A single-neuron architecture for imagination in the human brain (NeuroI)

PROJECT DESCRIPTION

1. Project vision

Episodic memory allows us to relive our past experiences[1] by mentally traveling back in time[2]. In our mind's eye[3], we re-experience the original event ("what"), embedded in its original spatial and temporal context ("where" and "when")[4,5]. Seminal studies discovered that humans with damage to a specific part of the brain—the medial temporal lobe including the hippocampus—exhibit severe deficits in episodic memory[6,7]. Since then, numerous studies set out to understand how exactly the medial temporal lobe facilitates episodic memory. Direct recordings of single neurons from the human medial temporal lobe identified "concept cells"[8,9], which increase their firing rates in response to particular persons or objects and are thus able to represent the "what" component of episodic memories[10]. Electrophysiological recordings in animals discovered hippocampal neurons that store memories for particular locations in the environment ("spatial cells" including "place cells")[11,12] and other neurons that store memories for particular time points during time intervals ("time cells")[13–15]. Spatial and time cells thus facilitate remembering spatiotemporal contexts ("where" and "when") by activating during episodic memory recall[15,16]. Together with concept cells, they form an integrated single-neuron architecture underlying episodic memory in the human medial temporal lobe (Fig. 1).

In this project, we will transcend the prevailing view of the medial temporal lobe as a memory system. Instead, our vision is to identify the role of its spatial, time, and concept cells for imagining the future. This is of broad relevance, because humans are not bound to their past and present: Using imagination, we break away from our continuous stream of perceptions and memories[17,18]. Among the different forms that imagination can take, imagining the future is particularly fundamental for human life: It allows us to simulate the effects of our actions, to assess the possible risks and benefits of future developments, and to plan steps towards achieving desired long-term goals[19]. The evolution of imagination supported survival by allowing humans to prepare for both beneficial and detrimental effects of future events[20,21].

Our proposed shift in perspectives is inspired by the intriguing but speculative "prospective brain hypothesis"[21]. This hypothesis makes the fundamental claim that the neural machinery for remembering the past also serves our ability to imagine the future[20–23]. Preliminary evidence for this idea comes from the observation that patients with hippocampal damage do not only suffer from episodic memory loss, but that they also are also unable to imagine their future[24,25]. Relatedly, neuroimaging studies in healthy participants showed that similar brain regions are active when subjects remember past or when they imagine future experiences[21].

The single-neuron mechanisms underlying human imagination are, however, completely unknown. In particular, whether spatial, time, and concept cells hold a crucial function in imagining the future is still unclear. One of the main reasons for this lack of knowledge is that adequate neuroscientific techniques to study imagination are missing: Animal studies cannot interrogate their subjects about the content of their imaginations and neuroscientific studies in humans (using fMRI, EEG, or MEG) do not have sufficient temporal and/or spatial resolution to examine the cellular processes that underlie imagination. We will overcome this barrier to progress in the field by performing direct single-neuron recordings from the human brain during carefully designed imagination tasks. With this unique experimental approach, we will attempt a major breakthrough in the neurobiological understanding of human imagination.

Overarching goal: Our goal is to identify a single-neuron architecture for human imagination that consists of spatial, time, and concept cells. We propose that *recombined* activity profiles of these cell types allow humans to imagine possible future experiences that they never encountered before. The detailed objectives are described in section 4.1.

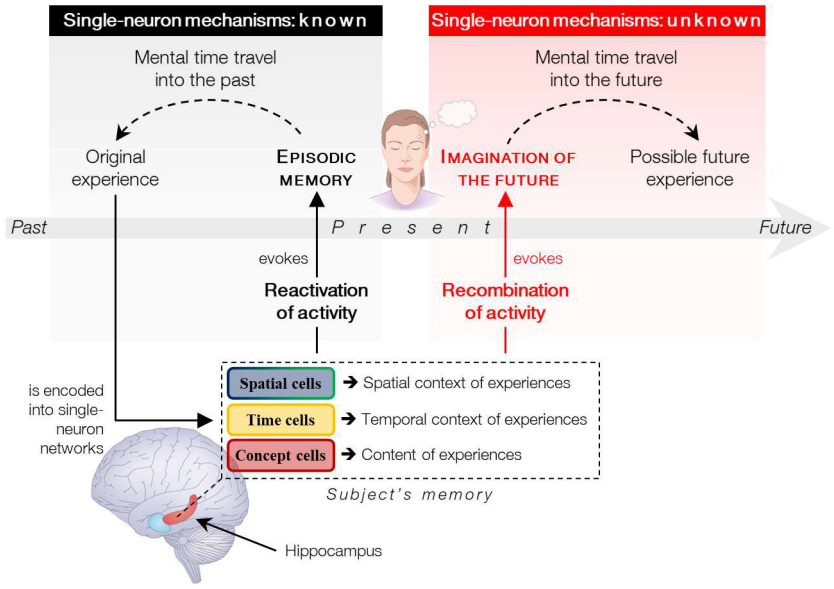

Fig. 1. Project vision. NeuroI proposes that a subject's original experiences of events in spatiotemporal contexts activate single-neuron networks composed of spatial cells, time cells, and concept cells. We propose that spatial cells encode the spatial contexts of the experiences, that time cells represent the temporal contexts, and that concept cells encode the actual content of the experiences. A given original experience activates a specific single-neuron network that is then stored in the subject's memory system. In our framework, **episodic memories** emerge via the ***reactivation*** of single-neuron networks composed of spatial, time, and concept cells—allowing the subject to mentally travel back into the past and to relive the original experiences. NeuroI hypothesizes that the ***recombination*** of activity in these single-neuron networks leads to the occurrence of **imaginations**—allowing the subject to mentally travel into the future and to "prelive" possible future experiences.

2. Significance

Imagination is one of the most fundamental capacities of humans, providing the source for creativity, innovation, and progress[26]. For centuries, philosophers and psychologists have developed theories on the functions, origins, and types of human imagination[17,18,26–29]. For survival, imagining the future is of particular relevance, because it allows humans to simulate the possible risks and outcomes of their future actions and to prepare for both beneficial and detrimental future events[20].

Seminal studies found that imagining the future is impaired in patients with lesions to the medial temporal lobe[24,25]. However, further neuroscientific insights into human imagination are hindered by the low spatial and/or temporal resolution of the lesion studies and related

neuroimaging work[19,30,31]. At the same time, recent electrophysiological recordings in rodents observed intriguing phenomena at the level of single neurons, which could potentially serve as real-time mechanisms for human imagination: Place-cell activity on each cycle of the theta rhythm (a 4–8 Hz brain oscillation, which is highly relevant for navigation[32]) appears to reflect future paths of rodents through their environment ("theta sequences")[33,34]. Moreover, place-cell activity on alternating theta cycles represents different spatial environments simultaneously (so-called "theta-paced flickering")[35,36]. We hypothesize that these phenomena of "theta sequences" and "theta-paced flickering" translate to humans, allowing humans to imagine temporally unfolding future experiences and to simulate competing possible futures at the same time.

NeuroI's unique approach to studying human imagination using single-neuron recordings will thus bridge the gap between the segregated fields of rodent electrophysiology, lesion studies in human patients, and human neuroimaging. This will allow us to answer big questions on the neurobiological foundations of human imagination and to change the way we think about medial temporal lobe function. We seek to identify a completely novel single-neuron architecture underlying humans' ability to imagine holistic future experiences. We hypothesize that spatial, time, and concept cells are the components of this architecture, whose activity enables humans to imagine possible events in possible spatial and temporal contexts. We describe the field's current understanding of these cell types below.

2.1 Single-neuron codes for the representation of space

Spatial cells in the medial temporal lobe comprise "place cells" and "grid cells" that activate when subjects are positioned in particular locations of the environment[11,12,37,38]. "Head-direction cells" additionally provide directional information by activating when the subject moves in a specific global direction[39]. Together, these cells form the neural basis of a "cognitive map"[40], enabling subjects to recall locations and directions relative to the external environment (in an "allocentric" way). For example, they allow a subject to know that it is navigating through the northern part of an environment.

The medial temporal lobe also contains a neural map that stores locations and directions relative to the first-person perspective of the navigating organism (in an "egocentric" way). The underlying cell types activate when features of the environment are ahead or behind the subject, to its left or to its right[41–45]. For instance, they inform a subject that its home base is ahead of it. Our own work has contributed to this literature by demonstrating "anchor cells" (via a paper that is in revision at *Neuron*), which activate when arbitrary reference points in the environment are at specific egocentric directions and distances from the subject[46] (Fig. 2)—showing, for the first time, that the human brain does not only contain the neural basis for an allocentric cognitive map, but also for an egocentric cognitive map[46].

Evidence in both rodents and humans indicates that spatial cells are involved in recalling memories[16,46,47]. However, it is unknown whether spatial cells support humans in imagining future paths and future spatial contexts.

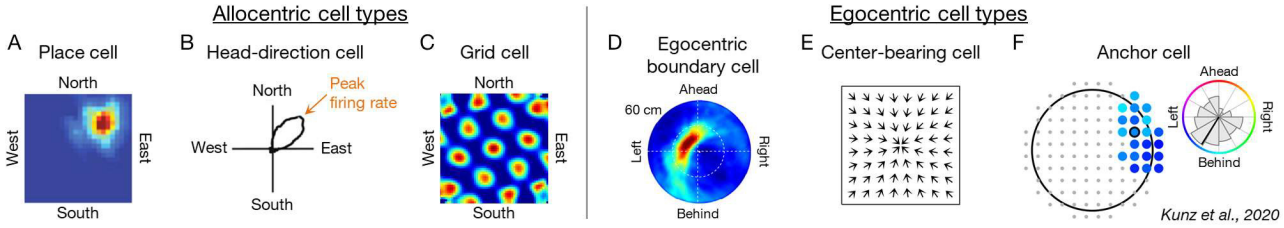

Fig. 2. Single-neuron codes for space. (**A**) Place cell, activating when the subject is in a particular location[48]. Red colors indicate high firing rates; blue colors indicate low firing rates. (**B**) Head-direction cell, activating when the subject moves in a specific global direction[39]. (**C**) Grid cell activating at multiple locations[37]. (**D**) Egocentric boundary cell, responding when a boundary is in a particular egocentric direction from the subject[44]. (**E**) Center-bearing cell, which increases its firing rate when the environment center is in a specific egocentric direction from the subject[42]. (**F**) Anchor cell that activates when an unmarked location is in a particular egocentric direction from the subject[46]. Each anchor cell has an anchor field (colored dots in the left panel). The anchor cell increases its firing rate when the anchor field is in a specific egocentric direction from the subject (right panel). In this example cell, the anchor cell increases its firing rate when the anchor field is behind the subject.

2.2 Single-neuron codes for the representation of time

Our experiences do not only take place in specific spatial contexts, but they are also bound to a particular time and unfold over specific time periods. A small number of studies in rodents has recently begun to identify neurons that represent time. These "time cells" activate at specific time points within circumscribed time intervals[13–15] (Fig. 3). Time cells track the flow of time and are thus able to provide information about when events occur. Initial evidence indicates that time cells also exist in the human brain and that their activity supports episodic memory[15]. In this project, we will identify the hitherto unknown role of time cells in imagining the future.

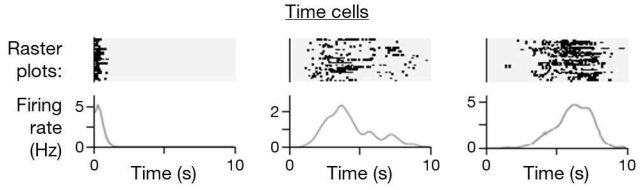

Fig. 3. Single-neuron codes for time. Three example time cells are shown that have their time fields at the beginning, in the middle, or towards the end of a 10-s time interval[14]. Upper panels show raster plots (each row is one experimental trial and each black dot is one action potential). Bottom panels show the peristimulus time histograms.

2.3 Single-neuron codes for the representation of semantic knowledge

Semantic knowledge stores information about both concrete and abstract concepts—allowing humans to know what a cat, a house, or a "Freigeist" is. In recent years, strong evidence has accumulated that human "concept cells" are a neural substrate for semantic knowledge[9,49]: they encode semantic knowledge by increasing their activity in a remarkably selective and modality-independent manner to particular persons or objects[9] (Fig. 4). Previous studies found that concept cells activate during direct presentation of concepts[8] and that they reactivate during cued or free recall[10,50]. For its proposed single-neuron architecture of imagination, NeuroI will discover whether concept-cell activity evokes the imagined events of future experiences.

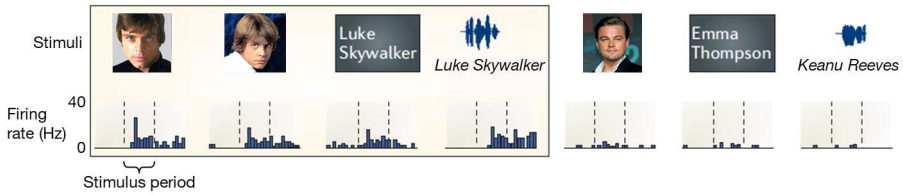

Fig. 4. Single-neuron codes for semantic knowledge. The depicted example concept cell selectively responds to Luke Skywalker (a movie character)[9]. Upper row shows stimuli, lower row shows peristimulus time histograms.

3. Innovation

- This project is innovative in that it seeks to discover—for the first time—how single neurons support our ability to imagine the future. In particular, it will improve our scientific knowledge of how spatial, time, and concept cells facilitate the imagination of future paths, future time points, and future events, respectively. To date, these cell types have been studied almost exclusively in relation to representing a subject's present or past states, as in our own work[46]. NeuroI will thus enter unknown territory by establishing their role in imagining the future.
- NeuroI will investigate the neural basis of imagination by recording single neurons directly from the human brain. This exceptional technique (only available at a few centers worldwide) allows us to observe the working principles of the human brain at the level of single neurons and in real time[51]. Our approach thus overcomes the major drawbacks of common noninvasive techniques in human neuroscience (fMRI, MEG, EEG): These techniques do not have sufficient spatial and/or temporal resolution to investigate the neural basis of human cognition at the level of single neurons, which are widely considered the primary functional units of the brain[52].
- We will implement a novel setup for recording single neurons during immersive virtual reality, in which subjects physically navigate on a motion platform. This setup is presumably necessary to fully evoke all neural signals that are also present during real-world navigation[53], allowing us to detect single-neuron responses that could not be observed in humans before.
- NeuroI is of broad significance because it opens up a new framework for understanding the function of the human medial temporal lobe. To date, the general framework for studying the neural cell types of the medial temporal lobe is to examine their relevance for memory and navigation[51,54,55]. This project will advance neuroscience by shifting our perspective on the function of the medial temporal lobe towards imagination.
- In addition to growing our fundamental knowledge of how the brain supports imagination, the proposed project has clinical relevance, because patients with damage to the medial temporal lobes are severely impaired in imagining the future[24]. Damage to the medial temporal lobes occurs in a variety of common brain disorders such as Alzheimer's disease. Recent studies indeed showed that Alzheimer's patients exhibit impairments in simulating future events[56]. NeuroI will provide a mechanistic explanation for these deficits at the level of single neurons.

4. Objectives and work program

4.1 Objectives

NeuroI will realize its vision of identifying a single-neuron architecture for human imagination (Fig. 1) by completing six objectives:

Objective #1: Establish single-neuron recordings during immersive virtual reality. We will implement a novel technical setup that will allow us to perform single-neuron recordings during

immersive virtual-reality tasks. We anticipate that this setup makes the tasks more realistic, leading to stronger and novel neural responses. By performing quality assurance measurements, we will ensure that the single-neuron recordings are compatible with the setup, otherwise we will proceed with our established method of laptop-based tasks[46,57,58]. We will program all virtual-reality tasks (using Unity software) and pilot them with patients at the behavioral level.

Objective #2: Demonstrate how spatial cells support the imagination of future paths. Patients will perform a virtual-reality task including both navigation and imagination periods. Using the data from the navigation periods, our analyses will identify various allocentric and egocentric spatial cell types in this task. We will then test how allocentric spatial cell types (such as place cells) activate during the imagination periods of the task when patients imagine future paths using allocentric strategies. Conversely, we will assess how egocentric spatial cell types (including anchor cells) activate when patients imagine future paths using egocentric strategies.

Objective #3: Investigate time cells and how they contribute to the imagination of future time points. Patients will complete a judgement of imminency task[59], which requires them to imagine imminent future time points. Our data analyses will identify time cells in this task and show whether time cells support the imagination of future time points via (i) rapid forward scanning up to the imagined time and (ii) sustained representation of the imagined time.

Objective #4: Reveal how concept cells facilitate the imagination of future events. We will detect concept cells using established concept-cell screenings[60] and will then study whether the activity of different concept cells recombines when patients imagine future events that they never experienced before.

Objective #5: Identify an integrated single-neuron architecture for human imagination. To achieve our overarching goal, we will assess how spatial, time, and concept cells activate while subjects imagine holistic future experiences consisting of possible events in possible spatiotemporal contexts. We hypothesize that spatial cells represent the spatial context of the imagined experiences, time cells the temporal context, and that concept cells represent the content of the experiences. We will examine the completeness of our proposed architecture by testing whether a brain-machine interface allows us to decode a subject's imaginations based on the cellular activity. Further experiments will show in which way "theta-paced flickering" supports the simultaneous imagination of different competing imaginations.

Objective #6: Examine the link of our neuroscientific approach to philosophical theories of human imagination. In an interdisciplinary collaboration with philosophers, we will determine to what extent different philosophical conceptions of imagination can be operationalized and empirically investigated. In a second step, we will identify and discuss the ethical implications resulting from our ability to decode a subject's imaginations (as done in objective #5).

4.2 Schematic working plan, time schedule, and approach to possible risks

NeuroI will achieve its overarching goal by completing six objectives (see above). This modular approach will allow us to react to possible risks and unforeseen difficulties in a timely and effective manner, ensuring a successful completion of the entire project. The planned total duration of the project is 5+3 years. One postdoctoral researcher will work on objectives #1, #2, and #3; another postdoctoral researcher will work on objectives #1, #4, and #5. I will oversee all work. All group members will work on objective #6. Figure 5 provides a schematic of the working plan and a timeline for the first five years of the project.

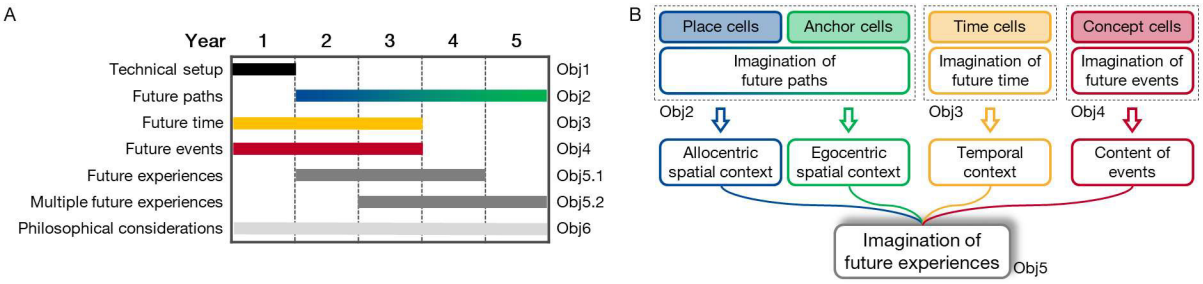

Fig. 5. Time schedule and schematic working plan. (**A**) Time schedule. (**B**) Schematic working plan. Objective #2 will examine the role of spatial cells for imagining future paths; objective #3 will assess the function of time cells in imagining future time; and objective #4 will test how concept cells contribute to the imagination of future events. Objective #5 will integrate the different cellular building blocks to establish an overall single-neuron architecture for imagining future experiences, which consist of future events in future spatiotemporal contexts. Obj, objective.

4.3 Detailed work program

Objective #1: Human single-neuron recordings during immersive virtual reality

NeuroI will establish the proposed neural architecture for imagination using single-neuron recordings from the human brain. These recordings are possible under rare and exceptional circumstances when epilepsy patients are implanted with intracranial electrodes for diagnostics[51,61]. Patients will provide written informed consent, all experiments will be performed in agreement with the hospital's ethics committee, and they will not pose any risks to the patients[62,63]. The spatial and temporal resolution of human single-neuron recordings is exceptionally high[64], allowing us to study the brain at the cellular level in real time (~30 kHz temporal resolution; spatial resolution of single neurons). Performing the recordings in epilepsy patients does not limit their generalizability to healthy populations, because neurons in epileptic brain regions generally exhibit similar responses to cognitive stimuli as neurons in non-epileptic regions[46,65–67]. NeuroI cannot be replaced by animal studies, because high-level cognitive capacities such as imagination cannot (easily) be examined in animals[9]. Data will be analyzed using state-of-the-art techniques[68,69] and strict statistical procedures[70,71]. Anonymized data and analysis code will be made publicly available to ensure transparency and reproducibility.

Objective #1 will establish a novel setup for performing human single-neuron recordings during immersive virtual reality, which will be used in objectives #2–#5. In this setup (Fig. 6), patients experience the tasks via head-mounted displays, shielding the patients from their actual

environment in the patient rooms. We anticipate that this increases the patients' focus on the tasks and the vividness of their imaginations. We will also establish the use of a motion platform[72] for the spatial navigation tasks. Due to the physical movement of the subjects on the motion platform and the more realistic experience of the environments via the head-mounted display, we expect to observe stronger and previously unobserved single-neuron activity related to human navigation[53]. Subjects' behavior will be logged with high temporal resolution (100 Hz), allowing us to exactly relate the neural activity to the subjects' task behavior. We will perform quality assurance measurements to ensure that the setup does not impair the quality of the neural recordings (otherwise we will proceed with our well-established method of laptop-based tasks[46,57,58]). Eye tracking in all experiments will allow us to determine the influence of visual input and eye movements on the neural activity.

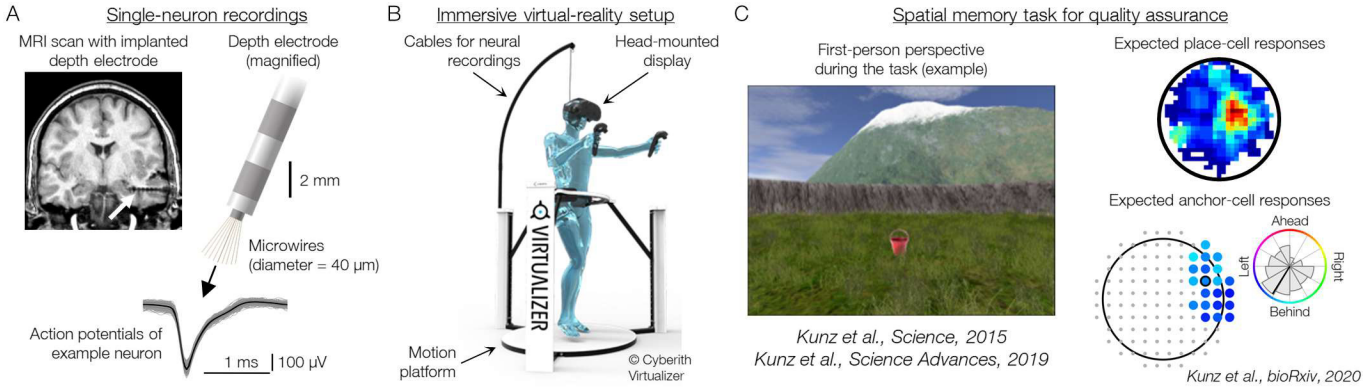

Fig. 6. Setup for single-neuron recordings during immersive virtual reality. (**A**) Patients are implanted with "microwires" that protrude from the tip of electrodes implanted in various regions of the medial temporal lobe. Microwires allow the recording of action potentials from individual neurons. (**B**) For the spatial navigation tasks in objectives #2 and #5, we will ask the patients to physically move on a motion platform and to wear a head-mounted display to experience the virtual environments as realistically as possible. For the tasks in objectives #3 and #4, patients will only wear the head-mounted display. (**C**) To ensure that the setup does not reduce the quality of the single-neuron recordings, patients will complete a well-established spatial memory task. We expect to observe various spatial cells whose tuning is similar or stronger as compared to our previous study with this task. In particular, we predict to observe strong activity of place cells and anchor cells.

Objective #2: Imagination of future paths using spatial cells

Objective #2 will test how the activity of spatial cells supports humans' ability to imagine future paths. Subjects will complete a spatial navigation task, in which they first learn the locations of different objects in a virtual environment during a learning period (Fig. 7A). Subjects will then complete multiple imagination trials, each time imagining their navigation path from a given starting location to the location of a given target object (Fig. 7B–C). We predict that the activity of spatial cells during imagination forecasts the subjects' future navigation paths through the environment. We expect to observe such anticipatory activity in place cells, grid cells, and head-direction cells, when subjects are required to imagine their paths using an allocentric strategy (Fig. 7D). In contrast, we predict to observe activity in egocentric spatial cells (including anchor cells) when subjects imagine their paths via an egocentric strategy (Fig. 7E). In addition, we hypothesize that "theta sequences"[33,73] organize the activity of the spatial cells during imagination such that early parts of the future path are represented early during a given theta cycle, and that late parts of the future path are represented late during a given theta cycle.

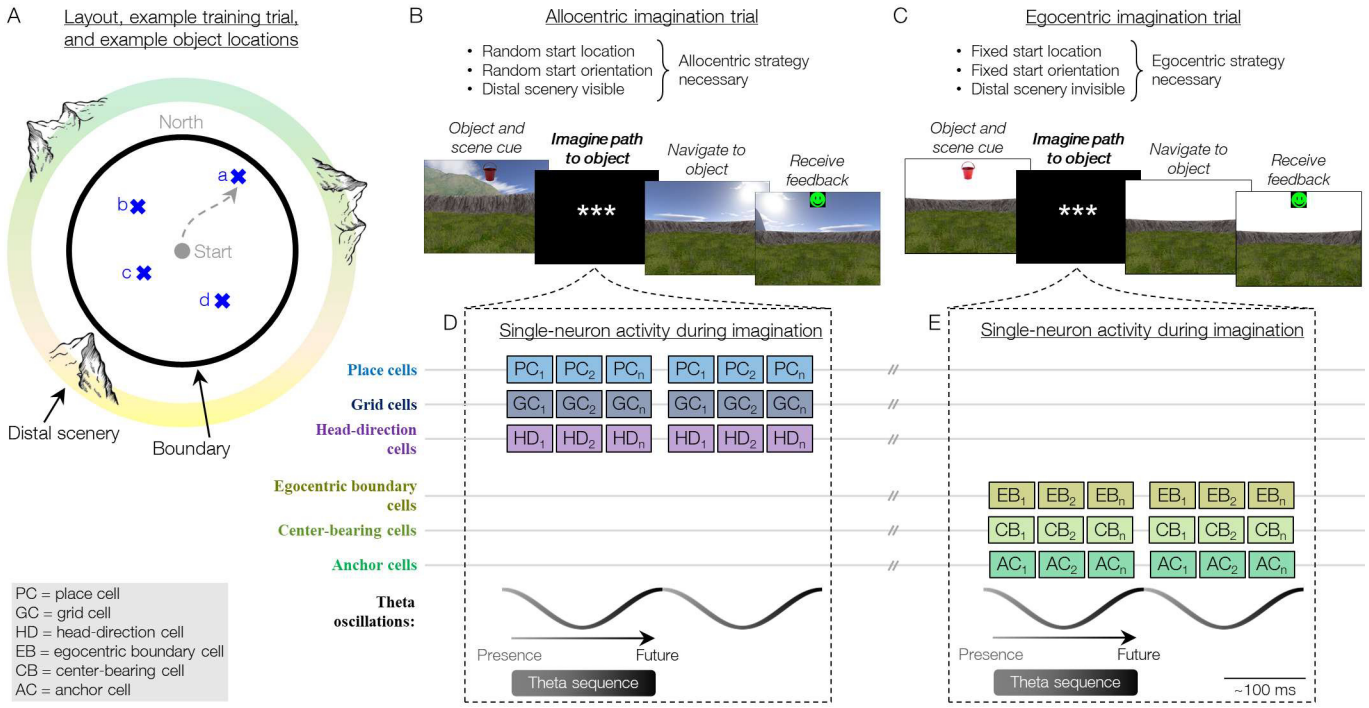

Fig. 7. Imagination of future paths using spatial cells. (**A**) Subjects navigate a virtual environment surrounded by a circular boundary and a distal scenery including mountains. During a training period, subjects learn the locations of four different objects (a–d) by repeatedly navigating from the same starting location (environment center, facing north) to the object locations. Subjects can encode the object locations by either remembering them relative to the distal scenery (allocentric strategy) or by remembering the performed sequence of rotations and translations necessary to navigate from the starting location to the object location (egocentric strategy). (**B–C**) After learning, subjects complete imagination trials. Each trial starts with an object and scene cue so that the subject is informed about its starting location, its starting orientation, and the target object. The screen then turns blank, and the subject imagines its future path through the environment from its starting location towards the location of the target object. After the imagination period, the subject navigates to the assumed location of the object and receives feedback about the accuracy of its path. (**B**) On allocentric imagination trials, the distal scenery is visible, and subjects start from a random location, facing any direction. (**C**) On egocentric imagination trials, the distal scenery is *not* visible, and subjects start from the environment center, facing north (as during the training trials). (**D**) For the imagination periods of *allocentric* imagination trials, we predict to observe activity in *allocentric* spatial cells (i.e., place, grid, and head-direction cells) that forecasts the subjects' future path through the environment. We hypothesize that the activity is temporally compressed onto single theta cycles ("theta sequences") such that earlier parts of the future path are represented early during the theta cycle (closer to "Presence"), whereas later parts of the future path are represented late during the theta cycle (closer to "Future"). During a given imagination period, the identical theta sequence repeats several times in a row. Indices differentiate between different cells of the same cell type. (**E**) For the imagination periods of *egocentric* imagination trials, we predict to observe activity in *egocentric* spatial cells (i.e., egocentric boundary cells, center-bearing cells, and anchor cells) that forecasts the subjects' future path through the environment. As in **D**, we hypothesize that the activity is temporally compressed onto single theta cycles ("theta sequences").

Objective #3: Imagination of future time points using time cells

NeuroI proposes that the activity of time cells enables us to imagine future time points and future temporal contexts. To provide the first empirical evidence for this idea, we will develop a judgement of imminency task[59] that allows the identification and analysis of human time cells. During the training period of this task (Fig. 8A–B), subjects perform multiple trials, in each of which the subject views a series of five letters over a fixed time interval (7 s). The letters are drawn from a predictable sequence of 13 letters. Over the course of the learning period, subjects aim at understanding the predictable letter sequence (which they do not know at the beginning of the experiment). After the training period (when they have understood the predictable letter sequence), subjects complete multiple imagination trials (Fig. 8C). Each imagination trial starts with a cueing letter sequence, followed by a probe letter. The subject is asked to imagine the time point at which the probe letter would occur during the next trial if the cueing letter sequence proceeded as expected from the predictable letter sequence.

We hypothesize to observe time cells in this task that increase their firing rates at particular time points during the training trials (Fig. 8D)[14]. We will then assess their activity profiles during imagination trials to test, for the first time, how time cells behave during human imagination. Specifically, we hypothesize two key phenomena for time-cell activity during the imagination periods: (1) We expect that time cells exhibit rapid forward scanning during the early part of the imagination period (so as to quickly "jump" to the imagined future time point; Fig. 8F). (2) We expect that time cells exhibit sustained activity during the middle and late part of the imagination period (to continuously represent the imagined future time point; Fig. 8F). By demonstrating these phenomena in time cells, our project will provide the first evidence for the involvement of time cells in imagining future time points.

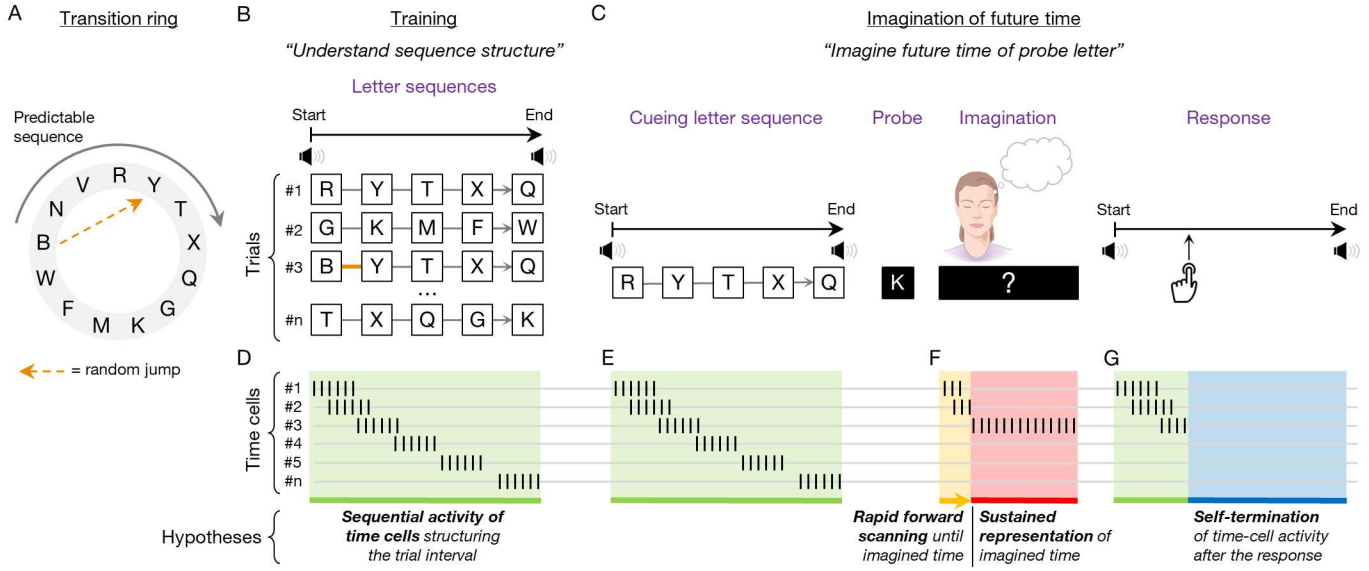

Fig. 8. Imagination of future time points using time cells. (**A**) Example transition ring that defines a predictable letter sequence (not shown to the subject). Occasionally, a random "jump" occurs. (**B**) During training, subjects view multiple iterations of the letter sequence, separated into trials of 5 consecutive letters each (trial starts and ends are signaled by a sound). Subjects are asked to develop an understanding of the predictable letter sequence over the course of training. They are asked to press a button whenever a random jump between two letters occurs (allowing us to assess whether they understood the predictable letter sequence). (**C**) After training, subjects perform multiple imagination trials in which they are cued with a specific letter sequence. Next, a probe letter is shown, and subjects imagine the time point of this probe letter during the upcoming trial (provided that the cueing letter sequence continues according to the predictable letter sequence). Subjects close their eyes and try to imagine the future time point as vividly as possible. After imagination, subjects hear a sound and press a button at the time point (relative to the sound) at which they anticipate the letter to occur during the upcoming trial. This provides an objective assessment of the subjects' accuracy to imagine the future time point of the probe letter. (**D**) We will use the training period to identify time cells that activate at the same time point during each training trial (green box). (**E**) During the cueing letter sequence, we expect to see the same time-cell activity as during training trials. (**F**) While subjects imagine the future time of the probe letter, we hypothesize to observe time-cell activity that shows rapid forward scanning up to the imagined time point (yellow box: "rapid forward scanning") and then continues to represent this imagined time point for the rest of the imagination period (red box: "sustained representation"). (**G**) During the response period, we predict to observe time-cell activity identical to time-cell activity during training trials (green box). We predict that this activity stops, however, as soon as the subject gives its response, because tracking time is then behaviorally not relevant anymore (blue box: "self-termination").

Objective #4: Imagination of future events using concept cells

In objective #4, we will identify the role of concept cells for the imagination of possible future events. Subjects will first complete a "concept-cell screening"[60], which allows us to identify concept cells as neurons that increase their firing rates in response to stimuli belonging to the same concept (i.e., their "preferred concept"; Fig. 9A). Afterwards, subjects perform multiple imagination trials, in which subjects are cued with two or three of the preferred concepts (e.g., *Table* and *Elephant*; Fig. 9B). Subjects then try to imagine a novel future event involving these

concepts as vividly as possible (Fig. 9C–D). For imagination periods, we predict to observe simultaneous activity in all concept cells whose preferred concepts are involved in the imagination. In addition, we predict to observe stronger theta–gamma phase–amplitude coupling[74,75] during trials in which the subjects imagine the future event more vividly (Fig. 9E). These results will provide the first insights into the single-neuron basis of humans' ability to imagine future events that they never experienced before.

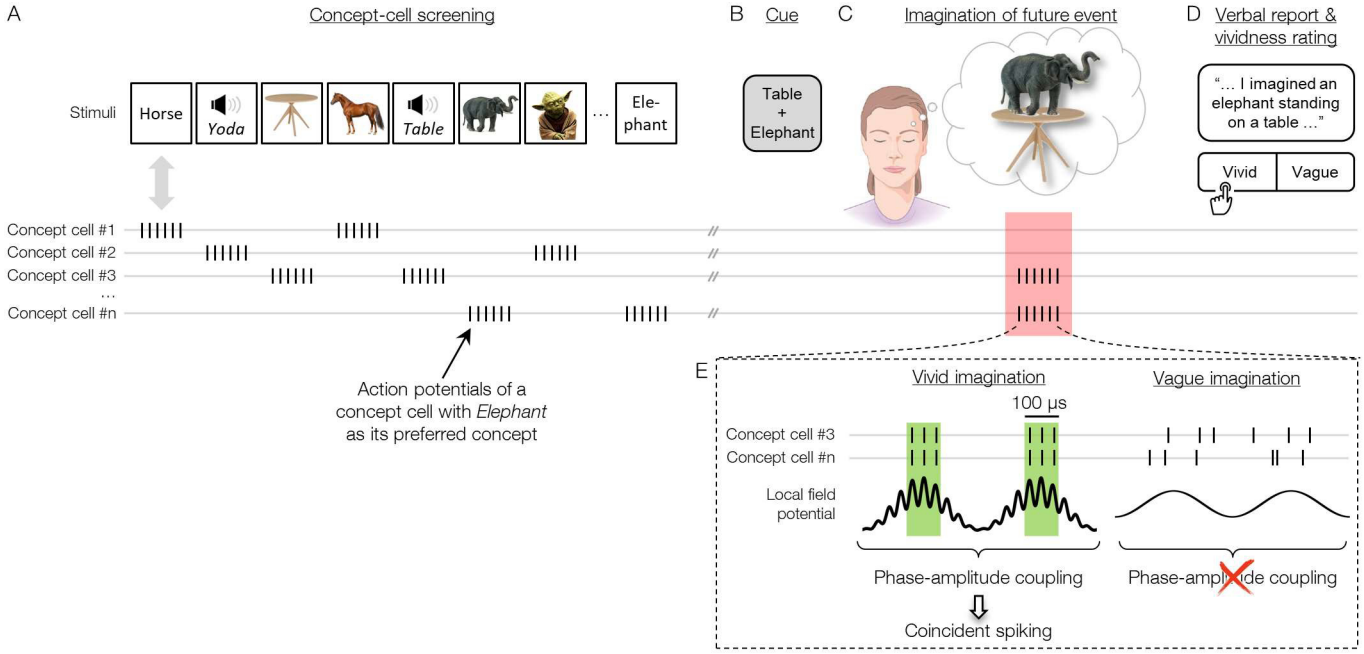

Fig. 9. Imagination of future events using concept cells. (**A**) During a concept-cell screening, multiple different stimuli (faces, written names, spoken names) are presented to the subject. We will identify concept cells and their "preferred concepts" using established techniques[60]. (**B**) After the concept-cell screening, subjects will perform multiple imagination trials. Each imagination trial starts with two or three preferred concepts being presented to the subject ("Cue"). (**C**) Subjects then try to imagine a future event involving all cueing concepts as vividly as possible (e.g., the subject imagines an elephant standing on a table). The imagined event shall be as novel as possible. We hypothesize to observe activity in those concept cells whose preferred concepts are involved in the imagination (red box). (**D**) After imagination, subjects verbally report their imagination and rate its vividness. (**E**) We hypothesize that vivid imaginations are associated with theta–gamma phase–amplitude coupling that leads to coincident spiking between all concept cells involved in representing the imagined event (green boxes).

Objective #5: A single-neuron architecture for the imagination of future experiences

Objective #5.1: Imagination of holistic future experiences

Objective #5.1 will identify the proposed overall single-neuron architecture for humans' ability to imagine future experiences. Because future experiences are imagined events embedded into possible spatiotemporal contexts[19], NeuroI proposes that the fundamental neural architecture of each imagined future experience consists of activity in:

- ❖ Concept cells that simulate the event of the imagination ("what");
- ❖ Spatial cells that construct the spatial context of the imagination ("where"); and
- ❖ Time cells that represent the specific temporal context ("when").

We will test our proposed neural architecture of imagination by tracking the activity of spatial, time, and concept cells while subjects imagine future experiences in a realistic virtual-reality task. In this task, subjects first explore a virtual city on multiple navigation trials (each with a fixed duration), allowing us to identify spatial cells and time cells in this task (Fig. 10A).

Subjects then complete a concept-cell screening to detect concept cells that respond to particular persons ("preferred persons"; Fig. 10B). On each of many imagination trials, subjects will then imagine routes through the environment along which they meet one of the preferred persons at a particular place and time (freely chosen by the subjects; Fig. 10C). We will study the activity of spatial, time, and concept cells during imagination and test whether their activity closely reflects the imagined experiences. To have a success criterion for this test, we will probe our ability of reading the subjects' imaginations based on the activity of spatial, time, and concept cells using a brain-machine interface (BMI)[76]. The BMI will be trained on the navigation periods and the concept-cell screening and will be tested on the imagination periods. After each imagination period, we will present the subject with the decoded imagination and the subject will rate whether the decoded imagination is similar to their actual imagination (Fig. 10D). If so, this will show that the combined activity of spatial, time, and concept cells represents a subject's imagined future experiences. This will also demonstrate whether our proposed single-neuron architecture is exhaustive or whether additional neural components have to be added.

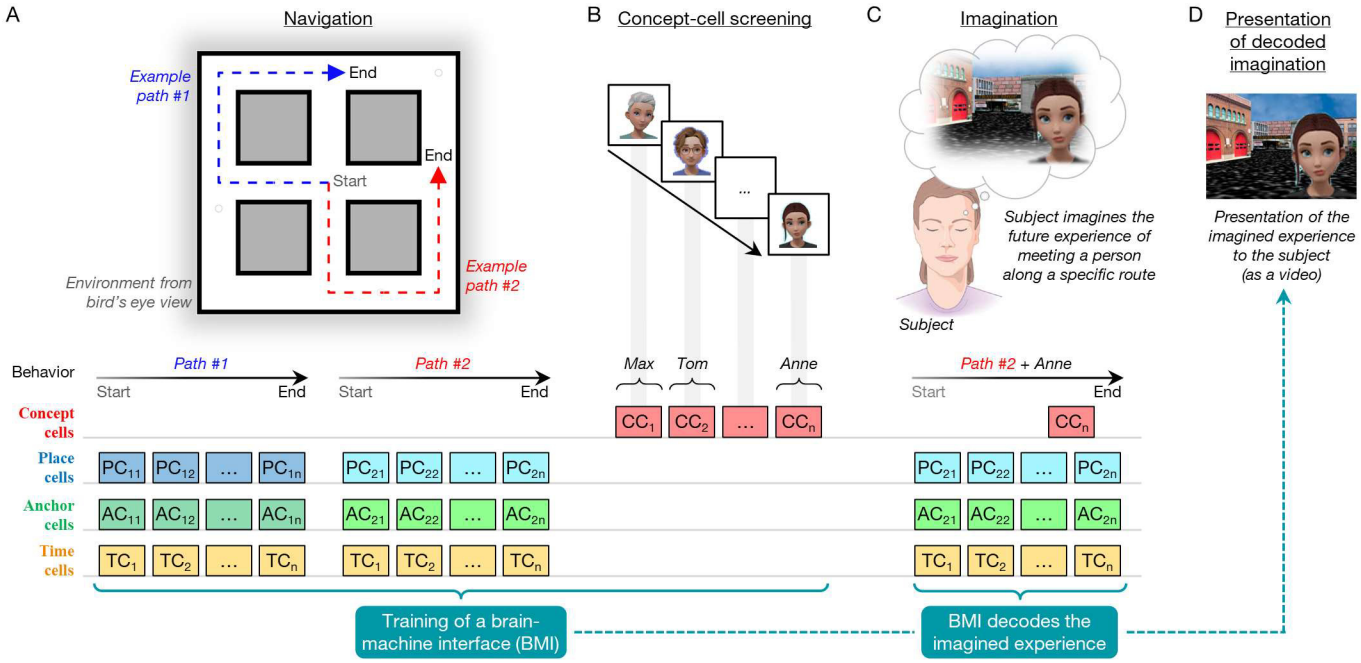

Fig. 10. Imagination of holistic future experiences. (**A**) During the navigation period of the task, subjects explore a virtual city (experienced from a first-person perspective). For instance, the subject may navigate along example path #1 to reach the northern part of the city. While the subject explores the environment, different place cells (PC), anchor cells (AC), and time cells (TC) are active. The subscript indices indicate the specific path (first index) and the specific cell (second or only index). (**B**) A subsequent concept-cell screening allows us to identify concept cells (CC) that respond to specific persons ("preferred persons"). (**C**) During imagination trials, subjects will imagine future experiences that consist of navigating through the virtual city and meeting one of the preferred persons at a particular place and time. We predict that all concept, place, anchor, and time cells will be active that encode the content (i.e., the preferred person) or the spatiotemporal context of the imagination. (**D**) Using the output of a brain-machine interface (BMI), we will decode the subject's imagination and present the decoded imagination to the subject. The subject then rates the similarity of the decoded imagination to their actual imagination. Turquoise text boxes: The BMI will be trained on the cellular activity from the navigation periods and the concept-cell screening. The BMI will then be used to decode the subject's imaginations based on the single-neuron activity of concept, place, anchor, and time cells during imagination trials.

Objective #5.2: Simultaneous imagination of multiple future experiences

In our complex world, humans need to prepare for multiple possible futures simultaneously to flexibly cope with the ever-changing influences of the external environment. Objective #5.2

will unravel key neural mechanisms underlying our ability to imagine different possible futures simultaneously. To this end, we will employ an imagination task in which subjects are asked to imagine and navigate routes in a virtual environment (Fig. 11A). On each trial, subjects will first imagine two or more possible paths between a start and a goal location ("unconstrained imagination"; Fig. 11B). We will then restrict their imagination to one possible future by blocking all but one possible paths ("restricted imagination"; Fig. 11C). After imagination, subjects will navigate from the start to the goal location.

For *unconstrained* imagination, we hypothesize that

(1) The different possible futures are represented by single-neuron activity in distinct sets of spatial, time, and concept cells (Fig. 11D).

(2) The different future paths are represented in a temporally compressed manner on alternating cycles of the theta rhythm (Fig. 11D). This constitutes our proposed mechanism for the simultaneous representation of multiple possible futures, which is inspired by the intriguing phenomenon of "theta-paced flickering" of place cells in rodents[35,36].

(3) Within each theta cycle, the temporal structure of the imagined future unfolds sequentially: Early parts of the imagined path are represented early during a given cycle, whereas late parts are represented late during the cycle (as predicted by "theta sequences"[73] in rodents).

For *restricted* imagination, we hypothesize that only the remaining possible future is represented by single-neuron activity in the corresponding remaining set of spatial, time, and concept cells (Fig. 11E).

By demonstrating these phenomena, objective #5.2 will provide the first neurobiological explanation for humans' ability to imagine multiple possible futures simultaneously.

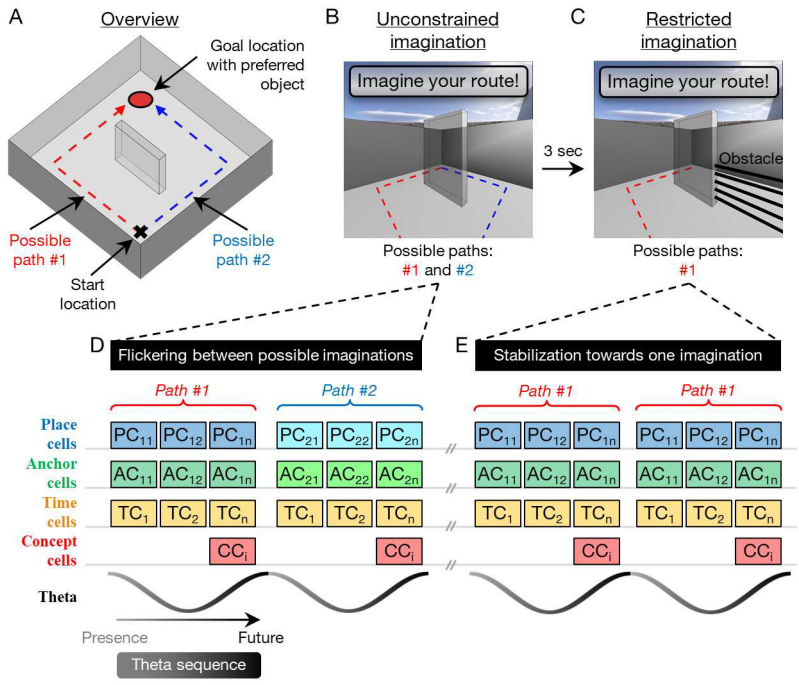

Fig. 11. Simultaneous imagination of multiple possible futures. (**A**) Subjects first explore the virtual environment and complete a concept-cell screening (not shown), allowing us to identify spatial, time, and concept cells as well as the "preferred objects" of the concept cells. Subjects will then complete multiple imagination trials, each starting with an "Overview" period, in which the subject views the virtual environment from an overhead view. The subject is asked to visually explore the possible paths between a given start and goal location. One of the preferred objects is placed at the goal location. (**B**) The subject is passively transported into the environment. The subject is asked to plan and to imagine its possible paths through the environment. The two possible paths are indicated as red and blue dotted lines (not shown to the subject). (**C**) After a few seconds, an obstacle is added to the environment, restricting the subject's imagination to one possible future path. (**D**) While the subject imagines the different possible paths, the single-neuron activity "flickers" repeatedly between representing one path or the other. The subscript indices indicate the specific path (first index) and the specific cell (second or only index). (**E**) As soon as the subject's possible future paths become restricted, the cellular activity stabilizes towards representing the remaining possible future.

Objective #6: Philosophical considerations

Throughout history, philosophers including Descartes[77], Kant[28], and Sartre[17] have thought about the nature of imagination. I am convinced that their insights are relevant to my neuroscientific approach of studying the neural substrates of human imagination—both from a content-related and from a methodological perspective. In collaboration with Prof. Dr. Markus Gabriel (professor of philosophy at the University of Bonn), who has already agreed upon the collaboration, we will thus complement our neuroscientific investigations with the examination of philosophical works on imagination. During year 1, we will focus on the question whether philosophical theories of imagination can generate empirically testable hypotheses and thus guide neuroscientific research on imagination[26,78,79]. This may include refinements of our task designs. During years 2–3, we will address the question whether and why there are forms of imagination that, in principle, cannot be investigated using neuroscientific techniques. A particular focus will be on Sartre's "The Imagination" and "The Imaginary", in which he rejects earlier philosophical and psychological theories that assume a close relationship between imaginations and perceptions[17,18]. We will study to what extent Sartre's view is compatible with our neuroscientific conception of imagination. During years 4–5, we will consider the ethical implications of being able to read a subject's imaginations[80], as demonstrated in objective #5.

TEACHING CONCEPT

I am passionate about how the human brain works and I would like to pass this passion to my students. I thus plan to teach a "Neuroscience of Human Cognition" course, in which all major topics of cognitive neuroscience are covered. The course will be interdisciplinary and open to students from the fields of neuroscience, medicine, psychology, philosophy, biology, and physics. The interdisciplinarity of this course will encourage the students to think outside the box and to get a sense for the various different—and equally valid—scientific approaches to complex phenomena such as the brain and mind. The first major goal of the course will be to teach students how to read primary literature and how to critically evaluate data presented in research articles. The second major goal of the course will be to teach students how to analyze neuroscientific data. We will use data from previous single-neuron, M/EEG, and fMRI studies and students will write their own code to replicate key findings. We will meet for 3 hours per week. Every first of two subsequent meetings will be dedicated to discussing primary literature related to a major neuroscientific topic. During the second meetings, students will receive hands-on training in analyzing data from the previously discussed studies. Moreover, I will teach the students general standards for good scientific practice, how to avoid common pitfalls when analyzing big, multi-dimensional datasets, and how to contribute to reproducible science.

REASONS FOR CHOOSING THE HOST INSTITUTION AND DESCRIPTION OF RESEARCH INFRASTRUCTURE

The research group will be hosted by one of the following potential host institutions:

- Epilepsy Center, University of Freiburg (head: Prof. Dr. Andreas Schulze-Bonhage).
- Department of Epileptology, University of Bonn (head: Prof. Dr. Rainer Surges).

Both institutions have accepted to host the Freigeist Fellow and his junior research group (please see the binding declarations). Both institutions provide excellent conditions for the successful realization of the proposed projects. NeuroI relies on high-quality and high-density single-neuron recordings from the human brain, which are currently only possible at two sites in Germany: Freiburg and Bonn. The applicant considers both sites as potential host institutions for the project.

Please see the attached document "Host & infrastructure" for detailed information.

DETAILS OF COOPERATION PARTNERS

Local collaborators at the University of Freiburg

Prof. Dr. Andreas Schulze-Bonhage (Medical Director of the Epilepsy Center); Prof. Dr. Marlene Bartos (Director of the Institute for Physiology I); Prof. Dr. Carola Haas (leader of the Experimental Epilepsy Research group); Prof. Dr. Monika Schönauer (Chair of Neuropsychology).

Local collaborators at the University of Bonn

Prof. Dr. Rainer Surges (Director of the Department of Epileptology); Prof. Dr. Dr. Florian Mormann (Lichtenberg professor of cognitive and clinical neurophysiology); Prof. Dr. Heinz Beck (Head of the Institute of Experimental Epileptology and Cognition Research); Prof. Dr. Markus Gabriel (Professor for Philosophy and Director of the Center for Science and Thought).

International collaborators

Prof. Dr. Joshua Jacobs, Columbia University in the City of New York, USA; Prof. Dr. Michael J. Kahana, University of Pennsylvania, USA; Prof. Dr. Bryan Strange, Universidad Politécnica de Madrid, Spain; Prof. Dr. Tobias Navarro-Schroeder, NTNU, Norway; Prof. Dr. Bernhard P. Staresina, University of Birmingham, UK.

INFORMATION, IF THIS OR A SIMILAR APPLICATION HAS BEEN OR WILL BE SENT TO OTHER FUNDING ORGANIZATIONS This application has not been sent elsewhere.

SCHEMATIC WORKING PLAN AND TIME SCHEDULE Please see section 4.2.

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