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## The brain during free movement – what can we learn from the animal model

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33 Abstract

34

35

36 **Animals, just like humans, can freely move. They do so for various important reasons, such as finding**  
37 **food and escaping predators. Observing these behaviors can inform us about the underlying**  
38 **cognitive processes. In addition, while humans can convey complicated information easily through**  
39 **speaking, animals need to move their bodies to communicate. This has prompted many creative**  
40 **solutions by animal neuroscientists to enable studying the brain during movement. In this review,**  
41 **we first summarize how animal researchers record from the brain while an animal is moving, by**  
42 **describing the most common neural recording techniques in animals and how they were adapted**  
43 **to record during movement. We further discuss the challenge of controlling or monitoring sensory**  
44 **input during free movement.**

45 **However, not only is free movement a necessity to reflect the outcome of certain internal cognitive**  
46 **processes in animals, it is also a fascinating field of research since certain crucial behavioral patterns**  
47 **can only be observed and studied during free movement. Therefore, in a second part of the review,**  
48 **we focus on some key findings in animal research that specifically address the interaction between**  
49 **free movement and brain activity. First, focusing on walking as a fundamental form of free**  
50 **movement, we discuss how important such intentional movements are for understanding processes**  
51 **as diverse as spatial navigation, active sensing, and complex motor planning. Second, we propose**  
52 **the idea of regarding free movement as the expression of a behavioral state. This view can help to**  
53 **understand the general influence of movement on brain function.**

54 **Together, the technological advancements towards recording from the brain during movement, and**  
55 **the scientific questions asked about the brain engaged in movement, make animal research highly**  
56 **valuable to research into the human “moving brain”.**

57

58

## 59 **Introduction**

60 Unlike humans, animals will not voluntarily sit still during the execution of scientific experiments.  
61 However, since they are also not able to respond to behavioral probing through speaking and only in  
62 a few cases can answer by a button press or a directed eye movement, animals actually need to move  
63 their bodies in order to convey information about the outcome of cognitive processes. Therefore,  
64 when studying the role of the brain in cognitive functioning, animal researchers have to embrace the  
65 movements of their experimental subjects rather than suppress them. Scientists indeed have come  
66 up with many diverse techniques to make this possible.

67 In comparison, studying the human brain, there seems less need to provide participants with the  
68 freedom to move. Language gives us the possibility to convey complex information without actually  
69 needing to enact it. Even looking at locomotion as the epitome of free movement, there are many  
70 possibilities to test single aspects of this while restricting the actual freedom to move to a minimum.  
71 Freely moving through space is an intentional action based on spatial navigation, active sensing and  
72 motor planning. Using elaborate setups including virtual reality, treadmills, and focusing on planning  
73 very small movements these aspects can be studied in humans without allowing actual locomotion.  
74 However, this is only possible to a limited extent, especially concerning the complex interplay between  
75 these processes. Additionally, recent behavioral research has made very clear that the movement of  
76 the whole body can also affect a surprising number of cognitive functions, which on first sight seem  
77 to be independent of large body movements. These include memory, attention, and sensory

78 integration (Schmidt-Kassow et al., 2013; Schmidt-Kassow et al., 2014; Kirsch et al., 2017; Schaefer et  
79 al., 2010; McMorris and Graydon, 2000; Smith et al., 2010). Animal studies have shown similar effects  
80 in freely moving animals, whilst concurrently starting to uncover how brain activity is affected by free  
81 movements (Niell and Stryker, 2010; Polack et al., 2013; Saleem et al., 2013). Since neurophysiological  
82 measurements in humans during free walking are exceedingly rare, this review focuses on locomotion  
83 in animals and omits other research on free movements such as from the arm or hand. Human  
84 research might profit most readily from these animal studies during locomotion.

85 Despite the fact that portable recording systems were developed in animals out of sheer necessity to  
86 allow the animal to convey information through body movements, findings from ongoing animal  
87 research can be most useful for human research in this field. The benefit can be at least twofold: 1)  
88 the technical advancements enabling researchers to study the animal brain during large movements  
89 might inspire technologies to record neural activity in the moving human brain, and 2) the ongoing  
90 animal research might help to formulate hypotheses or shape promising experimental questions  
91 based on results from the animal model. It is our belief that the full potential of these benefits has not  
92 yet been met.

93 This review is divided into two main parts: first, we address the methodological developments and  
94 challenges in research on freely moving animals. Second, we discuss experimental questions in animal  
95 research that specifically address the interaction between brain activity and free movements with a  
96 focus on locomotion in mammals. We discuss how important the role of free locomotion is for  
97 understanding spatial navigation, active sensing, and complex motor planning. Additionally, we  
98 propose the idea of regarding movement as the expression of a behavioral state. In this view, free  
99 locomotion is the most active state of a wide range of behavioral states, including sleeping and being  
100 quietly awake. We suggest thinking about freely walking as a specific behavioral state since it calls for  
101 very specific processing of external stimuli and generating motor output. This view helps to  
102 understand the general influence of movement on brain function.

103

104

## 105 **Methodological approaches**

### 106 **Recording brain activity during movement**

107

108 Broadly speaking, the techniques for recording neural activity from the brain fall into two categories.  
109 There are those that directly measure electrical activity from neurons using e.g. microelectrodes,  
110 electroencephalography (EEG) or electrocorticography (ECoG), and those that measure neuronal  
111 activity indirectly by imaging the metabolic activity of neurons, such as functional magnetic resonance  
112 imaging (fMRI), positron emission tomography (PET), and calcium imaging. These sets of methods  
113 have been refined to record from moving animals in many ways. For this review, we will describe the  
114 mobile versions of the above-mentioned techniques and refer to excellent reviews that specifically  
115 cover these techniques individually. It is also possible to measure neural dynamics intracellularly in  
116 moving animals (Lee et al., 2006). However fascinating, these methods have no comparable  
117 application in humans. We therefore will omit these techniques as well as those that actively  
118 manipulate neuronal activity like microstimulation or optogenetics, and focus on recording techniques  
119 only.

120

### 121 Direct measurements - electrophysiology

122 Neuronal activity can be assessed directly through the use of electrodes which measure the electrical  
123 communication of neurons.

124

#### 125 Micro-electrodes

126 Recording electrical activity from neurons in the animal brain is mostly done through extracellular  
127 recordings. In a typical set-up, part of the skull is removed, and single electrodes or electrode arrays  
128 (optionally with multiple contact points – often referred to as laminar electrodes) are either being  
129 inserted for every experimental session or implanted permanently (Okun et al., 2016) (Fig 1A). In the  
130 latter case, the skull and skin are placed back. The inserted electrodes measure voltage differences  
131 with respect to a neutral reference, for example from the skull. These voltage differences reflect either  
132 action potentials (called spiking) from single neurons (single unit activity – SUA) or populations of  
133 neurons (multi-unit activity – MUA), or the local field potential (LFP), which is an aggregate measure  
134 of local changes in electrical fields caused mainly by dendritic activity of the neurons. It contains no  
135 spikes but rather slow changes in the electric potential (Fig 1B). Which type of neuronal activity is  
136 recorded depends mostly on the surface area of the electrode; single electrodes usually have a small  
137 surface area and are therefore well-suited to pick up SUA, whereas electrode arrays and laminar  
138 electrodes typically have larger surface areas and therefore mostly pick up MUA and LFP. The neuronal  
139 activity, i.e. LFP and spiking, is then transmitted to an amplifier and passed on for storage and further  
140 processing. In a conventional set-up, this transmission is realized via wires connecting the electrodes  
141 to the amplifier and then to the storage. These systems are called *tethered systems*. Typically, the  
142 animal's head is immobilized during a recording session via a head-post secured to the skull, which  
143 allows for task designs in front of a computer screen, as well as reduces mechanical stress onto the  
144 amplifiers and excessive muscle activity from the head (Fig 1C). In order to record from neurons in a  
145 brain that is not stationary a number of adaptations are necessary, in particular to the transmission of  
146 the neural signals. One approach is to use rather long wires that run from the animal's brain to the  
147 amplifier, which are mounted elaborately to ensure that the animal can move without getting  
148 entangled, step on or rip out the wires. These systems allow long-term recordings with multiple  
149 electrodes at a high sampling rate (Fig 1D, left).

150 However, being tethered by wires can cause some distress to the animals (Kramer et al., 2001), and is  
151 specifically limiting for animals which do not mostly move on the ground but fly or climb and jump  
152 (Roy and Wang, 2012). Additionally, whenever the animal moves, the tethering wires also move, which  
153 interacts with electrostatic fields in the recording set-up, resulting in transient noise on the neural  
154 signal termed mains hum. To counteract this noise, the animal's body must be grounded with a low-  
155 impedance wire; however, this ground wire will itself add mains hum and movement artifacts to the  
156 signal (Chang et al., 2011).

157 To overcome these problems, there is a second approach in which a battery-operated system attached  
158 to the animal's body transmits the signals wirelessly. These systems are often referred to as *telemetric*  
159 *recording systems* (Fig 1D, right). Since in this case, there is no wired connection to the animal the  
160 mobile part of the technical devices (recorder plus transmitter/storage) must be carried by the animal  
161 and must obtain their power from a battery alone. This limits the possible time of recording and low  
162 power consumption of transmission is therefore necessary. Additionally, all equipment (electrodes  
163 and transmitter) must be small enough to be comfortably carried around by the animal, either  
164 strapped to the body, fixed to the head or worn subcutaneously (Chang et al., 2011). These challenges  
165 are shared with intracortical recording approaches in humans.

166

167 As early as 1982, successful recordings were done with a telemetric system; a rabbit wore a radio  
168 transmitter on a collar and neuronal activity in the hypothalamus was recorded from multiple  
169 electrodes (Summerlee and Paisley, 1982). Since then, a number of telemetric recording systems have  
170 been developed for various species, including birds (Nieder and Klump, 1999), mice (Fan et al., 2011),  
171 rats (Szuts et al., 2011), primates (Roy and Wang, 2012; Chestek et al., 2009), and sheep (Perentos et  
172 al., 2017). Ongoing developments constantly improve the size and weight, electrode number, and  
173 transmission distance. We want to briefly mention some of the fascinating advancements that have  
174 been achieved to date: 64 electrodes have been recorded in a rat from up to 60 m away, even if the  
175 rat runs in a tunnel (Szuts et al., 2011). Fifteen electrodes have been recorded from a wireless setup  
176 allowing a marmoset to freely jump or climb (Roy and Wang, 2012). Even rats swimming in a water  
177 maze can be measured with a wireless system carried on the head (Pinnell et al., 2016). Mice, long  
178 posing a problem due to their small size, are by now also subject to wireless measurements (Fan et  
179 al., 2011). This development can be of great importance keeping the large amount of transgenic  
180 mouse models in mind (Weiergräber et al., 2005). New technological advancements permit  
181 researchers to greatly increase the number of recorded electrodes. For example, bidirectional wireless  
182 communication made it possible to perform pre-processing on data recorded with a multi-electrode  
183 implant over multiple cortical areas in rhesus monkeys. This reduced the amount of information  
184 transferred wirelessly, allowing for the recording of up to 512 electrodes (Schwarz et al., 2014).  
185 All above-mentioned examples pertain to recordings with electrodes deep in the brain (depth  
186 electrodes), which can pick up voltage changes from one or more single cells. The single neuron level  
187 is largely ignored by human clinical neurology (Cash and Hochberg, 2015). However, insights from  
188 animal research will become more and more relevant as clinically indicated invasive recording  
189 techniques spread in human research. For example, certain movement disorders are treated with  
190 deep brain stimulation. During surgery, electrodes are placed within subcortical nuclei such as the  
191 basal ganglia. These micro-electrodes have a very small contact area and are therefore well-suited for  
192 single unit recordings. Once the correct site for implantation is found, a macro-electrode (with slightly  
193 larger contact area) is implanted for (deep brain) stimulation, which can then also be used for  
194 measuring population responses while the subject is awake after the surgery (Thompson et al., 2014).  
195 Neocortical single unit recordings are obtained from semi-chronic depth electrodes to localize  
196 epileptic foci for surgical removal in patients suffering from intractable epilepsies (see Engel et al.,  
197 2005 for review). To better characterize these foci, a linear multi-electrode with 20–24 contacts was  
198 developed which even allows laminar single unit recordings in humans (Ulbert et al., 2001; Ulbert et  
199 al., 2004). The above-mentioned examples show that SUA and MUA activity can be available for the  
200 human brain. Such recordings in animals might therefore provide a basis for future wireless recordings  
201 of these signals in the freely moving human.

202

### 203 ECoG

204 Another approach for localizing epileptic foci is via electrocorticography (ECoG) where voltage  
205 differences presumably caused by post-synaptic potentials synchronized over a large number of  
206 neurons, are picked up with electrode grids lying on the brain's surface beneath the skull and the dura  
207 mater (Ojemann et al., 2013). Such subdural ECoG is applied in animals and has also been developed  
208 into wireless systems. Rats can wear tiny single-channel ECoG systems in a backpack, which can run  
209 without a battery (Chang and Chiou, 2013). For larger primates, implantable and wireless multi-  
210 channel devices have been developed, able to provide long-term ECoG recording using a wireless  
211 rechargeable battery (Piangerelli et al., 2014). Implantable wireless ECoG grids with 64 electrodes

212 have been tested in monkeys (Mestais et al., 2015). While ECoG is applied in humans on a regular basis  
213 (if medically indicated), the application of wireless ECoG systems is still pending in humans. This could  
214 be an excellent case for combining knowledge gathered from animal and human data.

215

## 216 EEG

217 While the technique of ECoG seems almost directly comparable in humans and animals, EEG is less  
218 common in animal research and rather different in approach. One problem is that the human  
219 approach of placing an EEG cap on the head of the subject is rather prone to artifacts due to muscle  
220 activity and movement of the electrodes caused by the movement of the subject. Especially for moving  
221 animals, the human EEG approach is not very suitable. For a long time, rodent EEG techniques  
222 employed screw electrodes that are fixed to the skull of the animal. Due to the limited space on a  
223 rodent head, only a restricted number of such screw electrodes could be placed on their small skull.  
224 Recently, a wireless high-density polyimide-based microelectrode array allowing the recording of up  
225 to 26 active EEG and 2 active EMG channels on the skull of a rat has been developed (Stienen et al.,  
226 2016). From a translational perspective, especially the research on sheep using wireless EEG (Perentos  
227 et al., 2017) seems promising. Their approach using three different types of electrodes (epi- and  
228 subdural screw electrodes, disc electrodes and sharp microelectrodes) allows the recording of signals  
229 comparable to those recorded with human EEG, as well as more spatially specific neuronal activity,  
230 including spikes. Such approaches can be also particularly helpful to bridge animal invasive recordings  
231 to human non-invasive data since human wireless EEG systems have become available with increased  
232 quality and channel number.

233

## 234 Indirect measurements – brain imaging

235 Neuronal activity cannot only be assessed directly by measuring the electrical communication of  
236 neurons, but also indirectly by imaging their metabolic activity.

237

## 238 Calcium imaging

239 Two-photon calcium imaging measures changes in intracellular calcium concentration as a readout for  
240 neuronal activity. Within a neuron, the intracellular calcium concentration is constantly varying. When  
241 the neuron becomes active, calcium flows into the neuron due to the opening of voltage-gated calcium  
242 channels in the cell membrane. Dependent on the neuronal cell type and the cellular sub-  
243 compartment, more or less voltage is necessary to open the calcium channels (Catterall, 2000). The  
244 increase in calcium concentration during activation is often amplified by calcium release from  
245 intracellular calcium stores (Tsien and Tsien, 1990). On the other hand, calcium-binding proteins called  
246 buffers, such as parvalbumin, will negatively influence the calcium concentration. The amount of  
247 calcium in the neurons can be assessed via calcium-sensitive fluorescent indicators. These fluorescent  
248 molecules bind calcium ions and thereby change their fluorescence properties. There are two groups  
249 of calcium indicators: first, there are chemical dyes which are either injected into single cells (e.g. using  
250 a microelectrode or micropipette) or which label multiple neurons at the same time by various  
251 methods of loading (e.g. via air pressure pulses or electroporation) (Fig 2A). Second, there are  
252 genetically encoded calcium indicators (GECI), which are proteins expressed in all cells or specific  
253 cellular subtypes. The change in fluorescence properties of these calcium indicators due to calcium  
254 release can then be viewed using a fluorescence microscope (Fig 2B). A fluorescence microscope  
255 shines light within a certain wavelength range at the tissue via a laser, and then separates the much  
256 weaker emitted fluorescence from the excitation light via a dichromatic mirror. Only the emission light

257 should reach the detector/detecting photomultiplier tube (PMT) that transforms the light signal into  
258 an electrical signal. A common type of fluorescence microscope is called a two-photon microscope. A  
259 two-photon microscope uses two low-energy photons to excite the fluorescent calcium indicator so  
260 that it emits light. A scanner controls the exact location of excitation. This approach allows increased  
261 penetration depth and efficient light detection, while at the same time reducing damage to the tissue.  
262 The spiking activity can then be inferred from the recorded light signal (Fig 2C; see e.g. Chen et al.,  
263 2013; Grienberger and Konnerth, 2012 for review).

264 Recently developed mobile calcium imaging set-ups transfer a varying number of microscope  
265 components to the animal's head. For example, a complete miniaturized two-photon microscope has  
266 been developed that can be head-mounted (Fig 2D). It is connected to the laser and the control setup  
267 by a flexible tether which contains an optical fiber and electrical wires (Helmchen et al., 2001);  
268 (Piyawattanametha et al., 2009). Others minimized the size and weight of the mobile component by  
269 just placing the objective lens and the dichromatic mirror on the animals head while the rest of the  
270 components are external and immobile (Sawinski et al., 2009; Flusberg et al., 2005; Engelbrecht et al.,  
271 2008). To date, only systems suited to be carried by animals >70 g (e.g., rats) have been demonstrated  
272 to achieve calcium imaging with cellular resolution during freely moving behavior (Sawinski et al.,  
273 2009). An integrated fluorescence one-photon microscope with lower spatial resolution has been  
274 developed to be used in even smaller animals (Ghosh et al., 2011). For reviews, see Kerr and  
275 Nimmerjahn, 2012 and Hamel et al., 2015).

276

277 PET

278 Closer to methods applied in human neuroscience are other neuroimaging methods used in animal  
279 research, such as magnetic resonance imaging (MRI) and positron emission tomography (PET). While  
280 MRI can only be used in a stationary fashion, PET can be used in moving animals. A further advantage  
281 of PET is that it not only images metabolic activity, but also receptor occupancy and the activity of  
282 transporters and enzymes in the brain. The basic idea of PET is that a radioactive tracer coupled to a  
283 biologically active molecule (e.g. fludeoxyglucose) is injected into the subject. This molecule will be  
284 taken up by tissue, dependent on the metabolic activity. The uptake of the molecules will increase the  
285 concentration of the positron-emitting radionuclide (tracer). The PET scanner detects pairs of gamma  
286 rays emitted by the positron-emitting tracer. The assumption is that brain activity leads to locally  
287 increased metabolic activity in the active brain area, thereby leading to a measurable increase in  
288 radioactivity. The tracers can also be incorporated into molecules that bind to specific receptors.  
289 Historically, there has been an emphasis on dopamine transmission; now tracers for subtypes of  
290 serotonin, cannabinoid, and metabotropic glutamate receptors and others exist (for review see Virdee  
291 et al., 2012).

292 An early successful attempt to use PET on moving animals involved the use of small PET scanners along  
293 with fast optical tracking techniques. While the rodent is confined within a tube, information from the  
294 tracking device is used for motion correction (Weisenberger et al., 2005). This approach is now feasible  
295 in animals free to roam within a small space by keeping the rat's head within the PET field of view via  
296 a robot-controlled motion adaptive animal chamber (Zhou et al., 2013). While this approach will  
297 always limit the area the animal is allowed to stride across, another approach involves a miniaturized  
298 PET detector ring (RatCAP) which is surgically attached around a rat's head in a rigid manner (Schulz  
299 et al., 2011; Vaska et al., 2004). This pioneering approach eliminates the relative motion between the  
300 detector ring and the animal's head, offering motion-free functional brain images of a relatively

301 unrestrained animal. The development of a wearable PET scanner for humans is a very exciting  
302 prospect (Bauer et al., 2016).

303

#### 304 (F)NIRS

305 Near infrared spectroscopy (NIRS) is an increasingly popular technology for studying brain function.  
306 Like MRI, it provides measures of metabolic activity, however, a NIRS set-up is portable. Metabolic  
307 activity is measured through concentration changes in both oxygenated- and deoxygenated  
308 hemoglobin. For red and near-infrared light, oxyhemoglobin (HbO<sub>2</sub>) and deoxyhemoglobin (HbR) are  
309 the most significant absorbers in blood or tissue. Using red and near-infrared light from light-emitting  
310 diodes to penetrate through the brain to monitor their variation of relative optical transparency, the  
311 relative concentration changes of HbO<sub>2</sub> and HbR in relation to cerebral blood flow and oxygen  
312 metabolism can be calculated and transferred into current or voltage by photodiodes. This signal then  
313 has to be transmitted for storage and further analysis. In a wireless near-infrared spectroscopy system  
314 for rats, the signal acquisition module can drive the red and infrared light sources and acquire signals  
315 obtained from the photodiodes (Kuo et al., 2013). Such a setup could be used in freely moving small  
316 animals. A miniaturized wireless NIRS sensor has been successfully applied in freely moving sheep to  
317 investigate mood-modulated cerebral responses to a positive emotional stimulus (Muehlemann et al.,  
318 2011). Results from these animal studies could potentially be directly compared to (f)NIRS studies  
319 carried out in humans (Plichta et al., 2006).

320

321

#### 322 **Challenges for controlling the sensory input during free movement**

323 Recording during free movement does not only pose challenges to keeping the recording equipment  
324 stable. When studying the sensory systems in moving animals the sensory input cannot be precisely  
325 controlled anymore. Concerning vision, there have been two ways of dealing with this problem. The  
326 first one is to record all visual input the animal receives while freely moving about, by mounting a  
327 small, lightweight camera on the head. This has been done in cats freely exploring natural  
328 environments (Betsch et al., 2004). Equally important to this endeavor is a reliable system for tracking  
329 the gaze of both eyes. An ocular-videography system has recently been developed that uses two  
330 lightweight head-mounted cameras for recording the movement of both eyes in rats (Wallace et al.,  
331 2013). To our knowledge, neither filming the animal's visual input nor tracking its eye movements has  
332 been combined with concurrent neural recordings yet; this remains one of the big challenges for  
333 research in freely moving animals.

334 Another way to deal with this problem is to put the animal on a spherical treadmill, commonly made  
335 from a Styrofoam ball (Fig 3A). This allows for fixating the head of the animal, while the animal can  
336 move the rest of its body. Originally developed in insect research (Dahmen, 1980), this approach has  
337 been very successfully adapted for rodent research (Dombeck et al., 2007). In such a set-up, visual  
338 input can be controlled precisely by a virtual reality system (provided that gaze direction is known),  
339 consisting of either several monitors (Saleem et al., 2013), or a spherical dome (Harvey et al., 2009;  
340 Schmidt-Hieber and Häusser, 2013) around the animal on which the virtual environment is projected  
341 (Fig 3B). This allows for the rat or mouse to explore the virtual space and solve tasks (Hölscher et al.,  
342 2005; Thurley and Ayaz, 2016). Recently, an actual maze floating in the air has been developed through  
343 which head-fixed rodents can run (Nashaat et al., 2016). Virtual reality has also been used for testing  
344 behavior in fruit flies freely flying in a wind tunnel (Fry et al., 2008), and in monkeys, treadmills have  
345 recently been applied successfully to investigate primary motor cortex activity while the animal is  
346 walking (Foster et al., 2014). While until recently, such set-ups were not available for humans, the fast



347 development of virtual reality in combination with natural body movements for the gaming  
348 community, opens up new possibilities and can inspire exciting experiments.  
349 Do restrained movements in virtual reality sufficiently mimic free movement? Experiments in which  
350 rodents explore virtual spaces suggest they do, since these uncover the same underlying neural  
351 circuitry as that involved in navigation through an actual space (Dombeck et al., 2007; Domnisoru et  
352 al., 2013; Schmidt-Hieber and Häusser, 2013). However, one study has directly compared virtual  
353 reality (which provides only visual cues about the environment) with real world environments and  
354 found that the real world activates this neural circuitry much stronger than the virtual reality. This  
355 suggests that animals usually also rely on sensory input other than vision for navigation (Ravassard et  
356 al., 2013). In addition, restraining an animal is typically not the ideal method for studying issues  
357 relating to spatial navigation: head-fixed walking rodents tend to rotate excessively (Dombeck et al.,  
358 2009), something which can be partly overcome by training the animals. Also, virtual reality is typically  
359 applied as a ‘closed-loop system’; a system where the locomotion of the animal is used as feedback  
360 to update the sensory input coming from the virtual environment. The interaction between the animal  
361 and the environment must be parametric; that is, movements of the animal must map onto changes  
362 in some parameter space, which in turn correspond to updates of the virtual world. These parameters  
363 must be ‘tuned’, such that the animal’s movements result in virtual reality updates of a certain  
364 expected magnitude. While certain feedback loops are maintained during virtual reality experiments,  
365 several others are broken; for example, head restraint can disrupt the elaborate control systems that  
366 animals possess to regulate the position of the head and eyes (Zeil et al., 2008). Lastly, certain  
367 behaviors, such as complex social interaction, may prove to be nearly impossible to study using virtual  
368 reality (but see Kohatsu et al., 2011), and therefore studying the neural circuitry underlying these  
369 behaviors will require recordings in freely roaming animals. That said, virtual reality can also  
370 significantly enhance real world set-ups, for instance with the possibility of providing conflicting  
371 sensory information to the brain (Chen et al., 2013; Kautzky and Thurley, 2016; Saleem et al., 2013).  
372 In general, we can conclude that while studying moving animals, the sensory input cannot be precisely  
373 controlled. Although significant steps have been made towards this in the visual domain, other sensory  
374 input is not being controlled, let alone sufficiently monitored.

375

376

## 377 **Experimental questions**

### 378 **Movement as an intentional action**

379

380 Moving animals execute motor behavior; their muscles contract and relax in an organized fashion, as  
381 a result of which the animal moves. This can happen stereotypically, such as in reflex or in cases where  
382 a sensory input leads to a highly predefined motor output due to overtrained response behavior (e.g.  
383 button presses or saccades to a target). Free movement, however, is much more than this. Freely  
384 moving animals not only passively react to incoming information from the surround but also act on  
385 this information in an active, flexible manner. Therefore, free movement implies *intentional action*;  
386 flexibly based on incoming sensory input, the animal decides what movement to make, when to make  
387 it, and whether to move at all (Brass and Haggard, 2008). This means a freely moving animal has the  
388 freedom to choose. Just to what extent the possibility to freely move is an integral part of a general  
389 intention to execute actions is nicely illustrated by the necessity of free movement for behaviors  
390 seemingly unrelated to the movement, such as vocalization in songbirds (Long et al., 2010) and  
391 marmosets (Roy and Wang, 2012). When restrained in their free movement, animals will simply not  
392 display these behaviors albeit the motor act of vocalizing would be perfectly possible. The dependence  
393 of such behaviors on free movement underscores the importance of movement in the animal’s  
394 general intention to interact with its environment.

395 A fundamental form of free movement is walking, which results in a change in spatial location.  
396 Intentionally moving through space is called *spatial navigation*, and it implies that the animal  
397 possesses a mental representation of the space it moves through. Immediately upon moving, the  
398 impact of this movement on the surroundings is evaluated by the senses, assessing if the new sensory  
399 input should lead to another intention to move. This can include taking in more or more specific  
400 sensory input. This process is referred to as *active sensing*, a behavior permanently observed in freely  
401 moving animals. The intentional nature of free movement extends to the final stages of movement  
402 production; even the output signal from the motor cortex is heavily dependent on the intention of the  
403 animal on how to execute the movement, in a process called *motor planning*.

404 In this section, we will look at some basic cognitive processes that can only be observed and studied  
405 during free movement. We will focus on spatial navigation, active sensing, and motor planning, but  
406 there are many more. We will highlight how crucial free movement is when studying these cognitive  
407 processes in animals, and briefly emphasize the potential of this research for answering important  
408 questions about the human brain.

409

#### 410 Spatial navigation

411 Successfully moving through a space is something we do effortlessly all the time, yet in fact it is the  
412 final outcome of a complex chain of computations performed by our brains. Let's take a look at the  
413 major cognitive processes involved. Importantly, the brain has to keep track of any changes in spatial  
414 location. Information about the position of the animal in the spatial surrounding comes from the  
415 sensory input of the environment. When we move, this sensory input changes and will provide  
416 information about where we move to. However, the sensory input on the retina caused by moving  
417 objects in our immediate surroundings can be indistinguishable from the sensory input when we move  
418 about. The brain therefore needs a way to discriminate between *self-motion* and motion of the  
419 surround (Fig 4A). This is thought to be achieved by the use of an efference copy or collorary discharge;  
420 a prediction about the sensory consequences of self-motion which can be subtracted from the actual  
421 sensory input (Crapse and Sommer, 2008). The so identified self-produced changes in sensory input  
422 can then be used to calculate one's own movement through the environment.

423 The animal can integrate the information on self-motion and external cues from the environment to  
424 compute its own position and change in location, i.e. to know the path it has travelled. This process is  
425 called *path integration* (Fig 4B; Barlow, 1964; Etienne and Jeffery, 2004). The information about the  
426 spatial environment given by one's own position and the path travelled can now be used to construct  
427 a *spatial map* of the surroundings. If this process was successful, the environment has become familiar  
428 to the animal. Now, the spatial map can be used flexibly to reach certain locations without the  
429 necessity to retrace a previously taken path.

430 Animal research has been instrumental in unravelling the neural mechanisms behind these cognitive  
431 processes. A major step towards understanding these processes started with recordings from the  
432 hippocampus of freely moving rats in 1971, which revealed cells firing only when the rat was at a  
433 particular place in the testing environment (O'Keefe and Dostrovsky, 1971). These cells have been  
434 termed *place cells*, and they are the neural substrate of a spatial map of the environment (Fig 4C).  
435 Each neuron of the hippocampal cell population fires at a different location, such that the entire spatial  
436 surroundings of the rat are represented (Wilson et al., 1994). What gives rise to this spatial map in the  
437 hippocampus? The input into the hippocampus is given by the medial entorhinal cortex (MEC) (Fig 4C).  
438 MEC neurons that project to the hippocampus also exhibit sharply tuned spatial firing, much like place  
439 cells in the hippocampus. However, in the MEC each cell has multiple firing fields, meaning it fires at  
440 multiple places in the rat's spatial environment (Fyhn et al., 2004). These firing fields are not random,  
441 but neatly arranged in a grid-like pattern (Fig 4C) which led to the name *grid cells*. They provide the  
442 basic elements of a system for spatial navigation (Hafting et al., 2005), possibly by linearly combining

443 their multiple receptive fields to generate single receptive fields for place cells (O'Keefe and Burgess,  
444 2005, McNaughton et al., 2006).

445 If place and grid cells are used by the animal as a spatial map, how do these cells construct this spatial  
446 map based on the changing position of the animal during movement, i.e. how is information about  
447 path integration stored? A key role seems to be reserved for a network of cells in presubiculum and  
448 anterior thalamus called *head-direction cells* (Fig 4C; Taube, 1998). These neurons encode information  
449 about the animal's directional heading, independently from visual cues; they even provide information  
450 about the movement direction in complete darkness (Chen et al., 1994). They are also directly  
451 connected to the MEC, and it is thought that in this way, they update the angle of the grid-like pattern  
452 stored in the grid cell population with respect to the head of the animal. Another important structure  
453 for path integration seems to be the parietal cortex. Rats and humans with parietal cortex lesions fail  
454 to acquire spatial tasks and remember positional relationships (Kolb et al., 1983, Takahashi et al.,  
455 2012).

456 It thus seems that a network of place, grid, and head-direction cells is key to maintaining and updating  
457 the spatial map of the animal. Sensory areas, mainly the vestibular and visual system, feed into this  
458 network to provide the necessary information from the direct environment. Studies in macaque have  
459 pointed to the medial superior temporal area (MST) and the ventral intraparietal area (VIP) as key  
460 areas for the calculation of self-motion (Britten, 2008). Both areas are part of the motion system and  
461 their neurons possess complex receptive fields: in MST, the receptive fields contain a vestibular  
462 component, whereas VIP neurons possess somatosensory receptive fields that correspond to the  
463 visual receptive fields. For example, a VIP neuron with a foveal receptive field might have a  
464 somatosensory receptive field on the nose or the mouth, whereas a neuron with a more peripheral  
465 visual receptive field might have a somatosensory receptive field on the shoulder or arm (Duhamel et  
466 al., 1997).

467 Intriguingly, recent studies have also implicated a role for primary visual cortex in navigation. Neurons  
468 in V1 in the mouse integrate information on optic flow as well as self-motion, indicating that V1  
469 participates in a multimodal processing system that integrates visual motion and locomotion during  
470 navigation (Saleem et al., 2013). When there is a mismatch between the calculated motion signals in  
471 V1 and the visual feedback the mouse receives, certain neurons in V1 are activated (Keller et al., 2012).  
472 These mismatch neurons signal local deviations of actual visual flow from visual flow predicted based  
473 on self-motion. They could therefore underlie the detection of objects moving relative to the visual  
474 flow caused by self-motion (Zmarz and Keller, 2016).

475 Most of the work on spatial navigation has been done in rodents, although place cells have also been  
476 described in monkeys (Ludvig et al., 2004). Evidence for place and grid cells in the human brain has  
477 obviously been sparse. Recordings in epilepsy patients with implanted electrodes in the hippocampal  
478 formation have revealed both place cells (Ekstrom et al., 2003) and grid cells (Jacobs et al., 2013).  
479 Importantly, these cells were found while the patients were engaged in a virtual motion task and not  
480 actually moving about. Spatial navigation in humans has indeed been studied mainly in immobile  
481 volunteers engaged in virtual reality settings (Rodriguez, 2010; Doeller et al., 2010). If the presence of  
482 place and grid cells in animals actually moving about can be taken as a 'gold standard' for spatial  
483 navigation, then the evidence of such cells in humans immersed in virtual reality suggests that virtual  
484 motion systems are a good proxy of an actual brain during movement. However, as discussed above,  
485 virtual reality cannot mimic all relevant aspect of free movement, and to what extent sensory input  
486 other than visual input plays a role cannot be assessed to date. Additionally, having humans actually  
487 navigate in a real environment while measuring their brain activity would add to our current  
488 knowledge on spatial navigation, the understanding of complex ongoing cognitive computations that  
489 cannot be easily tested in the animal.

490

491 Active sensing

492 When moving about the environment, an animal is not only engaged in spatial navigation but also  
493 selectively samples and processes the external world. This is called active sensing, behavior greatly  
494 dependent on the animal's freedom to roam about. Active sensing strategies have been described for  
495 audition (Kondo et al., 2012) and vestibular sampling (Carriot et al., 2017) as well as for vision,  
496 olfaction, and tactile input (as will be discussed below).

497 Rodents deliberately touch the objects surrounding them with their whiskers to build up an internal  
498 representation of their environment. Many tasks rely on this active behavior. Gap-crossing is a skill for  
499 which free movement of the whiskers is essential: the animal perches at the end of a raised platform  
500 and uses its whiskers to localize a second platform before crossing the gap to retrieve a reward. The  
501 initial stages in the brain for active sensing are well-known: all whiskers are arranged in a certain  
502 topographical order on the snout, which translates into a fixed topographical order in a part of the  
503 brain called barrel cortex. Neurons in barrel cortex fall into three classes: 'whisking cells', which fire  
504 during whisking per se, 'touch cells', which fire upon contact with an object, and 'whisking/touch cells',  
505 which fire during both types of event (Szwed et al., 2003). These neurons work together to use either  
506 their firing rate or precise spike timing to encode an object's position relative to the rodent's head  
507 (Diamond et al., 2008). Apart from object localization, active sensing is also used for object  
508 identification. Research in this respect has focused mainly on texture discrimination, which happens  
509 by the same barrel cortex neurons during the late part of their response (Von Heimendahl et al., 2007).  
510 Also humans use an active strategy to touch objects for texture discrimination or to assess other  
511 physical features. Actually, if humans and rats are given an object localization task using vibrissae (rats)  
512 or plastic rods attached to the fingertips (humans), both species apply active sensing processes in a  
513 similar manner (Horev et al., 2011).

514 Another form of active sensing is observed in olfaction. Sniffing is closely related to respiration and  
515 therefore is an ongoing process. However, strong modulations are observed dependent on the  
516 movement state of the animal. While sniffing behavior is highly variable and dynamic, active rodents  
517 spend the majority of time sniffing at frequencies above 4 Hz while passive rats mostly stay below a 2  
518 Hz sniffing frequency (Wachowiak, 2011). The frequency of sniffing is thought to be modulated in  
519 order to acquire the stimulus more quickly rather than to directly influence the low-level neural  
520 processes underlying odor perception (Wesson et al., 2009). A compelling example of context-specific  
521 sampling strategies is found in hunting dogs. While they sniff at up to 4 – 6 Hz when tracking the scent  
522 of prey on the ground, dogs will stop sniffing and run forward when tracking the same scent in the air,  
523 forcing a continuous stream of air into the nose for up to 40 sec (Steen et al., 1996). Also humans will  
524 change their sniffing pattern in response to sensory input (Johnson et al., 2003); how such a pattern  
525 is affected by ongoing movement like walking is not known.

526 Saccadic eye movements is a well-studied field in human research. These eye movements follow an  
527 active sensing strategy to maximize relevant information input per fixation in humans (Yang et al.,  
528 2016). Whether such strategies follow the same optimization process throughout different body  
529 states is not known. Studies from animal research advocate carefully investigating eye movement  
530 strategies during free movements; the movements of the eyes in head-restrained rats are conjugate  
531 and infrequent, whereas in freely moving animals, both eyes are highly mobile and eye movements  
532 are asymmetrical, keeping the animal's binocular visual field above it. This behavior seems indicative  
533 of a strategy to detect predators coming from above during movement (Wallace et al., 2013). The  
534 same study highlights another interesting point by showing that these eyes movements are specific  
535 to free movement; head-restrained rats, even when running on a spherical treadmill, do not exhibit  
536 these eye movement patterns.

537

538 Motor planning

539 Free movement requires the animal not only to decide *when* and *whether* to move, but also *how* the  
540 movement should be executed (Brass and Haggard, 2008). This latter process is known as motor

541 planning (Gnadt and Andersen, 1988; Sanes and Donoghue, 1993). Traditionally, motor planning has  
542 been studied in the context of reaching and grasping, in seated, immobile humans or primates  
543 (Castiello, 2005). Such a set-up has made it possible to test hypotheses about the motor system with  
544 a great deal of control and precision. However, it limits investigations to a small subset of the full  
545 capability of the motor system.

546 Recordings in motor cortex during unconstrained arm movement show great diversity in neural  
547 responses (Aflalo and Graziano, 2007). Existing models, developed with constrained behavioral task  
548 data, were not able to capture the neural variability in these free movement data. This result exposes  
549 a weakness in the prevailing course of study: the limits of conventional task design can lead to  
550 impoverished models of the neural underpinnings of motor planning (or any other cognitive process).  
551 Wireless recordings in the motor system of primates allow the study of not only free arm movement,  
552 but free movement of the entire body, including jumping and running. It also opens up the possibility  
553 of continuous recording for days instead of hours, thus capturing an almost unlimited range of free  
554 movements and behaviors. Due to these developments, a new class of experiments can emerge.  
555 Instead of primates repeating the same constrained movement thousands of trials, long and complex  
556 datasets of free behavior can be used for data mining to answer experimental questions (Gilja et al.,  
557 2010). This requires experimenters to move away from multiple trial averaging and embrace single  
558 'trial' analysis, for which sophisticated analysis techniques have been developed in recent years  
559 (Brown et al., 2005; Yu et al., 2009).

560 One example of motor planning behavior of which our understanding can benefit greatly from such  
561 free movement recordings, is reaching and grasping in near and far space. Decades of research in  
562 movement constrained primates using a so-called memory-guided reach task have shown a network  
563 of areas, including the primary motor cortex, dorsal premotor cortex, and posterior parietal cortex, to  
564 be involved in planning a reach and grasp movement in near space (Mushiakhe et al., 1991; Murata et  
565 al., 1996). However, premotor cortex neurons activated by both the execution as well as the  
566 observation of movements (so-called mirror neurons) fire differentially depending on whether the  
567 movement happens in near (within arm's reach) or far (beyond arm's reach) space (Caggiano et al.,  
568 2009). Moreover, a subset of these neurons changes their activity according to the possibility that the  
569 monkey will interact with the object. Additionally, human patients with brain lesions in these areas  
570 can have neglect either in near or in far space (Halligan and Marshall, 1991; Vuilleumier et al., 1998).  
571 Recent work in humans on the hand-blink reflex (a blink elicited by stimulating the nerve at the wrist)  
572 showed that the motor system acts predictively on the transition from near to far space and vice versa:  
573 the hand-blink reflex was present only when the hand approached (and not receded from) the face  
574 (Bisio et al., 2017). These results suggest that a reaching movement towards an object in far space  
575 might be planned differently by these areas than a reaching movement towards an object in near  
576 space, a hypothesis which is currently being tested with wireless recordings from freely moving  
577 monkeys performing goal-directed reaching tasks (M Berger and A Gail, personal communication).

578 An important goal in recording and analyzing motor activity from freely moving primates is the  
579 construction and improvement of brain-machine interfaces (BMIs). The idea is simple: the translation  
580 of the cortical activity from the motor network into muscle movements is being used to control  
581 artificial limbs. Huge progress has been made in recent years in decoding complex motor activity  
582 patterns, and it is now possible to have monkeys navigate a wheelchair (Rajangam, 2016) and walk  
583 freely after a spinal cord injury (Capogrosso et al., 2016) using their brain activity. These studies are  
584 directly aimed at restoring mobility to severely paralyzed patients, and as such, human research could  
585 learn an incredible lot from these studies in primates.

586

587 **Movement as an active state**

588 Considering free movement within the framework of intentional action highlights the importance of  
589 free movement in a host of cognitive processes. However, movement, as compared to the absence of  
590 movement, can also be regarded as the expression of a bodily state accompanied by an underlying  
591 brain state. The brain perpetually transitions through a continuum of more or less active states, ranging  
592 from deep sleep through the various sleep stages, to the various awake states such as drowsiness,  
593 passively alert, and highly awake. Also included in this spectrum are certain non-natural brain states  
594 such as anesthesia and the vegetative state. The top of this scale, a state in which the animal or human  
595 is highly alert and active, often involves movement in the form of walking or running. The relationship  
596 is bidirectional; free movement can influence the animal's brain state and vice versa.

597 The view that the brains of animals moving about are in a behaviorally active state has a long history:  
598 studies in freely moving cats in the 1980s focused on subcortical nuclei such as the locus coeruleus,  
599 and their role in various arousal states (Rasmussen et al., 1986; Abercrombie and Jacobs, 1987). These  
600 studies found the activity of noradrenergic neurons in the locus coeruleus to be highly dependent on  
601 the behavioral state of the cats, with activity increasing as the cats transitioned from REM sleep to  
602 slow wave sleep to quiet waking to active waking (Rasmussen et al., 1986). These neurons were most  
603 active, however, with the application of a stressor such as visual threats, forced treadmill running  
604 (Rasmussen et al., 1986) or loud noise (Abercrombie and Jacobs, 1987). These studies suggest a  
605 general role for the locus coeruleus in the brain's response to stress.

606 The relationship between movement and brain state has been frequently investigated using spherical  
607 treadmills in combination with virtual reality (Fig 3B). Mice running on a spherical treadmill typically  
608 show increases in firing rate and local field potential power in the gamma frequency range, both in  
609 primary visual cortex (V1; Niell and Stryker, 2010) as well as in cerebellar granule cells and  
610 interneurons (Ozden et al., 2012). The pronounced firing rate increases in the visual cortex, without  
611 changes in spontaneous firing or stimulus selectivity, suggest a change in gain of these neurons. This  
612 is in line with the finding that locomotion reduces surround suppression in primary visual cortex,  
613 allowing V1 neurons to integrate over larger regions of visual space (Ayaz et al., 2013). V1  
614 interneurons, as well as neurons in the lateral geniculate nucleus (LGN), do not increase their firing  
615 with locomotion (Niell and Stryker, 2010), although recent results do report increased firing rates  
616 already in the LGN (Erisken et al., 2014). These changes in visual cortex activity are transient, but  
617 locomotion can also have long-term effects on the cortex, as recent findings on sensory deprivation  
618 and cortical plasticity show. Recovery from sensory deprivation is slow and incomplete in adult visual  
619 cortex. Visual stimulation during locomotion dramatically enhances recovery in the mouse (Kaneko  
620 and Stryker, 2014) as well as induces a rapid and persistent increase in cortical responses (Kaneko et  
621 al., 2017). Both effects are specific to the particular visual stimuli viewed by the animal during  
622 locomotion.

623 How do these changes in neuronal activity with locomotion come about? Whole-cell recordings in V1  
624 during locomotion showed decreases in membrane potential variability and an enhancement in the  
625 amplitude of visually evoked sub-threshold responses, which led to an improved signal-to-noise ratio  
626 and performance in a visual detection task during running (Bennett et al., 2013; Polack et al., 2013).  
627 These changes in membrane potential could be induced by nicotinic (Fu et al., 2014) and  
628 noradrenergic (Polack et al., 2013) inputs from the basal forebrain to vasoactive intestinal peptide  
629 (VIP)-positive neurons in mouse V1 during locomotion. Another key structure in the initiation of  
630 running is the mesencephalic locomotor region (MLR). Stimulation of the MLR in awake, head-fixed  
631 mice can induce both locomotion and increases in the gain of cortical responses (Lee et al., 2014). MLR  
632 stimulation below the threshold for overt movement similarly changed cortical processing, revealing  
633 that MLR's effects on cortex are dissociable from locomotion. This result agrees with recent findings  
634 on the effects of arousal and locomotion on activity in mouse V1. Arousal (as measured by pupil  
635 dilation) suppressed spontaneous firing, increased the signal-to-noise ratio of visual responses, and

636 reduced noise correlations. In contrast, increased firing in anticipation of and during movement was  
637 attributable to locomotion effects (Vinck et al., 2015). These findings suggest complementary roles of  
638 arousal and locomotion.

639 How important it is to consider this active state when interpreting measures of neuronal activity is  
640 shown by studies on cerebral blood volume and neural activity in the somatosensory and frontal  
641 cortex of head-fixed mice during locomotion (Fig 5A). In the frontal cortex, cerebral blood volume did  
642 not change during locomotion (Fig 5C), but firing rate and gamma-band power both increased (Fig 5B),  
643 indicating a decoupling of neural activity from the hemodynamic signal (Huo et al., 2015). These  
644 changes were resistant to pharmacological manipulations of heart rate, suggesting they arise from  
645 central processes (Huo et al., 2015). These results show that hemodynamic signals are not faithful  
646 indicators of the mean neural activity in the frontal cortex during locomotion. As mobile PET imaging  
647 becomes available for use in human subjects and NIRS is applied more frequently, researchers should  
648 be aware of this strong dependence of the hemodynamic signal on the behavioral state.

649

## 650 **Conclusion**

651 In conclusion, free movement can affect a surprising number of cognitive functions, which on first  
652 sight seem to be independent of large body movements. Besides the obvious necessity of motion for  
653 investigating motor activity, these other cognitive functions need to be considered also in human  
654 experimentation. We have shown that animal research that has been done in the fields of spatial  
655 navigation, motor planning and active sensing can directly help to understand these cognitive domains  
656 in humans. While the investigation of cognitive processes during free movement is intensified, more  
657 processes might be discovered that are significantly interlinked with free movement. Moreover, it is  
658 important to consider that the effect of movement reaches beyond specialized domains, impacting  
659 brain function in general, as we can think of moving as the top end of a continuum of arousal states.  
660 This urges us to take the behavioral state of our subject into account every time we interpret measures  
661 of neuronal activity. Also this is a highly important consideration for human research.

662 As the development of portable EEG, ECoG and PET devices for humans advances, the more  
663 comparable and therefore the more important the results from work on freely moving animals will  
664 become. The same holds for increased possibilities to measure single cell activity in humans.

665 We are optimistic that these technical advancements, in combination with the right scientific  
666 questions, will start to reveal a much more realistic and complete picture of brain function when  
667 considering free movement compared to what we have held until now. Human research in this field  
668 can profit greatly from ongoing animal research.

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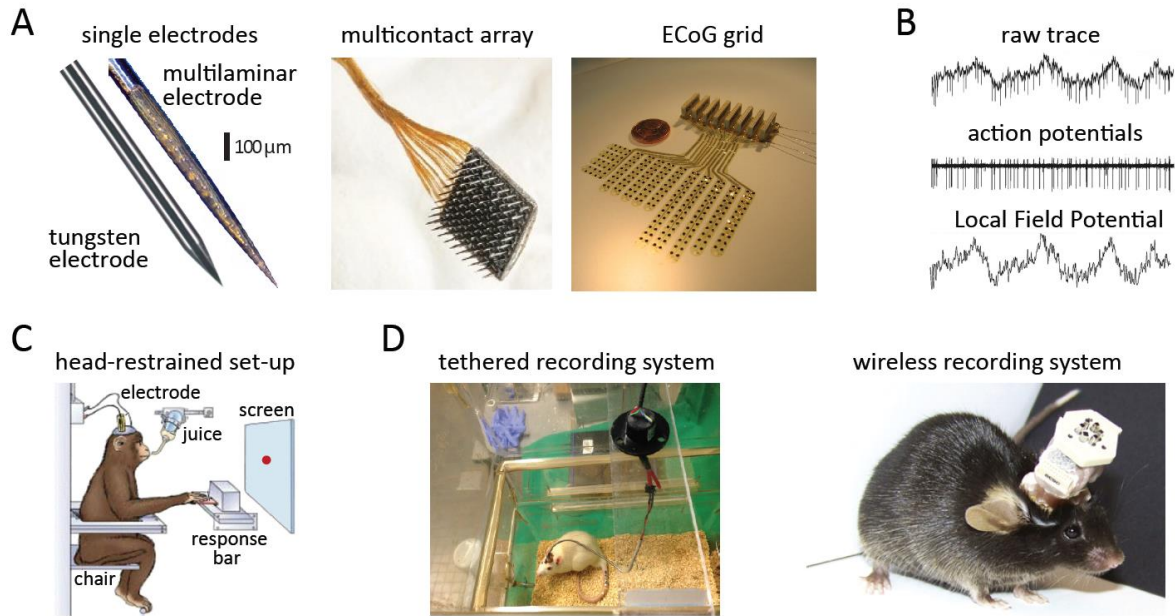
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678 **Figure and Figure Legends**

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**Figure 1**

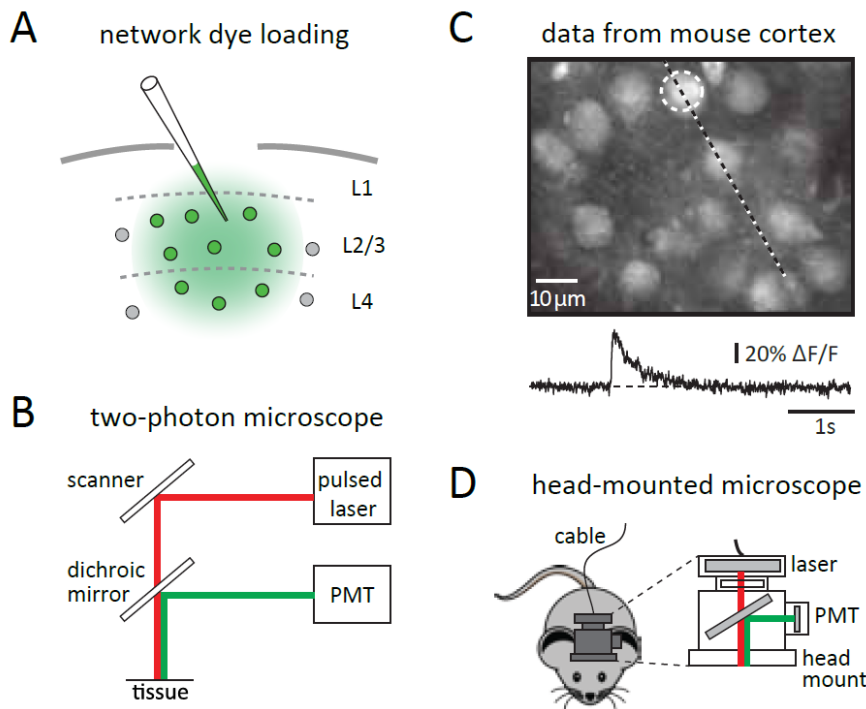


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**Figure 1.** Electrophysiology. (A) Four examples of electrodes commonly used in animal electrophysiology. Tungsten and multilaminar electrodes, as well as multicontact arrays, are used for recording single unit or multi-unit activity; ECoG grids record local field potentials. Tungsten electrodes record activity from a local cell population; multilaminar electrodes can record activity across the cortical column; multicontact arrays can record activity from part of a cortical area; ECoG grids can record activity across multiple brain areas. *Adapted with permission from Plexon Recording, Blackrock Microsystems, and Birthe Rubehn. The multilaminar electrode depicted is known as a V-probe and is manufactured by NeuronElektrod and exclusively distributed by Plexon; the multicontact array depicted is known as a Utah Array.* (B) Raw activity trace recorded with an electrode (top), which can then be high-pass filtered to obtain the action potentials (middle) or low-pass filtered to obtain the local field potential (bottom). (C) Monkey in a head-restrained recording set-up. (D) Tethered (left) and wireless (right) recording systems in rodents. *Adapted with permission from (Fluri et al., 2015) (left) and (Battaglia et al., 2009) (right).*

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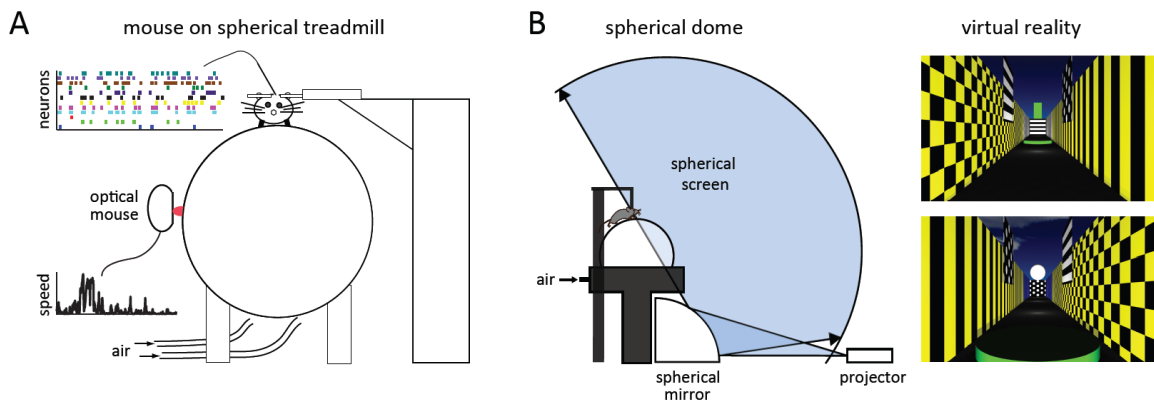


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709 **Figure 2.** Calcium imaging. (A) First, the neural tissue is exposed to calcium-sensitive fluorescent  
 710 indicators, in this example by ‘acute’ network loading: injection of a chemical dye. (B) Once the tissue  
 711 has incorporated the calcium indicators, it can be imaged, for example by a two-photon microscope.  
 712 A pulsed laser emits photons, which are steered towards the tissue by a scanner. Excitation light and  
 713 much weaker emission light from the tissue are separated by a dichroic mirror. The emitted  
 714 fluorescence is then detected by a photo-multiplier tube (PMT), which transforms it into an electrical  
 715 signal. (C) Example image data from the mouse cortex obtained with two-photon microscopy. Looking  
 716 at the activity in a single neuron (white circle) across time shows the calcium transient (bottom trace).  
 717 The peak in the trace is caused by sensory stimulation. (D) In some head-mounted microscopes, all  
 718 components are packed together into a compact microscope worn on the head. *Adapted with*  
 719 *permission from (Grienberger and Konnerth, 2012) (A-B) (Stosiek et al., 2003) (C) and Mightex Systems*  
 720 *(D; <http://www.mightexsystems.com/applications/WP002112816.html>).*

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729 **Figure 3**

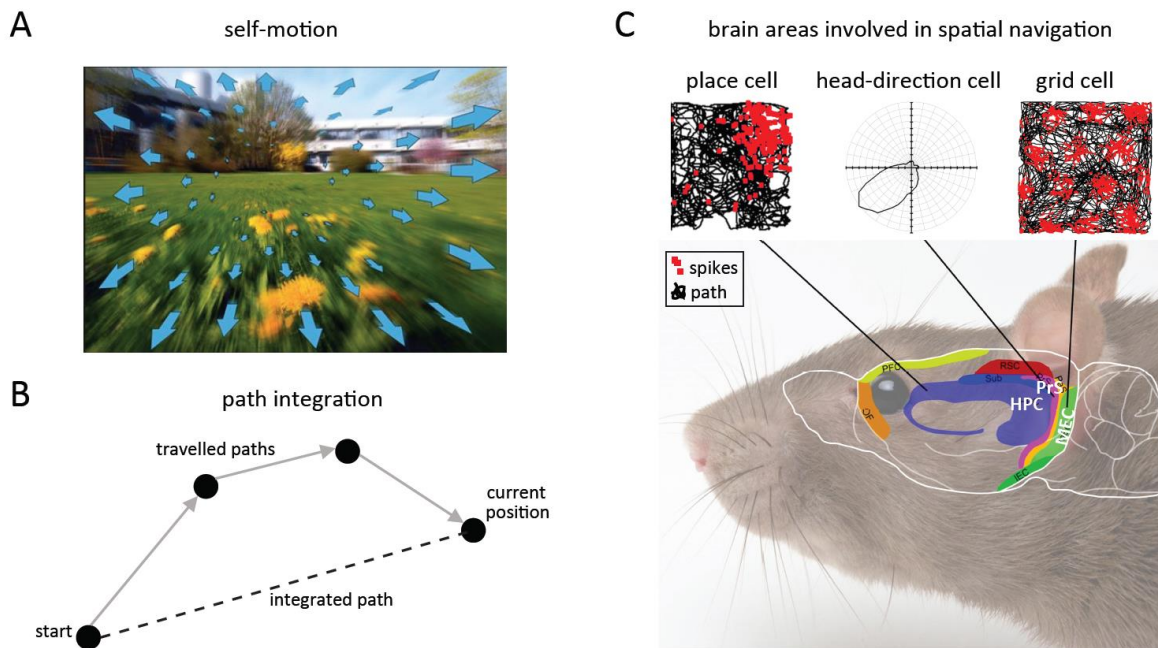


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731 **Figure 3.** Head-fixed yet mobile mice. (A) Set-up with spherical treadmill. Air keeps a Styrofoam ball  
 732 afloat, while an optical mouse tracks the movements of the ball. A mouse sits on top of Styrofoam ball  
 733 and can move the ball with its legs, while being recorded from. *Adapted with permission from (Niell*  
 734 *and Stryker, 2010).* (B) Spherical treadmill surrounded by a spherical screen (left) on which a virtual  
 735 environment can be projected (right). *Adapted with permission from (Schmidt-Hieber and Häusser,*  
 736 *2013).*

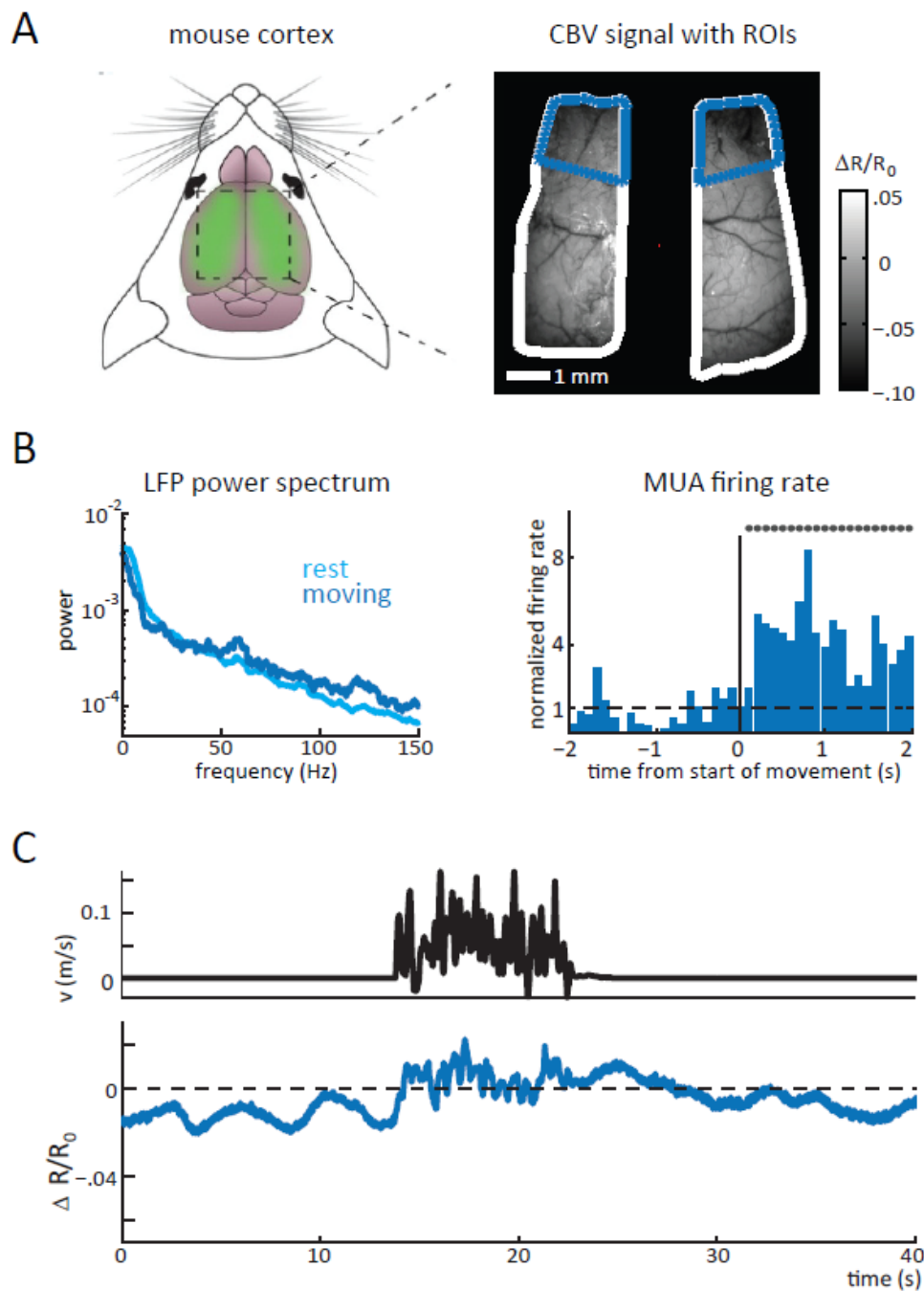
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738 **Figure 4**



739

740 **Figure 4.** Spatial navigation. (A) Self-motion. The arrows indicate the optic flow generated by self-  
 741 motion as one moves towards the trees in the background. (B) Path integration. Once the current  
 742 position is reached, one can use the travelled paths to calculate the integrated path. This integrated  
 743 path provides the direction and distance for a potential return journey. (C) Brain areas involved in  
 744 spatial navigation in rodents. In the hippocampus (HPC), presubiculum (PrS) and medial entorhinal  
 745 cortex (MEC), place cells, head-direction cells, and grid cells are found, respectively. On the top,  
 746 'receptive fields' of a place and a grid cell and a polar plot of a head-direction cell are shown. *Adapted*  
 747 *with permission from (Marozzi and Jeffery, 2012) (top) and (Grieves and Jeffery, 2017) (bottom).*



749

750 **Figure 5.** Measuring hemodynamic and neural activity during an active state (running) and an inactive  
 751 state (sitting still). (A) Window for measuring cerebral blood volume (CBV) in a rat brain, with two  
 752 regions of interest (ROIs) in the frontal cortex. (B) During running, neural activity increased compared  
 753 to sitting still, as evidenced by the power in the local field potential (LFP, left) and multi-unit spiking  
 754 activity (MUA, right). (C) However, the cerebral blood volume trace (bottom) showed no significant  
 755 difference between running and sitting still (c.f. the velocity trace on top). *Adapted with permission*  
 756 *from (Huo et al., 2014).*

757

758

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