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Why have "revolutionary" tools found purchase in memory science?

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Abstract
The study of the neural basis of memory has advanced over the past decade. A key contributor to this memory "renaissance" has been new tools. On its face, this matches what might be described as a neuroscientific revolution stemming from the development of tools, where this revolution is largely independent of theory. In this paper, we challenge this *tool revolution account* by focusing on a problem that arises in applying it to this "renaissance": it is centered around memory, but the tools were not developed for solving problems in memory science. To resolve this problem, we introduce an account that distinguishes tool *development* and tool *uptake*, and we argue that while theoretical considerations may not inform development, they do inform uptake. Acknowledging the distance between these stages of tool use draws our attention to the questions of why and how tool uptake occurs in the domains that it does.

Keywords
Memory · Scientific experiment · Scientific revolutions

1 Introduction

The study of the neural basis of memory has advanced over the past decade. A key contributor to this "renaissance" (Josselyn et al., 2017, p. 4647) has been the use of new tools. Memory researchers note that "the recent introduction of a vast array of powerful new tools to probe and manipulate memory function at the cell and neuronal circuit level has spurred an explosion of interest in studying the engram" (Josselyn et al., 2017, p. 4647), and the incorporation of new tools "into the study of memory has resulted in a tremendous leap in this field, initiating a revolution in our understanding of the networks underlying cognitive processes" (Goshen, 2014, p. 511). On its face, memory science is an exemplar of what Bickle (2016) describes as a "revolution" stemming "directly from the development and justification of a new experiment tool—at least one novel to neuroscience" (p. 2). Unlike

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Kuhnian paradigm shifts, these revolutions exemplify the "relative independence of experiment from theory" (Bickle, 2018, p. 1065).

Bickle's tool revolution account captures an important and under investigated dimension of neuroscientific practice. There is, however, a problem that arises in applying it to the memory "renaissance". First, this renaissance is centered around a particular cognitive capacity: memory. The revolution is focused on the nature of information retention, offering theoretical cohesion that appears antithetical to an independence of experiment from theory. Second, the tools that have driven recent advances in memory were not developed for solving problems in memory science. "Revolutionary" tools like optogenetics and whole-brain imaging tools, or what we call "clarifiers," were designed around distinct motivating problems, mostly in neuropsychiatry. This raises the question: why have these tools proven to be revolutionary in memory science?

In this paper, we argue that the "tool revolution" in memory science is reliant upon neuroscientists' working conceptualizations of memory.[1] For this reason, the selection and use of optogenetics and clarifiers cannot be understood without appeal to theoretical considerations. Making sense of this situation, we argue, requires a distinction between tool development and tool uptake. The latter has received limited analysis in the literature, and the few instances that gesture to uptake (such as Silva, 2021) focus on technical or practical considerations of the tool's dissemination, such as its ease of use. We argue, by contrast, that development and uptake have different motivators. By clarifying these stages of tool revolution, we argue that the memory "renaissance" cannot be explained without considering both tool and theory. Acknowledging the distance between development and uptake draws our attention to the questions of why uptake occurs in the domains that it does. In so doing, our aim is to encourage both further refinement of the tool revolution account and the incorporation of more examples of tool use in neuroscience.

In section 2, we review Bickle's tool revolution account in neuroscience. In section 3, we describe the history of two families of tools: optogenetics and clarifiers. We discuss the sense in which these tools are "revolutionary." In section 4, we discuss why these tools were taken up in the study of memory. We highlight two features of how memory is conceptualized: the characterization of memory as encoding, storage, and retrieval, and the synaptic scalability of memory. We argue that these concepts of memory are required for explicating why these tools have been taken up in memory science. In section 5, we discuss three lessons drawn from our examples: (1) tool development and uptake are distinct, (2) while theoretical considerations need not inform development, they can inform uptake, and (3)

[1] A parallel issue can be raised regarding whether Bickle's account really rises to the level of a scientific revolution. In this paper, we focus on the role of theory in these transitions in neuroscience, setting aside whether they are truly revolutionary. We follow Bickle's lead in calling them "revolutionary" but acknowledge the need for further consideration of the criteria for use of this term.

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we must look at tool revolutions in context, which includes but is not limited to analyzing how the uptake of one tool relates to the uptake of others.

2 Tool revolutions

In contrast to the traditional account of scientific revolutions that principally addresses the buildup of anomalies, scientific crisis, and theoretical change via a paradigm shift (Kuhn, 1962), Bickle (2016) argues that revolutions in neuroscience "turn exclusively on the development of new experimental tools" (p. 1). While he does not argue that this is true of all revolutions in neuroscience, Bickle's argument suggests that several bona fide revolutions in neuroscience "depart significantly from Kuhn's model" (p. 12). In so doing, he deemphasizes the role of mechanism discovery in neuroscience's advances (Craver & Darden, 2013), as well as the importance of reductionist commitments that he himself advocated for in earlier work (Bickle, 2003). Bickle's tool revolution account eschews the role of theoretical considerations, and he presents two metascientific concepts intended to replace those available in the Kuhnian program.

The first is the *motivating problem*, or the challenge that researchers must develop or adapt a tool to solve. These problems can be applicable to all neuroscience, such as researchers' need to "intervene into the hypothesized neuronal mechanisms: to activate and inhibit specific neurons" with the development of optogenetics (Bickle, 2018, p. 1068). Alternatively, these problems can be specific to a research context, such as "the experimental demand to block LTP without disrupting other aspects of synaptic function in order to test the alluring LTP → (rodent spatial) learning and memory hypothesis" with the development of gene targeting techniques (Bickle, 2016, p. 4). What motivating problems have in common, Bickle suggests, is that they are "technical" (2016, p. 4) or "engineering" (2018, p. 1073) problems: they reflect desires to perform certain measurements or manipulations rather than theoretical considerations.

Tools are developed to address motivating problems. Establishing their successful use introduces Bickle's second concept: *hook experiments*, which demonstrate the tool's ability to solve the motivating problem. There are two phases of hook experiments. There are initial hook experiments, which "demonstrate successful application of a new tool to professional scientists" (Bickle, 2018, p. 1069). An initial hook experiment is usually performed by or under the supervision of the tool's creators, and "there is usually not much controversy over which experiments constitute a revolutionary new tool's initial 'hooks' " (Bickle, 2016, p. 5). We construe an initial hook experiment as a proof-of-concept study.

A second-phase hook experiment is one that "garners the tool even wider appeal and application" (Bickle, 2016, p. 7). Second-phase experiments go beyond proof of concept, not just highlighting the tool's relevance for the motivating problem, but also demonstrating the tool's ability to solve this problem. These experiments constitute the "widespread dissemination of the tool and its results to a

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wider public, beyond the specialists working in the field that developed it" (Bickle, 2016, p. 7). In contrast to initial hook experiments, Bickle (2016) argues that "identifying the key second-phase hook experiments is more controversial" (p. 11). One way of deciding which experiment counts as a second-phase hook is to look at which experiments have high citation counts, as well as whether they enter the zeitgeist of the "general (scientifically literate) public" (Bickle, 2016, p. 11). From this permeation in the scientific community and beyond, one can argue that the development of a tool constitutes a genuine revolution in neuroscience.

Motivating problems and hook experiments are intended to capture the "relative independence of the development of these revolutionary new experiment tools from theory" (Bickle, 2018, p. 1074). Rather, "revolution here depend[s] first and foremost on tools, new or newly applied," which "are the result of engineering ingenuity and laboratory tinkering" (Bickle, 2018, p. 1076). During these revolutions, "deep theory lags behind" (Bickle, 2018, p. 1076). Thus, this account differs from the traditional Kuhnian view of scientific revolution in terms of the involvement of theory and its role in the revolution. The idea that the buildup of anomalies, perhaps based on the use of a new tool, precedes a paradigm shift is entirely consistent with Kuhn's account, so this idea cannot be what Bickle has in mind if this account is an alternative to Kuhn's. Correspondingly, whether tool development is revolutionary is independent of whether it results in theoretical or conceptual change on Bickle's account. What matters is that a tool solves a motivating problem and that the solution it provides results in its uptake within a neuroscience community, who use it to generate new findings.

What exactly constitutes "deep theory" is not specified on this account. One way to flesh out the idea is to note that a "theory of the technique," or a theory that "represents a technique's capabilities, if the technique is applied to a candidate target system with a specified set of prototypical features" (Colaço, 2018, p. 38), might be necessary in developing a tool. However, a corresponding "theory of the system," or a theory that "represents the target system and its components," (Colaço, 2018, p. 38), is not necessary and not present in exemplars of revolutions in neuroscience that are based on tool development.

3 Two "revolutionary" tools

Many tools are deployed in memory science, now and throughout its history. To illustrate our concerns with tool revolutions in memory science, we focus on two (families of) tools: optogenetics and clarifiers. We highlight the motivating problems that have contributed to their respective developments and the second-phase hook experiments that take place in memory science. Importantly, we show how these motivating problems did not arise from memory science.

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3.1 Optogenetics

Neuroscientists are broadly committed to studying information processing in terms of neural activity. This commitment is in the background of cognitive and systems level research, where patterns of activation are understood as population-level aggregates of neural activity. Researchers working at the cellular level often adhere to the stronger *neuron doctrine*, according to which the neuron is the functional unit of interest. For these adherents, the ability to conduct neuroscience at the cellular level has been limited by the size and fragility of neurons. Developing electrodes capable of recording from single neurons without destroying them was a major achievement of 20th century neurobiology. The ability to intervene, by contrast, remained elusive, but it recently has been achieved with the introduction of optogenetics: neural interventions performed with light, using opsins (light-responsive proteins).

Bickle characterizes the motivating problem for optogenetics in terms of a general interest in intervening into the neural systems of living, behaving organisms at the cellular level, allowing researchers to investigate their role in cognition and action directly. Deisseroth and his co-creators certainly show this general interest, and their discussions of optogenetics show appreciation for the significance of this tool across neuroscience. Their motivations were not, however, only this general interventionist puzzle. For Deisseroth, who is not only a neuroscientist but also a practicing psychiatrist, the ultimate motivating interest is in securing the kinds of interventions that make it possible for researchers to address the causes of mental disorders. In an interview with *The New Yorker*, Deisseroth made his motivations clear:

> A cardiologist can explain a damaged heart muscle to a patient. With depression, you cannot say what it really is. People can give drugs of different kinds, put electrodes in and stimulate different parts of the brain and see changed behavior—but there is no tissue-level understanding. That problem has framed everything. (as quoted in Colapinto, 2015)

The inaugural paper from the Deisseroth lab (Boyden et al., 2005) demonstrated that opsins are genetically encoded and could be targeted at specific neuron types. It was not, however, until two years later that the lab produced the first hook experiment. Adamantidis and colleagues (2007) demonstrated the use of optogenetic intervention to target specific neurons and alter sleep/wake behavior in mice. This paper provided proof of concept: optogenetics could be used to alter behavior.[2]

The second-phase hook experiment for optogenetics, as identified by Bickle, is Liu et al. (2012), followed by Ramirez et al. (2013). These studies show first (Liu

[2] Deisseroth (2015) identifies two 'proof of concept' papers: the Adamantidis paper and Aravanis et al. (2007). Only the former meets Bickle's criteria because of its publication in *Nature*, in comparison to the *Journal of Neural Engineering*.

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et al., 2012) that optogenetics can be used to isolate and activate an engram and, second (Ramirez et al., 2013) that the engram can be manipulated and re-activated. These articles demonstrate that optogenetics can be applied to a particular domain. Specifically, this work couples the optogenetic technique with established methods for identifying engrams in model organisms, demonstrating the ability to activate and then manipulate neural engrams via the light-sensitive opsins with which the engram neurons have now been tagged.

Activating the engram directly is a breakthrough. The impact on engram theory, and memory science more broadly, becomes clearer once this basic technique is coupled with manipulation of other features of remembering. The experiments show how optogenetics allows researchers to effectively place a "light switch" on the engram, making it possible to turn the engram on and off without employing standard retrieval processes.[3]

3.2 Clarifiers

The use of optical and fluorescent microscopy is a precise means of observing anatomical structure. However, the benefits of microscopy have historically been limited by the need to slice tissue into segments that are thin enough for light to penetrate them. This slicing destroys larger structures like neural populations. For this reason, researchers have developed tools that render intact tissue transparent and amenable to microscopy. While there is no collective name for them, we call this family of tools "clarifiers."[4]

One clarifier is 3DISCO, which involves the application of chemicals that fix anatomical structure but also dissolve lipids that scatter light (Ertürk et al., 2012). This chemical cocktail does not interfere with the embedding of fluorescent markers that are used to label anatomical structures. This feature is critical for 3DISCO, as its motivating problem was the desire to observe the structure of "organs under normal and disease states," where anatomical differences cannot be observed in slices (Ertürk et al., 2012, p. 1983). Its later variants iDISCO (Renier et al., 2014) and uDISCO (Ertürk et al., 2016), which tweak the chemical components of 3DISCO and their application, were introduced for similar disease-marking purposes in the brain.

Shortly after the introduction of 3DISCO, CLARITY was introduced by the Deisseroth lab. Like 3DISCO, this tool involves the removal of light-scattering lipids from cellular tissue, so larger pieces of tissue can be observed via microscopy without the need for slicing (Chung et al., 2013). While CLARITY differs from -DISCO in how the tissue is fixed and the light-scattering lipids are removed, CLAR-

[3] From here, as further experiments from the Tonegawa Laboratory demonstrate, researchers can disrupt storage and retrieval processes and observe the influence of these interventions on the engram.

[4] We speculate that there is no collective name because they stem from different groups, each of which wants to have their tool become dominant.

ITY was designed around the resolution of similar problems. Like -DISCO, CLARITY's motivating problem was related to the study of brain disease. This fact is unsurprising, given Deisseroth's psychiatry background.

A third clarifier, SHIELD, was introduced in response to dissatisfaction with previous ones. Park and colleagues (2019) note that "existing methods for spatial mapping of biomolecules in intact tissues suffer from information loss caused by degradation and tissue damage" (p. 73). SHIELD uses different chemical and procedural components than -DISCO and CLARITY to achieve the clarification of tissue (see Park et al., 2019). Its creators claim that SHIELD is a "versatile method that simultaneously preserves key molecular information—protein fluorescence, protein immunoreactivity and nucleic acids—in cleared intact tissues by using a polyfunctional, flexible epoxide" (Park et al., 2019, p. 73).[5]

When clarifiers are taken as a group, their revolutionary status is defensible. -DISCO, CLARITY, and SHIELD have become tools in neuroscience laboratories. In 2016, a brain that had CLARITY applied to it was featured on the cover of *Scientific American*, along with a feature article by Deisseroth. These see-through brains, often depicted in a stunning green due to the use of fluorescent markers, were featured in initial articles on clarifiers (Deisseroth, 2016).

Second-phase hook experiments using clarifiers have occurred as well. Using iDISCO, researchers now aim to label memory traces in intact neuronal structure (Pavlova et al., 2018). Likewise, CLARITY experiments have widened into molecular phenotyping and the study of connectivity in intact brain tissue (Chang et al., 2017). These studies now include the investigation of fear conditioning (Kim et al., 2017) and the relation between dendritic complexity in the hippocampus and enhanced learning in mice (Gradinaru et al., 2018). Some researchers now use iDISCO, CLARITY, or SHIELD to investigate the idea that memory engrams spread out across multiple brain regions (Roy et al., 2022). Together, these studies show that clarifiers have proven their place in productive, cutting-edge research. The move from second-phase hook experiments is captured in a quote about CLARITY:

> Since our 2013 publication of the technique, even this single version of the tissue-hydrogel technique has been adopted for diverse basic science applications and also applied clinically (for example, to postmortem brains of individuals with autism or Alzheimer's), as well as to spinal cords and brains of mice (for example, in discovery of previously unknown pathways for control of fear and anxiety behavior). Many papers from labs around the world have now been published using this general approach to understand the basic structure of the nervous system, often in combination with optogenetics, and to provide fresh ideas for understanding adaptive and maladaptive brain circuitry. (Deisseroth, 2016, p. 35)

[5] SHIELD's creators note that this tool can redress earlier limitations of the use of clarifiers on studying disease tissue, including cancer research (Park et al., 2019).

This increase in use shows the uptake of clarifiers within the scientific community and beyond. While these second-phase hook experiments involve different targets, including the disease targets that initially motivated them, they have proven revolutionary in memory science.

4 How "revolutionary" tools relate to memory

Bickle is not alone in recognizing the significance of tools like optogenetics in neuroscience's recent advances. Craver (2021) and Sullivan (2018) have also discussed this tool's impact. Likewise, Robins has addressed how optogenetics research challenges models of false memory (2016) and provides novel avenues for intervention in memory processes (2018). The question of why this progress happens in memory science, however, has not received attention. With the focus on optogenetics as a single case, the question might not seem particularly pressing. Philosophers like Bickle may understandably be focused on highlighting the fact that the tool crossed over disparate research areas, setting Deisseroth's psychiatric inspiration and Tonegawa's study of memory aside as interesting but irrelevant details about their individual profiles.

However, considering multiple tools, and in particular clarifiers, draws attention to this pattern, as the motivations for developing and taking up these tools are similar. Both tools were motivated by problems in neuropsychiatry. When speculating about the applications of their tools, these tools' creators did not list memory as a likely venue for uptake. Against this background, the fact that memory has served as the domain for second-phase hook experiments for these tools is puzzling. Further, there are no simple sociological explanations for this uptake. There is no clear personnel connection between the laboratory groups who performed initial and second-phase hook experiments. The groups responsible for the second-phase hook experiments were not chasing a trend; they were instead the trend-setters. Neither optogenetics nor clarifiers are the most "productive" tools, or tools that are "easy and efficient for researchers to reliably produce useful data" and facilitate "publishing high-impact work, getting funding, and building one's professional reputation" (Colaço, 2021, pp. 225–226), when compared to (say) the massively popular CRISPR (Horvath & Barrangou, 2010). They are likewise not the most, adaptive, easily used, or transferable tools (Silva, 2021). That the jump to memory has happened for multiple tools raises a question: is there something about memory that might explain why these tools were taken up in memory science?

4.1 Clarifying theoretical considerations

Noting the appearance of memory in second-phase hook experiments for multiple tools highlights that the first and second phase experiments are distinct. The first phase is centered on tool development—using optogenetics to intervene in the

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behavior of a living organism, applying a clarifier that dissolves lipids and other tissues while leaving neuroanatomy intact. The second is centered on tool uptake. The second-phase hook, which reflects use of the tool by researchers who did not play a role in its development, puts pressure on the idea that theory is absent from these revolutions.

Before defending the role of theoretical considerations in the uptake of optogenetics and clarifiers, we must address a pertinent question: what are theoretical considerations? Philosophers might have in mind systematic, explanatory frameworks, perhaps involving laws or formalized models, when they think of theories. This might be what Bickle has in mind when he uses the term "deep theory." However, this sense of theory does not exhaust the ways in which theoretical considerations might inform empirical research, nor does it seem to capture work in contemporary neuroscience. Comparatively mundane theoretical considerations, such as characterizations of the target system, the phenomena that occur in this system, the relations between phenomena, and the tool itself, must also be considered, as these considerations make up the backbone of theorizing in neuroscience.

In this paper, we focus on conceptualizations of the target system. One might refrain from calling them "deep theory," as they look different from the traditional account of theory found in works by Popper or Kuhn, but they are nonetheless falsifiable, ampliative claims or representations about the target system that inform what we think about this target, its relation to other targets, and how we investigate it. This includes characterizations of phenomena, which might be revised over time (Colaço, 2020). These conceptualizations equally might persist over systematic theory change (Bollhagen, 2021; Colaço, 2020; Feest, 2010; Haueis, 2021).

We think that it is fair to investigate conceptualizations as theoretical considerations in response to the tool revolution account for two reasons. First, conceptualizations are theoretical, even if mundane compared to "deep theory," and the power of the tool revolution account as an alternative to Kuhn's depends on its stance on the relative independence of theoretical considerations from scientific revolutions. Second, even if the tool revolution account does not rule out mundane theoretical considerations, it does not leave them any clear role to play, either in the specification of motivating problems and hook experiments or in the move from initial to second-phase hooks. Thus, at minimum, our analysis of the role of conceptualizations of memory in second-phase hook experiments clarifies how tool revolutions occur.

4.2 Optogenetics and ESR

Memory begins with the acquisition of information about some experience. This acquired information is then stored in some medium, which later can be retrieved. This core component of our concept of memory "is that of an event happening to someone, it somehow being recorded in their brain, and then this person later bringing to mind some representation of that same event" (Takeuchi et al., 2014, p.

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2). The basic idea that memories are encoded, stored, and then retrieved constitutes the established *ESR model* around which memory is conceptualized and empirically investigated.

Researchers are guided by this ESR model, conceiving of the engram as the neural trace that results from encoding and is activated during the process of retrieval. Manipulations of encoding and retrieval processes license many inferences about the intermediary engram, but there has never been a way to access the engram directly. This relation between storage and retrieval has been called the methodological challenge (Robins, 2018). Optogenetics is exciting to memory researchers because it provides a previously unavailable opportunity to activate engrams directly, distinguishing their storage from both encoding and retrieval.

It has long been supposed that encoding a memory requires significant alterations to the neurons involved, changes significant enough to involve transcription and translation of immediate early genes (Liu et al., 2012). By applying optogenetics to neurons in the areas known to support memories of a given type, researchers have been able to tie the production of light-responsive proteins to the neural activity that accompanies memory encoding. With this "light switch" now tied to an engram, it can be activated directly, circumventing standard retrieval processes. Researchers can then vary encoding processes and see how this influences which neurons are recruited to the engram and its ultimate size (Morrison et al., 2016; e.g., Zhou et al., 2009). Researchers can also manipulate the activated engram in a range of ways, determining how this alters subsequent remembering (Ramirez et al., 2013; Redondo et al., 2014). Most intriguingly, researchers can use optogenetics to search for engrams in cases where retrieval is not possible, demonstrating that there are at least some cases where the engram remains intact even after retrieval processes are damaged (Roy et al., 2017; Ryan et al., 2015).

The availability of optogenetics has encouraged scientists investigating the neural basis of memory to make their commitments to the ESR model more explicit, as it highlights opportunities for novel interventions. Appeal to the model also helps these researchers connect their work on the cellular and molecular mechanisms of memory with broader areas of memory science, including investigations of false memory in cognitive psychology, models of long-term consolidation in neuropsychology, and the treatment of Alzheimer's. These connections are made possible by the recognition of a shared theoretical framework—namely, the ESR model.

4.3 Clarifiers and synaptic scalability

The substrate of memory must underwrite a variety of memories. We can remember that the capital of Montana is Helena, that we ate granola yesterday, and how to ride a bike. These memories not only differ in their subtype—semantic, episodic, and procedural, respectively—they also differ in their degree of detail. This fact

entails that the substrate of memory must be scalable, or capable of storing information of varying contents and complexity.

The idea of scalability is exemplified by the synaptic plasticity and memory hypothesis: "activity-dependent synaptic plasticity is induced at appropriate synapses during memory formation and is both necessary and sufficient for the encoding and trace storage of the type of memory mediated by the brain area in which it is observed" (Takeuchi et al., 2014, p. 1). Despite having relatively simple base components—neurons and the synaptic connections between them —this hypothesis captures that the number of neurons as well as the number and location of their connections can vary between memory traces. Each of these components is thus scalable: this hypothesis permits the idea that a single memory trace may involve any number of neurons with any number of connections between them.

Synaptic scalability suggests that memories of varying content and complexity can be stored via synaptic connections. As a result of the popularity of the synaptic plasticity and memory hypothesis, researchers aim to investigate neuronal populations of various sizes throughout the brain. This aim cannot be achieved if researchers cannot observe large neuronal populations without breaking them apart via slice microscopy. Hence, a tool that allows for the observation of intact neuronal populations, which keep their anatomical connectivity undamaged, are well suited for observing memory traces on this hypothesis.

Clarifiers allow for the observation of neuronal populations at larger spatial scales. For instance, studies of fear-conditioning engrams illustrate the use of clarifiers, where researchers use this tool to investigate how this engram might be spread out across multiple brain regions (Roy et al., 2022). These researchers recognize that they cannot simply look at a single synapse or small circuit or brain region. Rather, they must assess the connectivity between many neurons across many areas of the brain. The idea that memory is synaptically scalable helps to explain why memory researchers have chosen to use these tools. Clarifiers allow researchers to observe neuronal populations that they could not perceive in their totality before. With this ability to observe intact neuronal populations, researchers can now test their hypotheses and search for populations of arbitrary size and complexity, exploring a wider set of possible substrates for a particular memory. A commitment to engrams could provide even more specific motivation the uptake of clarifiers, in a few distinct ways. Use of these tools could reflect an attempt to dislodge the traditional focus on the hippocampus as the basis of declarative memory (e.g., Wood et al., 1999) or in support of the memory-index view (Tanaka & McHugh, 2018), according to which the hippocampus indexes information spread throughout brain regions. Alternatively, it could reflect an attempt to defend traces that are non-local but nonetheless discrete (Robins, 2023).

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5 The role of theoretical considerations in tool revolutions

In the previous section, we showed how theoretical considerations about memory's conceptualization relate to the uptake of "revolutionary" tools in memory science. In doing so, we also showed how these theoretical considerations are needed for explicating how and where tool uptake occurs, and why we might find initial and second-phase hook experiments in different domains of neuroscience. Our analysis of how memory is conceptualized makes salient three lessons about how a tool revolution in neuroscience should be understood.

5.1 *Tool development versus tool uptake*

First, tool development and tool uptake are distinct metascientific ideas. While motivating problems might explain proof-of-concept initial hook experiments, one must also explain why the tool is taken up, especially when uptake in second-phase hook experiments occurs years later and in a distinct domain of inquiry.[6] The reason a tool is developed might not be the same reason that it is taken up, but an account of tool revolutions must nonetheless satisfactorily explicate both development and uptake.[7] This claim indicates that the metascientific analysis of tool use in neuroscience cannot presuppose that a motivating problem for tool development automatically provides an explanation for tool uptake.

One might object that shared motivations for tool development and uptake should be expected, as the cases in this paper—optogenetics and clarifiers—involve the use of the same or relevantly similar tool in at least roughly the same way. It is not as if the cases are comparable to (say) a fictitious, comedic example in which development of a microscope as an observational tool is later taken up because it is a very good paperweight. Because these tools play a roughly equivalent role across hook experiments, one might argue that this role matches the motivating problem behind their development, which, by implication, also motivates their uptake. If this were not the case, the objection might continue, then we lose the ability to explain why the developed tool is taken up in a different domain.

This objection trades on a vagueness in the tool revolution account, related to the appropriate level of detail in a motivating problem. While Bickle makes it clear that motivating problems are technical or engineering problems, it is unclear with what degree of precision a motivating problem might be specified. Bickle's own examples vary considerably on this matter. Consider the differences between

[6] Additionally, one might consider how other aspects of tool use, such as tool refinement, fit into tool revolutions. Given that refinement can amount to different things, including optimization, tweaking for specific purposes, or simple iteration, we take the minimal stance that refinement is at least sometimes also motivated by theoretical considerations.

[7] These reasons need not be distinct; they merely can be, and it seems to have been the case in both optogenetics and clarifiers.

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the general desire to intervene into neuronal mechanisms and the specific desire to "block LTP without disrupting other aspects of synaptic function *in order to test* the alluring LTP ⟶ (rodent spatial) learning and memory *hypothesis*" (Bickle, 2016, p. 4, our emphasis). While these motivating problems both capture things researchers want to do, the latter problem specifies a domain, phenomenon, mechanism, and even hypothesis.[8] While one might be able to argue that the motivating problem is shared between tool development and uptake for the former, the proposal is not nearly as plausible once all the specifics are included in the latter.

The range across these examples raises the question of what degree of detail is appropriate for a motivating problem. The immediate, intuitive answer is that the problem's detail should be representative of what factors actually motivated development of the tool. However, ascertaining this apt level of detail is no simple task. While one could look to outwardly available materials—published research articles but also memoirs, grant proposals, and other public discussions of the tool—these materials might present a skewed rationale of the tool development's motivations, especially after the fact. It would be prudent for us to deploy sociological methods like interviews and in situ laboratory observations that can supplement or audit these materials' accuracy.

How we determine a motivating problem thus might be up for debate. Nonetheless, there is one way of determining a motivating problem that seems inappropriate. We should not retroactively determine a motivating problem from post-hoc evaluations of what a tool can do. Motivating problems are meant to capture the inspiration for developing a tool, not what resulted from its development. Thus, even if a tool turns out to be applicable in different domains, we should not assume that this outcome means that the motivating problem was correspondingly broad. It is possible that this tool was developed to resolve a comparatively specific motivating problem, and its wide applicability was only recognized after the fact, perhaps once a theory of technique was developed that made clear the systems to which the tool can be applied.

5.2 What might inform tool uptake

Second, theoretical considerations, such as how memory is conceptualized, can inform tool uptake, even if they do not inform their development. As we have argued, it is unclear whether all of Bickle's own examples of motivating problems can be fairly described as being independent of theory, especially when these motivating problems include a reference to a hypothesis. Leaving aside this worry, section 5.1. provides a defense of the idea that tool development and uptake are distinct and therefore can have distinct motivators. In the case of tool uptake, our optogenetics and clarifier examples show that the conceptualization of memory played a key role in motivating the uptake of these tools.

[8] To our knowledge, Bickle does not explain how this clear appeal to a hypothesis' test can be aligned with a relative independence from theory.

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One method of showing the role of conceptual commitments in tool uptake is to reason about how this uptake might have been different had these commitments been different. While this is defeasible—we rely in part on counterfactual reasoning—this method provides us a means of thinking about how our conceptualization of the target system shapes the kinds of available tools that we might take up and deploy on this system. Namely, this method provides us a means of thinking about how memory might be studied were ESR and synaptic scalability not key components of how memory is conceptualized.

Consider first how tool uptake might change if researchers abandoned the ESR model. Explicit disavowals of this framework are uncommon, but many have challenged it by moving toward models of memory where the primary function is not retention but instead some other cognitive activity: episodic simulation (Schacter & Addis, 2007), scene construction and spatial navigation (Maguire, 2022), or modeling and predicting the world's trajectories (Buzsáki et al., 2022). Researchers building these programs do not take up optogenetic tools for identifying particular memories, presumably because they do not think there are such memories to be found. More moderately, work on memory reconsolidation (Nader, 2015), where memory retrieval initiates revision to the stored memory, may lead to a dynamic view of ESR, according to which intervention into any one stage is improbable or even impossible, limiting the perceived utility of optogenetic tools. The interest in broader conceptualizations of memory and dynamic models of its processes also changes whether and how researchers might be interested in clarifiers, which offer a view of the brain's interconnectivity, but only at an instant.

Suppose further that the idea that memory is stored in molecules, rather than the synaptic plasticity hypothesis mentioned above, were the dominant view. This sort of view is not purely speculative; several neuroscientists defend the idea that the substrate of memory is intracellular and molecular (e.g., Gallistel, 2017; Gershman, 2023; Gold & Glanzman, 2021). If the molecular view were dominant, would one expect optogenetics and clarifiers to be taken up in memory science? In considering this question, we can hold the origin of these tools fixed, as their creation was not related to memory science. Thus, in this counterfactual, the tool development is the same, but the conceptual commitments are different, and the probe is whether we would expect any change in uptake.

Let us begin with optogenetics. What could motivate a molecular memory supporter to use a tool that manipulates synaptic activity? Perhaps they want to study the relation between synaptic encoding and molecular memory storage (Gold & Glanzman, 2021). Perhaps they want to study the relation between molecular memory storage and synaptic memory expression via retrieval (Gershman, 2023). Perhaps they want to show that synaptic activity plays no role in memory encoding, storage, or retrieval (Gallistel, 2017). All three of these motivations for the uptake of optogenetics are plausible. Nonetheless, they all involve appeals to ESR and the molecular view of memory, highlighting how theoretical considerations seem to

be part of the explication for why researchers might be motivated to take up a tool like optogenetics.

What about clarifiers? A supporter of the molecular view might embrace the core idea of scalability but argue that the components that scale up are not synaptic. Rather, they might look to intracellular epigenetic or genomic components as the units that build up to underwrite memory phenomena. For instance, one who takes memory to be genomic might look to genetic codes as scalable memory traces. For this reason, it would be comparatively surprising for memory scientists to use clarifiers—a tool that allows researchers to observe large cell populations—were they to conceptualize memory as molecular and intracellular. How one conceptualizes memory affects where one looks for its substrate. Were one to not conceptualize the neurobiology of memory as synaptic and intercellular, why would one use tools that are designed for the study of large sections of biological tissue? If the predominant conceptualization of memory were molecular, we might expect that tools that can allow researchers to better observe epigenetic and genomic mechanisms, such as in vivo microscopy, would be more likely to be taken up.

This counterfactual is substantiated in recent research. Supporters of a molecular model of memory have identified a possible mechanism for the neural read-out of a molecular engram (Mollon et al., 2023). In positing tests of this mechanism, they suggest "that the engram might be experimentally approached via a genome-wide association study (GWAS) of performance in long-term memory tasks" (Mollon et al., 2023, p. 3). GWAS is a popular technique that has been taken up in diverse areas of biology, but it is not usually taken up for studying memory storage. This is likely because a technique that is used to associate genes only makes sense to take up if one is sympathetic to a molecular, and specifically genomic, account of the engram. If one were sympathetic to synaptic scalability or synaptic memory storage, it is unclear why one would be motivated to use GWAS for this purpose, regardless of how productive GWAS is in other contexts.

Evaluations of these real and hypothetical cases support the idea that one's theoretical considerations influence one's motivation for taking up a tool. Many researchers might make use of the same tool, but their motivations for doing so might nonetheless be different. If this is the case, it shows that theoretical considerations can influence tool uptake. This conclusion does not entail that revolutions are exclusively theory-driven; rather, it highlights that theoretical and experimental factors might both have a role to play in neuroscientific change.

One might object that the uptake of optogenetics and clarifiers in memory science is not due to researchers' theoretical commitments towards memory. Rather, their uptake is due to researchers recognizing facts about memory, which are related to technical motivating problems. Memory *is* synaptic, the objector might continue, and this fact has been proven by countless empirical studies and more than a half-century of research. Thus, the objector might conclude, there is no theoretical commitment that informs tool uptake in these cases.

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In response to this potential objection, we first point out that, though dominant, not all neuroscientists agree that memory is synaptic. Moreover, these dissidents have some evidential support for their alternative views. This initial response skims over the more important issue with this objection. The fact that a theoretical commitment is widely held in a scientific community does not turn the commitment into a fact. Despite their popularity, ESR and synaptic scalability remain ampliative, falsifiable claims and representations about memory, which are refined and tested over time. Wholesale incorporation of reconsolidation (Nader, 2015) into views of memory processing may lead to the rejection of the ESR model. Synaptic scalability might be falsified by research on the molecular engram, such as the recent work of Mollon and colleagues. Thus, they are theoretical. That these conceptualizations of memory are mundane is not a sign they are atheoretical. In fact, one might argue the opposite: that these conceptualizations of memory are treated as benign is evidence of problematic levels of theory-ladenness in memory science. Widely-accepted theoretical considerations might be taken for granted, influencing how memory science is done.

5.3 Tool development and uptake in context

Third, looking at tool revolutions in terms of a single tool in isolation encourages a myopic perspective on how neuroscientific revolutions occur. Keen readers might notice that the use of clarifiers in memory science follows the years when optogenetics supposedly revolutionized the field. Further, these tools do very different kinds of things: optogenetics narrows into specific synapses and permits intervention, while clarifiers broaden out to populations of neurons and permit observation. These facts are not coincidental, and they call into question why researchers now use clarifiers when "revolutionary" optogenetics were already available. Any laboratory change is costly and must therefore be motivated, and clarifiers are complex tools that are difficult to master (Colaço, 2021).

The fact that memory science is not solely conducted with optogenetics does not entail that this tool is not revolutionary, but the long-term impact this tool will have on memory science is difficult to predict. If optogenetics were to reveal limitations of ESR, then this conclusion might lead memory scientists to scale up (or look elsewhere) in their search for the engram. One could take this as a challenge to the neuron doctrine. While exploring this conclusion goes beyond the scope of this paper, it shows that the neuron doctrine is yet another manifestation of mundane theoretical considerations that motivate tool uptake. This doctrine is often taken for granted, but challenges to it become more salient when we investigate more than one tool at a time. In fact, this situation would end up more than superficially resembling a scientific crisis in the vein of a Kuhnian account. This story very well might be the case, and the picture it paints is one of our tools, our conceptualization of the target, and the way the two inform one another.

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This line of reasoning brings us back to the question at the heart of this paper: why were memory scientists motivated to take up optogenetics and clarifiers? The answer to this question now seems like it will be far more complex than merely appealing to the problem that motivated the developments of these tools. Some theoretical considerations regarding memory seem to be needed in answering this question. Likewise, we cannot discount sociological considerations in this development and uptake.[9] Equally and not wholly separately, it seems that part of the answer to this question relates to the other tools that have been and continue to be used in memory science. What have prior tools shown? What concerns were raised by their use? What are their limitations? At the same time, we can ask questions about the revolutionary status of other tools. Were these tools once considered revolutionary? Are they still?

These questions become salient once we look at optogenetics and clarifiers in shared context, as we have not discussed other tools that are commonly deployed in memory science. We speculate that adding more tools to the conversation, especially tools that are newer or more cutting-edge than the examples we address, will only heighten the salience of these questions when addressing revolutions in neuroscience. For this reason, it is unwise for us to look only at a single tool's development in neuroscience and consider its revolutionary status, even if it is taken up. Theoretical considerations can play a critical role, and the relations between the uptake of different tools might reveal this fact.

6 Conclusion

The discussion of tool revolutions in neuroscience has provided philosophers a way of analyzing scientific change that does not depend on Kuhnian paradigm shifts or so-called "deep theory." On this issue, we argue that a tool revolution account is powerful in offering a rigorous way of reshaping this debate. Nonetheless, we have argued that theoretical considerations, namely the conceptualization of the target, play a critical and indispensable role in tool uptake, which we also have argued ought to be distinguished from tool development. Our arguments are supported by a close analysis of recent research in memory science, where "revolutionary" tools like optogenetics and clarifiers have been taken up in the service of addressing outstanding technical *and theoretical* questions about the neurobiology of memory. Ultimately, our arguments support a more sophisticated way of assessing how theory informs the use of tools in neuroscience. Our assessment thus illuminates the context of tool development and uptake, which, amongst other things, includes the use of other tools.

[9] Interest in memory may in part reflect sufficient distance from the "memory wars" (Loftus, 2004) over repression and child abuse, as well as increased interest in effects of trauma and its role in disorders like PTSD.

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