object pair were 1 or 3, and if it was of green color then the potential outcome values were 2 or 4. ii) If the shape of the second object (form and line thickness) was identical to the first (*big-big* or *small-small*), the higher value was correct (i.e. 3 if the first object was red and 4 if green); otherwise if the shapes of the objects were different (*big-small* or *small-big*) the lower value was correct (i.e. 1 if the first object was red and 2 if green). Crucially, to solve HCT participants had two resolve two levels of contextual dependency: First, each object in the pair did not have in itself a value (*big* or *small*), except for the value given by its role in the pair (*big-big* or *small-small*). Second, the value of a particular pair was determined by the context given by the color of the first object. Thus, determining the value (*v*) of the pair required processing the hierarchical structure *v* = [color obj1, [shape obj1, shape obj2]], where [color obj1] modifies the value of the set [shape obj1, shape obj2].

The control task ICT was designed to resemble HCT in all its elements except for the task rule. Exactly the same setup and object pairs were used. However, determining the value of object pairs in ICT did not necessitate the processing of a hierarchical structure. In ICT, each individual object class had a particular value (e.g. small-red = 2, small-green = 2, big-red = 1, big-green = 0) and the object pair value was simply the addition of the values of its constituents (e.g. big-red [1] + small-green [2] = 3), thus *v* = shape obj1 + shape obj2.

Participants completed both tasks consequently, with a minimum of 30 trials per task. The setup ensured that all possible class pairs (excluding one) were contained at least twice in a set of 14 trials. In order to assess learning success, we conceived of a two-step criterion. First criterion was 5/8 correct trials within a shifting window. The window had to contain at least one trial that started with a red object and a trial trial that started with a red object. If this first criterion was reached early on, participants had to continue the task until they at least completed 30 trials. After reaching the first criterion, participants then had to pass a test (minimum 7/8 correct) containing trials for all 8 possible class pairs (second criterion). These trials only made use of the most representative objects of each class in order to control for potential classification errors and thus allow for a more confident measure of abstract rule learning success. Within this test, no response feedback was given. Crucially, one specific object class pair was only presented during the test, but never during normal trials. Participants hence could not simply memorize the pair-value association but instead had to generalize the respective rule to this unseen pair. The task was aborted if the participant had not yet reached the second criterion by the 98th trial. In this case, participants did not complete the task successfully. For each task, we assessed the following

measures: Number of trials until the first criterion (nfc) was reached, number of trails until the second criterion (nsc) was reached and the percentage of correct trials within the first 30 trials (f30).

Single Trial of either Task
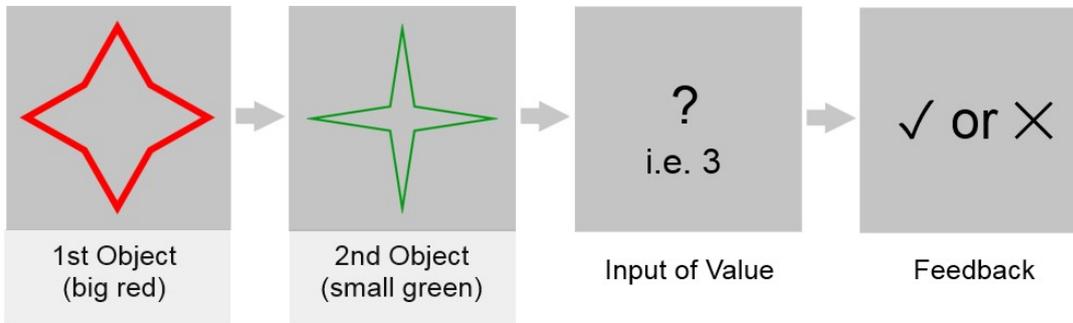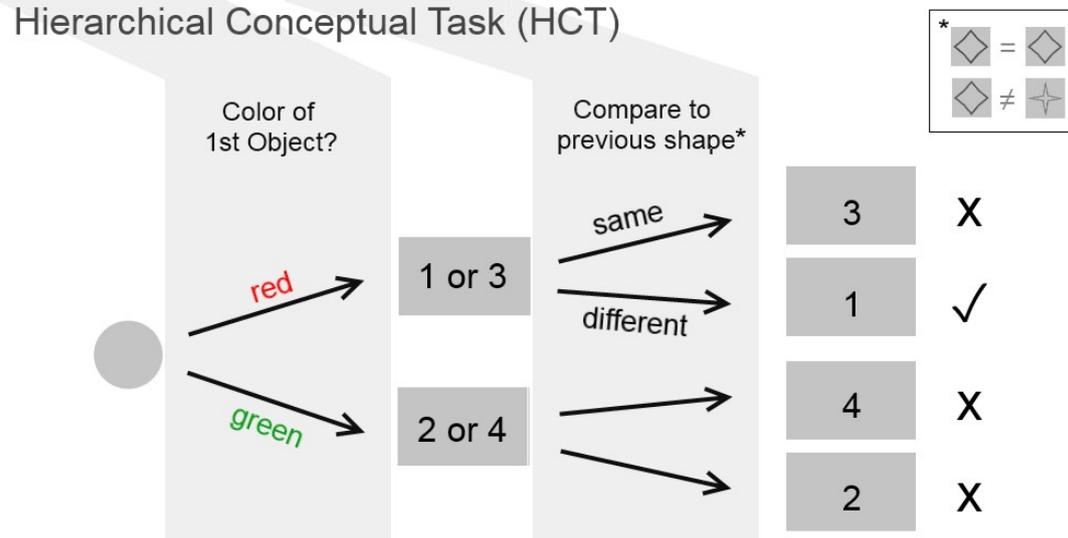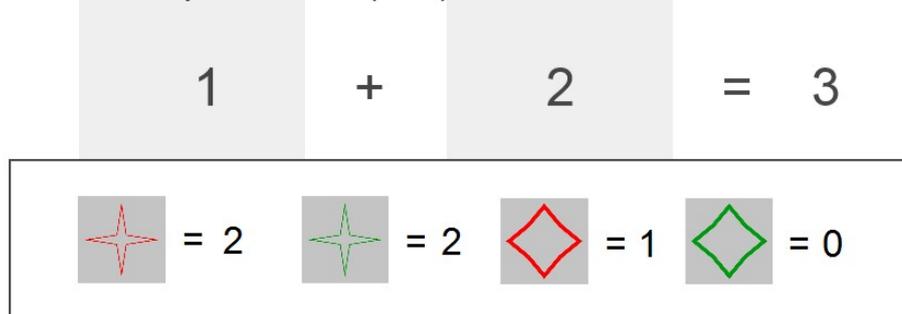
Figure 3: Upper part: Schematic description of an exemplary trial. Middle part: The HCT rule set. For shape comparison, the binary shapes were used (a shape could either be "big" or "small"). Lower part: The ICT rule set. Individual values for the ICT objects are shown in the white box.

Procedure

Participants completed both tasks (ICT & HCT), and task order was counterbalanced across participants. Before starting with the first trial of the first task, participants saw a video that

provided a walk-through with audio-commentary of the task with two exemplary rules different from HCT and ICT. Each highlighted a specific parameter of the object pair (order of colors and composition of shapes) that might be of importance for rule application. The first rule depicted in the walk-through required the comparison of the shapes of the two objects. This was also necessary but not sufficient for solving HCT. The second rule was to count the number of presented "big"-type shapes. Counting is similar to addition, as required in ICT.

During the tasks, trials were structured specifically to maximize learning success, i.e. minimal trial pairs were presented in direct succession (t_1: big-green + big-red, followed by t_2: big-green + small-red, or alternatively t_{2b}: big-red + big green). This reduced the memory load necessary to retain the values of past relevant trials and incentivized rule-based learning rather than rote learning.

After ICT and HTC, participants filled in short questionnaires about the solved the tasks. Then, they completed two working memory tests (Corsi and DigitSpan [DSpan], see Richardson, 2007), Tower of Hanoi (TOH), Visual Recursion Task (VRT) and embedded Iteration Task (EIT). For Corsi and DigitSpan, memory span (MS) was used as the measure for analysis, in the case of TOH it was the shallice scoring system 2 (SS2; Michalec et al., 2017). For both VRT and EIT the percentage correct of trials with a timeout of 6000ms and no repetition of trials upon error was used.

Analysis

In order to assess the cognitive specificity of HCT relative to ICT, we completed a range of exploratory statistical tests that include the assessment of standard descriptive parameters (using the standard R function *stat.desc*), a correlation table, comparisons of linear models and a principal component analysis (PCA). Specifically we were addressing the hypothesis that the HCT specifically correlates with TOH and VRT, whereas the ICT should correlate with the EIT. To compute the correlations and significance levels, we used the *cor* and *corr.test* functions from the R-package *psych*. Furthermore we assumed that we could significantly increase model fit for explaining the HCT by adding either VRT and TOH to a base linear model that already included a range of unspecific factors (as accounted for by the EIT, Corsi and Dspan), such as general mnemonic capacity. Similarly, an extended model for explaining the ICT should benefit significantly from adding the EIT to a linear model that contained all the other variables. We used the standard R function *glm* to create the linear models and the likelihood-ratio test (*lrtest*) function from the R-package *epiDisplay* for model comparison. Lastly, we predicted that the specific contribution of hierarchical processing capability to test scores may be reflected in one of the components of the

PCA (i.e. having high coefficients for only the HCT, TOH and VRT). As for the PCA normality of the used variables had to be ensured, we used *stat.desc* to assess normality and if needed used the tukey transformation (as included in the R package *rcompanion* as *transformTukey* function) to transform the variables into normally distributed ones. All 28 participants were included in the analysis. One participant did not manage to reach the first criterion in the HCT, therefore we based the analyses pertaining to this variable only on the remaining 27 data points.

Results

Training – Acquisition of basic categories

On average participants repeated 13.14 (SD = 6.15) trials of the minimum 84 forced choice trials, due to incorrect answers. This suggests that participants did not need extensive training to acquire the object categories. Meta-cognitively as part of the post task questionnaire, 22/27 participants rated their performance as "good" or better, 2 "intermediate" and 4 as "not so well". Interestingly 16/28 participants rated the category acquisition as the hardest part of the experiment, which suggests that this might be a bottleneck.

Iterative and Hierarchical Conceptual Tasks

The average number of trials needed to reach the first criterion (nfc) was 23.75 (*SD* = 13.04) in the case of the ICT and 24.67 (*SD* = 10.77) in the HCT. Given that the earliest possible point to reach the first criterion was after completing the 14th trial and participants only had seen all used object class pairs by the 18th, this suggests that participants quickly acquired a working understanding of the task rules. The corresponding learning curves are plotted in Figure 4.
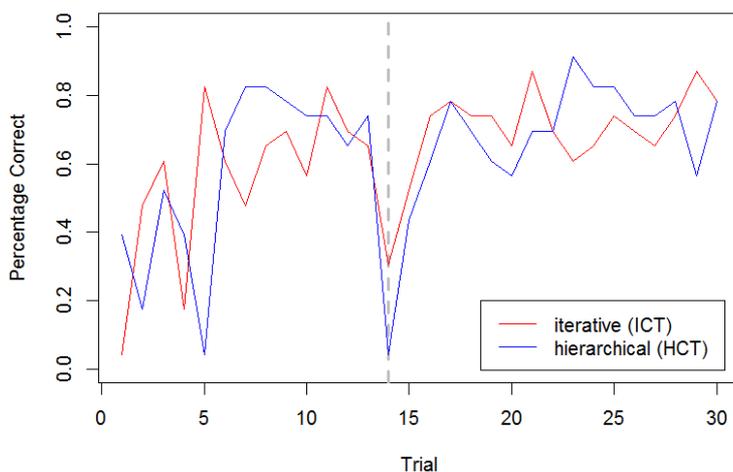
Figure 4: Learning curves for the two rules, showing percentage of participants that completed a given trial correctly. Participants already show high proficiency early on. Grey dotted line indicates the first occurrence of a trial where the first object was of green color. Prior to that, trials started always with a red object. Chance level is at 25%.

Second, the number of trials till second criterion (nsc) was equally low for both ICT (*M* = 43.39, *SD* = 23.81) and HCT (*M* = 39.89, *SD* = 21.45), relative to the absolute minimum of 30 (Table 1). This

supports the idea that the learning process was quick. This also holds true for the percentage of correct trials of the first 30 trials (f30) for ICT (M = 16.11, SD = 3.87) and HCT (M = 16.63, SD = 4.02). Comparing the scores between the two tasks, we do not find any significant differences for nfc (*Wilcox' V* = 113.50, p = .30), nsc (V = 103.00, p = .46), and f30 (V = 145.50, p = .66), suggesting that both tasks were equally difficult. Furthermore we also verified the assumption that both EIT (M = .83, SD = .11) and VRT (M = .84, SD = .09) do not differ significantly in difficulty. The scores on all the conducted tests are summarized in Table 1.

	min	max	mean	std.dev	skewness	kurtosis	normtest.p
ICT nsc	30	98	43.39	23.81	1.55	0.64	0
ICT nfc	14	79	23.75	13.04	2.7	8.69	0
ICT f30	9	24	16.11	3.87	-0.14	-0.8	0.63
HCT nsc	30	98	39.89	21.45	2.12	2.85	0
HCT nfc	14	63	24.67	10.77	1.66	3.37	0
HCT f30	4	21	16.36	4.02	-1.18	0.99	0
TOH (SS2)	0	21.46	13.96	5.49	-0.84	0.14	0.05
DigitSpan (MS)	5	10	7.11	1.31	0.47	-0.19	0.02
Corsi (MS)	4.5	7.5	5.79	0.82	0.19	-0.93	0.22
EIT %correct	0.59	0.96	0.83	0.11	-0.81	-0.51	0.01
VRT %correct	0.63	0.96	0.84	0.09	-0.44	-0.75	0.19

Table 1: Descriptive statistics of the different test scores. Normtest.p are the significance values of the Kolmogorov–Smirnov test for normality. Abbreviations: ICT – Iterative Conceptual Task, HCT – Hierarchical Conceptual task. Nsc – nnumber of trials till second criterion was reached. Nfc – Number of trials till first criterion was reached. F30 – percentage of correct trials assessed on the first 30 trials. TOH – Towers of Hanoi. SS2 - shallice scoring system 2. MS – memory span. EIT – Embedded Iteration Task. VRT – Visual Recursion Task.

From the 27 participants, 23 successfully derived both rules, and 19 had a perfect score on the second criterion for both tasks. As this test includes a specific object-class pair that has not been part of learning process, we can assume that participants did not simply memorize the previous pair-value associations but actually derived a rule which they then applied to the previously unseen pair. This was also corroborated by their post-task oral reports. 18 of the 23 people reported narrowing down the set of choices in the HCT immediately after presentation of the first object, speaking for representation of the hierarchical level already at this time point.

Interestingly, from the post task interviews we gathered that out of the 23 people who managed to derive both rules, 10 derived an unintended more complicated rule for solving the ICT. Specifically,

for object class pairs that would result in the values 2 and 3 the following relationship was described: If the first object was red then big + small = 3, small + big = 2; and if the first object was green, the opposite would be true. Both of these rules (intended and complicated iterative rule) lead to the same results, but the latter contains a hierarchical part, whereas the first one does not. This could be a confound in the further analysis that tries to show a differential association of ICT and HCT with hierarchical processing capacity. Furthermore, only a minority (n=3) actually assigned number values to the different object classes in the ICT, the rest (n=10) conceptualized it in a different yet still iterative manner (two small objects = 4, two big objects = 1, a set of one big and one small object leads to 2 or 3 depending on if the big object is red or green).

|	TOH	DSpan	Corsi	EIT	VRT	ICT nsc	ICT nfc	ICT f30	HCT nsc	HCT nfc	HCT f30
HCT f30	0.26	-0.1	0.15	0.23	0.38 *	-0.46 *	-0.26	0.53 **	-0.72 ***	-0.43 *	
HCT nfc	-0.11	0.15	-0.23	-0.07	-0.33	0.17	0.33	-0.2	0.47 *		
HCT nsc	-0.17	0.03	-0.28	-0.22	-0.26	0.52 **	0.32	-0.51 **			
ICT f30	0.18	0.1	0.12	0.45 *	0.23	-0.59 ***	-0.16				
ICT nfc	-0.05	0.13	-0.17	-0.21	-0.11	0.02					
ICT nsc	-0.22	-0.26	-0.05	-0.35	-0.19						
VRT	0.23	0.03	0.17	0.41 *							
EIT	-0.07	0.17	0.04								
Corsi	0.13	0.15									
DSpan	0.06										
TOH											
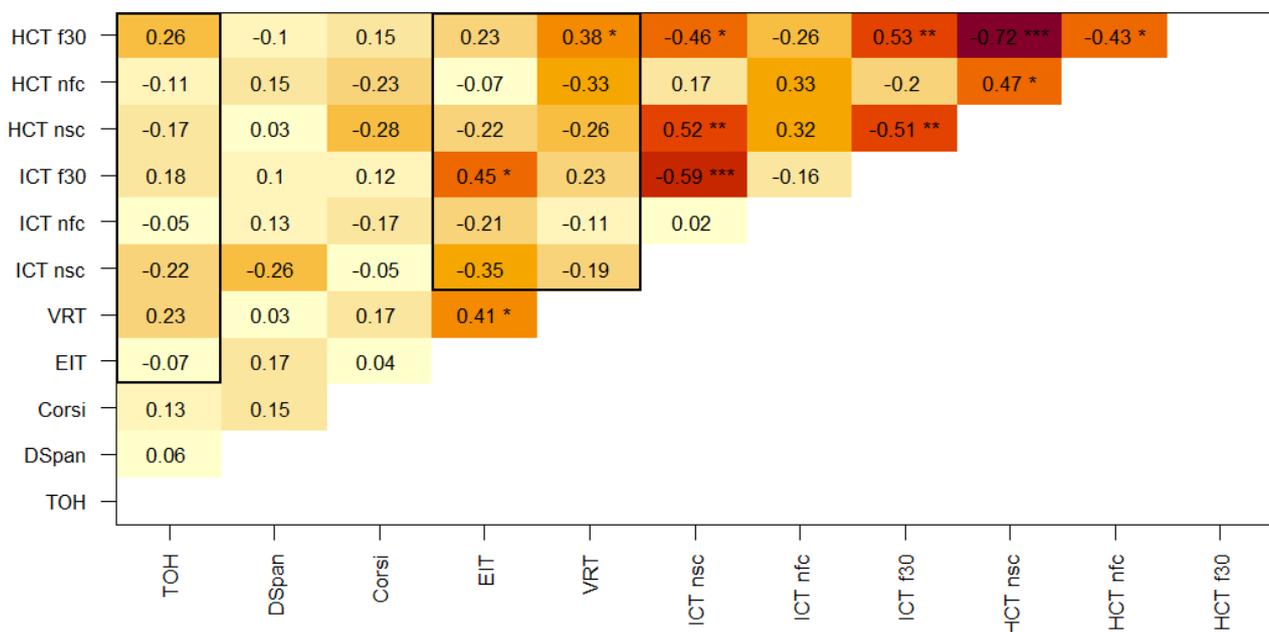
Figure 5: Correlation table for the different test scores of all 28 participants. Colors indicate absolute strength of correlation but not direction. Relevant correlations for assessing the specificity of our test are marked in blue. For comparison: Specificity of the VRT and EIT tasks as used here with TOH. Sections of interest are framed in black. Correlation was computed using Kendall's W. *p<=.05, **p<=0.01, ***p<=0.001, for corrected p-values using Benjamini-Yekutieli adjustment for multiple comparisons.

Correlation data

We then computed the correlations between our measures of interest (Figure 5). We found that a visual iteration task (EIT) specifically correlated with our novel ICT in the % correct in the first 30 trials (f30). Conversely, a Visual Recursion Task (VRT) specifically correlated with the f30 measurements of our hierarchical task (HCT). Furthermore all HCT measures show a stronger relationship with the VRT scores than their ICT counterpart measures. The reverse is true for association of HCT and ICT with the EIT. We could replicate our previous findings that evidenced a

stronger relationship between VRT and TOH scores (r = .23), than between EIT and TOH scores (r = -.07). Furthermore, the HCT measures correlate slightly better with TOH scores than their ICT counterparts (i.e. TOH with HCT-nfc yields a correlation coefficient of .26 vs TOH with ICT-nfc which yields 0.18). None of the described significant relationships survive the Benjamini & Yekutieli (2001) [BY] correction for multiple comparisons.

Partial Correlations

We furthermore sought to pinpoint more clearly the individual contributions to the shared variance between our experimental measures (HCT and ICT) and the reference tests. By accounting for the variance shared among a range of variables, the influence of unspecific factors such as motivation or overall experience with similar types of tasks can be removed, and contributions by more specific factors (such as the ability to generate hierarchies) can be identified that can only be accounted for by individual reference measures (such as TOH or VRT). Hence we looked at the changes in model fit (quantified by a likelihood ratio test) that are caused by minimal modifications to a base linear model through the addition of a single variable of interest as regressor.

Two different kinds of base models were employed (Table 2): The first model included all the three measures of either the HCT or the ICT as independent variables and were termed hierarchy only (HOM) and iteration only model (IOM). A more comprehensive second type of model listed two standard psychometric measures as additional regressors, as well as either the VRT or EIT score and were labeled hierarchical (HFLM) and iterative full linear model (IFLM) respectively. The base models and the model comparisons conducted are listed in Table 2 and Table 3 respectively.

Base Model	Constituents
HOM	HCT nfc * nsc * f30
IOM	ICT nfc * nsc * f30
HFLM	HCT nfc * nsc * f30 * Corsi * Dspan * VRT
IFLM	ICT nfc * nsc * f30 * Corsi * Dspan * EIT

Table 2: The four base models used for the model comparisons.

Predicted Variables	Base Model	Minimal Additions	# Comparisons
ICT nfc | nsc | f30	HOM	EIT | TOH	3 x 1 x 2 = 6
ICT nfc | nsc | f30	HFLM	EIT | TOH	3 x 1 x 2 = 6
HCT nfc | nsc | f30	IOM	VRT | TOH	3 x 1 x 2 = 6
HCT nfc | nsc | f30	IFLM	VRT | TOH	3 x 1 x 2 = 6

Table 3: Listing of all the conducted model comparisons.

Adding VRT as regressor to the IOM significantly improves the model fit when predicting HCT-nfc (χ^2 = 5.155, df = 1, p = .024). Also the IFLM similarly benefits from the addition of VRT when predicting HCT-nfc (χ^2 = 7.425, df = 1, p = .006). None of the ICT prediction model fits benefit from the addition of VRT. Thus it seems that VRT can explain some more of the variance in the HCT scores above what can be explained by any of the other measures (ICT, EIT, Corsi and DSpan). Conversely, when adding EIT as regressor, model fits significantly improve only when predicting ICT measures: Predicting ICT-nsc using the HOM (χ^2 = 5.856, df = 1, p = .016) and predicting ICT-f30 using the HOM (χ^2 = 5.47, df = 1, p = .019) and HFLM (χ^2 = 8.746, df = 1, p= .003), but not when predicting any other dependent variable. None of the presented significant relationships survive BY correction for multiple comparisons (n = 36). Addition of TOH as regressor did not significantly increase model fits in any case.

Taken together there seems to be an almost exclusive relationships between HCT measures and VRT, as adding the latter to the base models improves model fit in 2 out of 6 relevant cases ([HCT-f30, HCT-nfc, HCT-nsc] * [IOM, IFLM]) significantly but in no other, and between ICT and EIT, whose addition improves model fit in 3 out of 6 relevant cases but in no other.

Principal Component Analysis

We conducted a principle component analysis on the basis of the data given above. This analysis did not include the two variables HCT nsc and ICT nsc, as they could not successfully be transformed into normally distributed variables. The first component, explaining 33% of the variation in the data with high values for all tests with no contribution by TOH might be seen represent some common processing capability, whereas the remaining 8 components - each explaining from 1 to 17% of the variance (median of 7% and standard deviation of 5%) - do not lend themselves to any interpretation of systematic relationships between the tests.

Discussion

Our novel task was designed to test for the ability to process hierarchical structures, while retaining features essential for a future fMRI experiment targeting the EC grid cells. Here we showed that the novel task 1) is easily learnable by most participants, and 2) specifically targets hierarchical processing in comparison with a novel control task. These results provide confidence that we can proceed with the fMRI experiment (further described in part III).

The majority of participants managed to learn both rule sets and complete the tasks without

particular difficulty. We found that the HCT, but not the ICT, correlates well with other tasks that necessitate hierarchical processing (especially VRT). In a range of model comparisons, we showed that the addition of a single regressor (VRT) significantly increases model fit when predicting HCT scores - but not ICT scores - even when the shared variance that likely can be contributed to unspecific factors has been accounted for by a range of other model variables.

Exploratory analysis revealed that when excluding the 5 non-learners (that is people who did not successfully complete either the ICT or the HCT) - whose scores are highly different from the rest of the sample and thus could be the source of a strong bias in the data - from the analysis, 6 out of the 6 relevant model comparisons become significant for HCT when adding VRT to the model. Crucially also two out of 6 relevant model comparisons become significant when adding TOH as regressor for the prediction of HCT, but not ICT measures, with further two showing a slight tendency. The relationship between ICT and EIT and the presented correlations remain comparable to what has been described before for the full sample.

The difference in association strength between VRT and TOH with the HCT can have multiple reasons: Firstly, HCT and VRT may be more similar to each other than HCT and TOH. Alternatively, the VRT task might be more sensitive to hierarchical processing than TOH with the specific scoring system used. Lastly it could be that recursion/hierarchical processing is not a single discrete capacity, but might consist of multiple constituents or could be separately implemented in or accessible to different domains. The fact that only a few significant findings survive correction for multiple analysis can be most likely attributed to the small sample of participants. Crucially, all the analyses conducted were hypothesis driven.

A number of participants (n=7) solved the ICT using a partially hierarchical strategy which could have lead to stronger correlations between ICT measures and both TOH and VRT. On the other hand, significance estimates for the improvements in model fit for the addition of either TOH and VRT when predicting HCT scores might be on the conservative side, as ICT regressors likely have already accounted for some variance that can be attributed to individual difference in hierarchical processing capacity, which is thought to underlie the specific relationship between HCT and TOH/VRT. These seven participants may have also been also the reason for why we did not find any interpretable components in the exploratory analysis using PCA. Due to the already small sample size, further analysis excluding those seven participants would lack sufficient power.

Conclusion

In the current study we have presented a set of tasks that aim to enable the identification of the mechanism and cellular substrate that underlies hierarchical processing in the MTL at early stages of rule acquisition. We provided evidence for the assumption that the novel HCT specifically taps into this capacity and that the ICT qualifies as control condition. Thus we can confidently use these tasks to isolate the neural processing of hierarchies in a future fMRI experiment.

Part III: Outlook on the future fMRI-Experiment

We presented two tasks suited to investigate the role of the MTL in the generation of hierarchies in humans. In order to use these same experimental tasks during scanning, a few adaptions to the experimental setup had to be made. These will be motivated and detailed in the next section, followed by a short summary of the planned analysis and study limitations. The thesis is then concluded by a short summary.

Modifications to the experimental setup

As the planned analysis approach necessitates trajectories through the implicit concept space (CS), the presentation of two static objects during each trial will be replaced by morphing objects. The morphing hereby mimics a trajectory through the CS along a specific angle that will be used for grid analysis. The participants are asked to derive the value of the object combination on the basis of the morph outcome (i.e. the final configuration of the object at the end of the trajectory). The ratio of change between the two parameters (line thickness and form) determine the angle of the trajectory. An integral part of the analysis is the computation of the main grid direction for each individual voxel (Doeller et al., 2010). The firing fields of an individual grid cell are distributed along three principal axis that are equally spaced along 360°, each 60° apart from the next one. Forward and backward movements along either of these three axes elicits higher activity in that individual grid cell compared to when moving on a misaligned trajectory. Because of the regular arrangement of these main axes, it is sufficient to only look at one axis that minimally deviates from a reference axis to characterize a grid cells' orientation. This minimally deviating axis is also called the grids main axis and falls in the range of 1-60°. As there is no way of knowing this main direction *a priori*, we have to ensure that the trajectories covered in the experimental tasks span this range sufficiently. Trajectories are thus chosen from all 360 available directions in a way that ensures that for any potential main direction there are sufficient aligned and misaligned trajectories in order to enable analysis. Furthermore we ensured i) that the length of the trajectories does not differ between conditions (first vs. second level), between types of trajectories (i.e. staying within the same category subdivision of the CS or crossing it) and between concept spaces (red or green) and ii) that the number of trajectories does not differ between type of condition and concept spaces. The identical set of trials is used for the HCT and ICT, shuffled anew for each participant and presented in alternating blocks. Each block is preceded by a screen that cues the current task

condition (either HCT or ICT) that will be valid throughout the ensuing block. There are three blocks for each task and each block contains 32 trials. The order of blocks (either first HCT then ICT or vice-versa) is counterbalanced across participants. This blocked design was chosen in order to minimize habituation effects.

As the available scanning time is limited and the experiment exhausting, we decided to give both rules explicitly before the start of the scanning procedure, which is in contrast to the behavioral validation presented in the preceding section. This change will maximize the amount of trials in which the participant is applying the correct rule and that can then be used for consecutive analysis. Additionally, this may prevent the participants from using a different strategy to solve a specific task, as has happened in the current study for the ICT in a few cases. Yet by explicitly telling the rule, we cannot image the actual phase of rule learning. Our assumption is that the structures that enable initial acquisition is identical to the structures that support initial application. This interpretation is supported by the fact that all the tasks (TOH, VRT and EIT) used for external validation of our experimental setup require application of a previously acquired rule rather than the de-novo acquisition of a new rule. Irrespective of this assumption, we may be able to show the involvement of grid cells or more generally the MTL during the application of recently learned rules.

Lastly, the oral reports indicated that the object classification subtask, which was preparatory for the ICT and HCT, was the hardest part of the experiment. Hence we will focus on improving this part before continuing with the study in the scanner, as a good representation of object class boundaries is crucial to our planned analysis approach.

Analysis approaches

For the analysis we are mainly interested in the BOLD response elicited by object presentation. As previously indicated, each trial contains two consecutive morphed object presentations, followed by the input of an integer value by the participant and feedback. In order to derive the correct value, the participant has to apply one of two rules onto the previously seen objects. This yields two main effects: The effect of rule (HCT vs ICT) and position (first vs second object). In a first analysis, we run this contrast along with the interaction effect of task and position. A significant interaction within the MTL of appropriate valence would mean that the MTL encodes information about the preceding context (first object) during the presentation of the second object when preforming the HCT but not the ICT.

In a second analysis, we will look at potential grid modulation of the signal. Using half of the data for a subject, we estimate the grid orientation using regressors akin to $\beta\_sin * \sin(6*\theta(t))$ and $\beta\_cos * \cos(6*\theta(t))$, where $\theta(t)$ is the trajectory angle for each trial, and predict the activity for aligned vs misaligned trajectories in the other half. In congruence with similar studies Constantinescu et al., 2016), a F-test will be used to assess significance of hexagonal modulation. This gives information about weather grid cells are involved in object encoding. A correlational analysis of the strength of hexagonal modulation and task performance score may establish behavioral relevance of this coding. Within the mask of voxels displaying grid-activity for each subject (in any of the 4 conditions), we then repeat the pevious contrast: Task (Iteration, Hierarchy) x Position (1,2). This will yield information about the involvement of grid cells in tracking the hierarchical level.

Differences in grid activity between conditions can be analyzed to greater detail: We may compute centroid statistics (position and mean distance of voxel from centroid) for significantly grid-modulated voxels in each of the 4 conditions. Using a standard t-test we can then compare the distances (and variance differences) of centroids responsible for object encoding at position 1 and position 2 for each of the two tasks. A more elaborate analysis could furthermore take the curvature of the cortex into consideration. This may yield more dedicated information about condition differences in the recruitment of grid cells.

Other potential analyses include the assessment of differences in grid main direction between conditions and the usage of multi-voxel pattern analysis (MVPA) / representational similarity analysis (RSA) to decode hierarchical level/context but also other cognitive variables, such as tracked sum of integer values in case of the ICT, and thereby pinpointing the underlying substrate. Lastly we may explore the potential of an increasing involvement of the PFC towards later trials.

Limitations

We specifically hypothesize that grid cells are involved in the initial encoding of rules and that hierarchical level influences the coding properties. This may be the result out of a differential recruitment of grid modules. Yet there is evidence that contextual color cues – similar to the context cue in the HCT which determines the potential values from which can be chosen on the second level - influence specifically the phase of grid coding in the entorhinal cortex (Marozzi et al., 2015). Unfortunately, there is no way of assessing grid phase in the current setup nor with any other known tools in humans. Alternatively, one might could hypothesize a reorientation of GC firing fields, akin to what is observed during spatial exploration, when a transition to a different

environment is made (Fyhn et al., 2007; Monaco and Abbot, 2011). This may be addressed in a further analysis step that has been described in the previous section. Lastly we may not fully reject the possibility that grid cells are not necessary for nor involved in hierarchical processing.

Summary

The ability to generate hierarchies is a core function for many cognitive domains such as language, motor action and sequential planning, and the neural mechanisms underlying this capacity are still under discussion. Part of the circuit involved in hierarchical generativity and rule acquisition is located in the MTL (Opitz & Friederici, 2003; Theves et al. 2016, McKenzie et al., 2014). Pinpointing part of the cellular substrate within that area that underlies this capacity will give a clearer understanding of how the multitude of functions that have been assigned to the MTL - including spatial navigation, the formation of concept-concept associations and episodic memory - can be realized. Furthermore, we aim at establishing a link to the wealth of findings from anatomical and invasive studies predominantly conducted in rats and primates (Rowland et al., 2016; Kitamura et al., 2017; Donato et al., 2017; Duszkiewicz et al., 2018) and motivate an evolutionary view on the emergence of (complex) hierarchical processing.

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