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Understanding the development and use of tools in neuroscience. The case of the tungsten microelectrode

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Abstract

The philosophical interest in experimental practice in neuroscience has brought renewed attention to the study of the development and use of techniques and tools for data production. John Bickle has argued that the construction and progression of theories in neuroscience are entirely dependent on the development and ingenious use of research tools. In Bickle's account, theory plays a tertiary role, as it depends on what the tools allow researchers to manipulate, and the tools, in turn, are developed not in order to test theories but as solutions to engineering problems. However, Bickle's account is not entirely precise in explaining what informs researchers' decision-making in their atheoretical laboratory tinkering. Identifying the sources that guide researchers in tool development and use is crucial if one wishes to contribute to the philosophical or meta-scientific understanding of experimental practice in neuroscience. In the following paper, I claim that decision-making in tools' development and use in neuroscience is doubly guided. Pre-existing theory and concepts determine information's relevance, whereas tools' functioning in controlled situations determines information's reliability. Accordingly, experimenters' decision-making is situated both in the context of analysing, modelling or interpreting information and in the context of producing information. I study the case of the tungsten microelectrode developed by David Hubel during the 1950s. First, I show that pre-existing theory and concepts (in particular, the "neuron doctrine" and the concepts of "receptive field" and "cortical column") determine in advance what information would be relevant to obtain from the microelectrode. Second, I show that Hubel's tinkering follows the guidelines derived from the very structure of what we recognise as reliable experimentally produced information. Finally, I suggest that data-production processes allow experimenters to assess what to expect from an experimental system in terms of concept- and theory-generation and confirmation, thereby endorsing Bickle's tenet on the tertiary role of theory in neuroscience.

Keywords

data-production, experimental tools, electrophysiological recording, tungsten microelectrode, visual neuroscience

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1. Introduction

The philosophical interest in experimental practice in neuroscience has grown markedly in the last two decades. Philosophers have been studying, among others, the role of hypothesised mechanisms (Craver 2007; Gervais and Weber 2015; Baetu 2016; Kästner 2017; Kästner and Andersen 2018; Kästner and Haueis 2019; Atanasova, Williams, and Vorhees 2022), the experimental planning in the neurobiology of molecular and cellular cognition (Silva, Landreth, and Bickle 2013; Bickle and Kostko 2018), the theory-ladenness of data-production in electrophysiology (Hardcastle and Stewart 2002, 2003), experimental protocols, methodological pluralism and the validity of experimental models or paradigms (Sullivan 2007, 2009, 2010; Sullivan 2015; Sullivan 2018). These efforts seek to account for the factors determining experimenters' decision-making and how experimentation conditions our understanding of brain functioning.

The interest in experimental practice in neuroscience has brought renewed attention to the study of techniques and tools for data production (see the texts recently collected in Bickle, Craver, and Barwich 2022). John Bickle has argued strongly that the construction and progression of theories in neuroscience are entirely dependent on the development and ingenious use of experimental tools (Bickle 2016, 2018, 2019, 2020, 2022). In his account, theory plays a tertiary role, as it depends on what the tools allow researchers to manipulate, and the tools, in turn, are developed not in order to test theories but as solutions to engineering problems. A theory of the molecular mechanisms of cognitive functions (i.e., of the linkages between mind and molecules) depends directly on our ability to intervene in molecular processes, for example, through gene targeting techniques or optogenetics (Bickle 2016, 2018). In turn, research tools are developed in the context of engineering problems that are not guided by pre-existing theories but respond to a process, as Bickle calls it, of atheoretical laboratory tinkering (Bickle 2019, 2022).

However, Bickle's account is not entirely precise in explaining what informs researchers' decision-making in their atheoretical laboratory tinkering. Identifying the sources that guide researchers in tool development and use is crucial if one wishes to contribute to the philosophical or meta-scientific understanding of experimental practice in neuroscience. What properties do experimenters expect from tools in general, and what guidelines do they follow to decide whether a tool allows them to produce reliable, useful and relevant information in a given research context? What problems, if not problems that in one way or another engage with pre-existing theory and concepts, might guide experimenters in tool design and use? In what sense and to what extent do pre-existing concepts and theories inform experimenters' decisions?

The following paper shows that tools' development and use in neuroscience are doubly guided. Experimenters need tools to produce reliable information, and they need this reliable information to be relevant. Pre-existing theory and concepts determine information's relevance, whereas the well-functioning and productivity of tools in controlled situations determines information's reliability. Accordingly, experimenters' decision-making is situated both in the context of analysing, modelling or interpreting information and in the context of producing information. I argue that both contexts guide the atheoretical laboratory tinkering in different but complementary ways. Pre-existing theory and concepts guide through the establishment of research goals (e.g., capturing the behaviour of single neurons) but do not determine the actual technical solutions for data detection (e.g., the physical properties of the terminals with which the relevant signal could be captured). Technical solutions, on the other hand, only take into account the infrastructural conditions, so to speak, for tool's productivity and well-functioning. They secure the processes of localised experimental detection of reliable and usable information. One remarkable feature of this double orientation of laboratory tinkering is that both requirements of relevance and reliability, although different, are not conflicting and seem to converge productively. On the one hand, clarity about the information's relevance is a valuable asset when designing research tools. On the other hand, data-production processes allow experimenters to assess what to expect from an experimental system in terms of concept- and theory-generation and confirmation.

In the following paper, I take up one of the cases recently analysed by Bickle (2022), namely the development and use of the tungsten microelectrode in the second half of the 1950s by the Canadian neurophysiologist David Hubel. In section 2, I briefly present the case and summarise Bickle's analysis. In section 3, I show how pre-existing theory and concepts (in particular the "neuron doctrine" and the concepts of "receptive field" and "cortical column") determine in advance what information is relevant to obtain from research tools and how this relevance guides the development and use of the tungsten microelectrode. Based on an interpretation of experimental paradigms in neuroscience as "ways of doing" or "ways of producing information", in section 4, I describe the structure of reliable information at three different levels. First, experimentalists must produce the phenomenon they want to observe and study. Secondly, experimenters need to ensure the functioning of the apparatus that collects information about each of the relevant variables in an experiment. It is at this level that experimental work concentrates more specifically on developing tools (especially detection tools, such as microelectrodes). Finally, experimenters develop and use their tools in localised contexts. In section 5, I synthesise the results of this paper, point out the consequences they have for understanding the generation of testable predictions, and show how both aspects, productivity and relevance, are virtuously articulated in the experimental process.

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2. Bickle's account of the development and use of tungsten microelectrodes

Undoubtedly the development of the tungsten microelectrode stands as one of the most significant tool revolutions in the history of neuroscience. The philosophical literature has dealt with this episode of experimental innovation in considerable detail. The predominant approach in this literature focuses on how the development and use of the microelectrode are put to the service of locating, finding components and understanding the organisation of sensory processing mechanisms (Bechtel 2008, Chapter 3; 2009, 2013; Abrahamsen and Bechtel 2012; Haueis 2016, 2020; Haueis and Kästner 2022). Philosophers study how the development and use of the microelectrode enable the progression of experimental knowledge about these mechanisms. Their analyses concern how experimenters manage to control different experimental variables (e.g. between physical stimuli and their neurophysiological correlates) and establish invariant connections between them in order to test claims about the phenomena under study. The properly technical and engineering challenges posed by tools such as the tungsten microelectrode are typically put in the background. When analysing an electrophysiological recording system, a philosopher will typically assume that experimenters managed to make tools work properly (namely, in this case, that the implanted microelectrodes stably detect variations in the behaviour of neurons). What interests them is how experimenters figure out behavioural patterns in their devices' reports and the factors that might explain them.

Philosophical literature has also studied the theory-ladenness of electrophysiological recordings and signal processing (see especially Hardcastle and Stewart 2003). Hardcastle and Stewart have suggested that the development and application of recording and processing techniques depend theoretically and conceptually on what the field has previously validated about the phenomenon under study.

In this context, Bickle's (2022) analysis of the development and use of the tungsten microelectrode offers a rather original approach. He considers the challenges of tools' engineering and the (tertiary) role tools play in the generation and validation of claims about the phenomenon of visual processing. Bickle sees the tungsten microelectrode as originating in "atheoretical laboratory tinkering" rather than in experimental research oriented towards the search for mechanisms. Bickle's analysis seems thus to take quite seriously that the tungsten microelectrode was first developed and applied, as I will later recall, in overtly exploratory experiments rather than experiments designed to answer precise research questions or test claims. The motivating experimental problems (or "motivating problems"), which are essential according to Bickle for understanding the development of gene targeting techniques and optogenetics (2016), seem, at least prima facie, less crucial in a case of exploratory experimentation (I will return in section 3 to examine the role that "motivating problems" play in the case of the tungsten microelectrode).

This paper seeks to contribute to the line of research opened by Bickle's work on laboratory tinkering in experimental practice in neuroscience, particularly in the case of electrophysiology. As already pointed out in the introduction, Bickle's account is not entirely precise in explaining what informs researchers' decision-making in their atheoretical laboratory tinkering. I will try to show that pre-existing concepts and theories do indirectly inform, in this case, experimenters' decision-making. They guide the production of "relevant" knowledge to answer research questions without necessarily providing clues to find properly technical solutions that eventually make the development and use of microelectrodes feasible (section 3). Furthermore, I will show that what directly informs researchers' decision-making in their tinkering are the properties of the experimental tools in their localised functioning (section 4).

Before summarising Bickle's analysis, let me briefly recall the episode of the tungsten microelectrode. David Hubel developed the tungsten microelectrode in the 1950s and used it to record single neurons in the cat's visual cortex. These microelectrodes are tiny insulated wires with sharpened, voltage-sensitive tips that reach diameters of less than 5 µm for extracellular recording (Hubel 1957, 1959). Through a fixed piston-cylinder assembly implanted in the skull, researchers could position the wires at different depths to capture the current emitted by the action potentials of single neurons in the cortex. Using physical, parameterised visual stimuli, initially light spots projected onto dark screens, David Hubel and Torsten Wiesel conducted a series of experiments to map the receptive fields of neurons in the visual cortex. Until then, it had only been possible to map the receptive field of retinal ganglion cells (Kuffler 1953) and it was uncertain that such a simple correlation between stimuli and receptive field would also occur at the level of the visual cortex. By a relatively fortuitous set of concurring circumstances, Hubel and Wiesel's experiments allow them to discover that neurons in the visual cortex respond to thin bars of light. They further found that neurons' receptive field is selective with respect to the bars' orientation. Neurons responded better when bars were tilted to a certain degree with respect to the vertical or horizontal position (Hubel and Wiesel 1959, 1962). They also found evidence confirming the functional architecture of the cortex that Vernon Mountcastle had observed some years earlier (Mountcastle 1957), according to which sets of neurons with similar physiological properties are arranged in columns (Haueis 2016). They also found that certain cells - called "simple" - respond discretely to the presence or absence of simple features (Hubel and Wiesel 1959), others - the "complex" neurons - are activated by the presence of any one of a set of simple features (Hubel and Wiesel 1962) and finally cells - called "hypercomplex" - that respond to combinations of features (Hubel and Wiesel 1965). The existence of simple, complex and hypercomplex neurons confirms the idea that visual information processing is organised in a hierarchical manner, where simple neurons feed on to higher-order neurons (Barlow 1972). In sum, the evidence collected by the tungsten

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microelectrode provided robust confirmation for the doctrine that individual neurons are the anatomical and functional units of visual perception. The case of tungsten microelectrodes thus confirms eloquently that "the history of neuroscience is the history of its methods", and, in particular, that the "focus on the properties of individual neurons was a natural consequence of the use of single-cell anatomical and physiological techniques" (Yuste 2015).

I move now to Bickle's account. John Bickle believes that the development and use of tungsten microelectrodes exemplify the logical and chronological secondarity of neurobiological theories with respect to the instruments allowing researchers to manipulate the systems under study.

> The genesis of every piece of theory (…) can be tied directly to the development of new research tools. Theoretical progress in this paradigmatic science of our times *is secondary to and entirely dependent upon* new tool development, both temporally and epistemically. (Bickle 2022, 14)

Just as a theory concerning the molecular mechanisms of cognitive functions (i.e., the linkages between mind and molecules) depends directly on our ability to intervene into molecular processes on the laboratory bench, for instance, through gene targeting techniques or optogenetics (Bickle 2018, 2016; see also Silva, Landreth, and Bickle 2013; Silva 2022), the doctrine that individual neurons are the anatomical and functional units of visual perception depends on the development of methods that allow experimenters to record single neurons (Bickle 2022). From the fact that theory is logically and chronologically secondary to tools' development and use in neuroscience, Bickle seems to infer that tools might not originate in view of theory testing. He states that tools develop in trial-and-error processes or in an atheoretical laboratory tinkering (Bickle 2022, 2019). Bickle's position can be described as "tools first method" or "anti-theory-centric method" (Johnson 2022), where theory plays a tertiary role since it depends on what the tools allow us to manipulate and the tools, in turn, are developed not in order to test of pre-existing theories, but as solutions to engineering problems.

> Rather than being the crux point on which everything else depends, (…) theory turns out to be doubly dependent, and hence of tertiary, not primary, importance. Our best confirmed theory is totally dependent on what our experiment tools allow us to manipulate. And those tools developed by way of solving engineering problems, not by applying theory. (Bickle 2022, 578)

Bickle applies the idea of theory's tertiary role to the episode of the tungsten microelectrode development. According to him, Hubel's main concern focused on achieving a well-insulated tungsten wire, thin enough to reach the vicinity of neurons.

> He [Hubel] quickly discovered that one of the then-standard techniques for steel electropolishing worked to generate tips of the required dimensions in tungsten wire. Hubel consulted or appealed to no theory; he discovered this strictly by trial-and-error, working with then-standard electropolishing techniques. He also quickly discovered, by trial-and-error tinkering, that he could obtain almost any degree of taper in tungsten tips by raising and lowering the wire during all but the final stages of electropolishing. (Bickle 2022, 16-17)

The same applies to the challenge of insulating the wire appropriately. Hubel undertakes a trial-and-error approach that leaves solutions to chance rather than planning. In a passage quoted by Bickle, Hubel recalls:

> I tried every coating I could find but nothing seemed adherent enough or viscous enough. Formvar did not adhere and in any case was available only in tank-car amounts. A solution of Lucite in chloroform came close to working. One day while I was playing around with this my neighbor in the next lab walked in with a can of something called 'Insulex' and said, 'Why not try this?' I soon found that when Insulex was thickened by evaporation it became viscous enough to adhere to the wire, and suddenly I had an electrode that was recording sensational single units. (Hubel 1996, 303)

In my view, the question remains as to what guides the "dedicated tinkerer" in the construction of "new tools through ongoing trial-and-error" (Bickle 2022, 33). Hubel's reasons to insulate a tungsten wire and sharpen the tip in the micrometre scale guide decision-making, even though this guidance is not that of pre-existing hypotheses to be tested through experiments. Where do the engineering problems Hubel must face come from? How is he to assess the appropriateness of solutions? What causes some insulators to be discarded and what makes experimenters choose tungsten as suitable material in the first place? Are we going to say that new tools derive simply from curiosity and patience and skill and fortune, or do researchers count on some guidelines to orientate their decisions and determine the appropriateness of solutions? What role do theories and concepts play within all this, if they play any?

It seems to me that Bickle (2022) 's presentation does not contextualise sufficiently Hubel's tungsten microelectrode development. It presents Hubel already resolved to make a tungsten microelectrode, sure of what he needs and prepared to guess when good fortune comes knocking. However, as we reconstitute the context of the microelectrodes development, we perceive that Hubel's decisions move in a space highly determined by pre-existing theory and experimental guidelines for assessing the well-functioning and productivity of the new tool. Laboratory tinkering, even if atheoretical, follows rules and serves particular purposes, which in no way diminishes its importance in the process of developing new tools.

In what follows, I attempt to show that pre-existing theory plays a role in developing the tungsten microelectrode insofar as it conditions the relevance of the information that this new tool is expected to generate (section 3). The goal of recording single neurons guides the tinker's decision-making regarding materials and tool design. However, this goal emanates from the earlier theoretical assumption that neurons are the anatomical and functional units of the brain. The interest in studying the behaviour of individual neurons in the visual cortex does not result from the development and use of the tungsten microelectrode, but on the contrary, it is the interest in individual neurons and their function in the mechanisms of visual processing that leads the technological innovation.

The relevance of the information researchers need to generate is not the only guideline for assessing the productivity and usefulness of a tool. As I will try to show in section 4, the development of a tool seeks to generate reliable information, and reliable information is information that can be traced back to localised and controlled data-production systems. What in this case prevails as heuristics for laboratory tinkering and researchers' decision-making is not pre-existing theory but the tool's proper functioning as it is applied to a particular experimental situation. Tools are causal devices that take part in data-production systems (in the case of the tungsten microelectrode, this system involves, among others, cortical tissue, parameterised stimuli, and anaesthetised cats).

3. Pre-existing theory and concepts as a guiding source for the tungsten microelectrode development and use

David Hubel developed the tungsten microelectrode to fulfil a particular goal: to study in vivo the behaviour of individual neurons in the visual cortex while presenting parameterised visual stimuli. Theoretical assumptions of different kinds are implicit in this goal. I suggest that the pre-existing concepts of "neuron", "receptive field", and "columnar organisation" guide Hubel and Wiesel's tinkering despite the overtly exploratory character of their experiments. Pre-existing theoretical knowledge guide experimenters' tinkering by indicating what kind of information an experimental system needs to produce in order to pursue some research questions. However, as I will try to show later (section 4), the information's relevance is insufficient to guide tools development and use. The causality of data-production processes is another guiding source of tool development and use.

I begin by briefly reviewing the concepts of "neuron", "receptive field", and "columnar organisation". First, it is clear that the "neuron doctrine" (Shepherd 2016, 2010) provides the general conceptual basis for predicting that neurons in the visual cortex are functional and anatomical units of visual perception. Understanding how the brain processes visual information entails collecting information about individual neurons' behaviour in the visual cortex. A scalp electrode may record the activity of thousands or millions of neurons simultaneously, which constitutes very relevant information for studying the system's coordinated behaviour or activity patterns as a whole but is nearly irrelevant for understanding the role of individual neurons in the mechanisms of visual processing.

A second pre-existing idea guiding laboratory tinkering was introduced during the 1930s by Haldane K. Hartline when studying optic nerve fibres from dissected crab's, eel's and frog's eyes. The concept of "receptive field" refers to the area of the retina or the visual field that activates the response of a particular cell. Hartline found that a spot of light over certain areas of the retina can activate the response of one kind of cells but not of the others; other cells were activated when the light stimulus over certain areas was turned off (Hartline and Graham 1932; Hartline 1938, 1940). Using a multibeam ophthalmoscope that allowed researchers directly to stimulate small, discrete areas of the retina with light or dark spots, Stephen Kuffler studied retinal ganglion cells in cats in the early 1950s. Kuffler succeeded in mapping the centre-surround concentric receptive fields that activate different cells depending on whether the centre or the surround was illuminated (Talbot and Kuffler 1952; Kuffler 1953). At that moment, it was not clear that there were neurons in the visual cortex with receptive fields defining their functional properties.

Finally, a third pre-existing concept guiding the use of tungsten microelectrodes concerns an idea introduced in the 1950s by Vernon Mountcastle about the columnar architecture of the sensory cortex (Mountcastle 1957; Powell and Mountcastle 1959; Haueis 2016, 2020). Hubel indicates that the concept of "column" was in the "back" of his and Wiesel's minds when using their microelectrode (see Hubel and Wiesel 2005, 62). The concept of "column" allows the experimenters to anticipate the existence in the visual cortex of groups of cells gathered in small cylinders (0.5 mm wide) with the same functional properties and sharing the same receptive fields (Hubel and Wiesel 1962, 120-123). The concept of "column" thus invites them to vary the inclination of the microelectrode, for which they use a device (an "advancer") that allows them to control the position of the cable at a micrometre scale. The use of the microelectrode is thus theory-laden - or concept-laden, as Philipp Haueis prefers to say because the columnar organisation of the cortex does not at that moment have the status of a well-accepted theory (Haueis 2016).

In designing the tungsten microelectrode, Hubel knew what he needed it for. He needed a tool to collect information for studying the functional properties of neurons housed in the visual cortex. The role of the concepts of "neuron", "receptive field" and "columnar organisation" in Hubel and Wiesel's recordings of single neurons in the cortex is certainly limited in scope. These concepts do not guide the whole experimental process. Even though evidence collected in Hubel's and Wiesel's experiments eventually had a highly confirmatory value (Yuste 2015), the purpose of these experiments was not theory testing but the exploration of visual processing. In other words, Hubel and Wiesel study of the visual cortex was mainly exploratory. As Torsten Wiesel recalls,

> David and I approached the visual cortex as explorers of a new world. Neither of us had any preconceived ideas about what we would find on our journey; instead, we let our discoveries dictate what questions to ask next. At times we felt more like naturalists of a bygone era. We made every effort to carry out experiments twice a week, beginning early in the morning and working late into the night. (Hubel and Wiesel 2005, 35)

A series of hazardous events eventually allowed Hubel and Wiesel to discover that the appropriate stimulus to activate a neuron was a light bar and not a light or dark spot, and to discover orientation selectivity:

> Our first real discovery came about as a suprise. We had been doing experiments for about a month. We were still using the Talbot-Kuffler ophthalmoscope and were not getting very far; the cells simply would not respond to our spots and annuli. One day we made an especially stable recording. (We had adapted my chronic recording system, which made use of Davies' idea of a closed chamber, to the acute experimental animals, and no vibrations short of an earthquake were likely to dislodge things.) The cell in question lasted 9 hours, and by the end we had a very different feeling about what the cortex might be doing. For 3 or 4 hours we got absolutely nowhere. Then gradually we began to elicit some vague and inconsistent responses by stimulating somewhere in the midperiphery of the retina. We were inserting the glass slide with its black spot into the slot of the ophthalmoscope when suddenly over the audiomonitor the cell went off like a machine gun. After some fussing and addling we found out what was happening. The response had nothing to do with the black dot. As the glass slide was inserted its edge was casting onto the retina a faint but sharp shadow, a straight dark line on a light background. That was what the cell wanted, and it wanted it, moreover, in just one narrow range of orientations. (Hubel and Wiesel 2005, 438)

In fact, the discovery of orientation selectivity was produced by an accidental movement of the experimenters' hands, which unexpectedly activated a response of neurons:

> I slowly became convinced that cortical cells required for their activation fancier stimuli than simply turning on or off the room lights. I started casting about for ways to make them react. My first successes came one day when out of desperation I waved my hand back and forth in front of a cat. My electrode was lodged between two cortical cells that gave unequalamplitude spikes that I could easily tell apart, neither of which reacted to turning on and off the room lights. But to my amazement they responded vigorously to the hand-waving, and my amazement increased when I saw that one of the cells was responding to left-to-right movement and the other to right-to-left. Clearly the cortex must be doing something interesting! I observed similar cells

> several times, but with the cat free to look around it was hard to stimulate any one part of the visual field for more than a few seconds. It was only a few years later that Torsten and I managed to learn more about how these cells were working. (Hubel and Wiesel 2005, 21)

There is no reason to distrust Hubel and Wiesel's dominant narrative regarding the exploratory nature of their research (for the concept of "exploratory experimentation", see Burian 1997; Steinle 2016). It is hard to imagine that the discovery of selective orientation could have come about by testing predictions derived from the bulk of available theoretical knowledge about the receptive field of neurons. It must have been discovered by "fooling around", as its discoverers describe. Exploratory research, in any case, does not inhibit pre-existing theory from guiding experimentation and decision-making in various ways different from theory testing (Franklin 2005). For example, in the case I am now considering, one could safely conjecture that the "neuron doctrine" and the concept of "receptive field" guide experimentation as would do "auxiliary hypotheses" in the sense of David Colaço (2018). According to Colaço, the application of techniques entails hypotheses about the system to which they are applied, even though experimenters are not concerned with testing them. When applying techniques, experimenters "appeal to theories of the [target] system in order to determine that the [target] system is an appropriate candidate for the application of a technique" (2018, 38). This is very plausibly the case of the tungsten microelectrode, designed to reach the proximity of single neurons and sense their behaviour in response to the presentation of visual stimuli. The development and use of the microelectrode assume that neurons are components of and play a role in the brain's mechanisms to encode the visual environment. In that sense, Gregory Johnson seems to be right in pointing out that, in laboratory tinkering, the conceptual and hypothetical representation of "neural mechanisms" may precede and even guide the development and use of new tools (Johnson 2022), tools that will allow in turn for more detailed investigations about these mechanisms.

Concepts such as "neuron", "receptive field", and "column" can be interpreted in the light of what Bickle calls "motivating problems" (Bickle 2016, 2018; see also Johnson 2022). These scientific problems guide experimenters in developing and applying new technologies to produce relevant information for testing hypothetical claims. Gene targeting techniques and optogenetics respond, according to Bickle, to the experimental purpose of selectively blocking some specific molecular processes without altering others in order to test claims about these processes.

> To test causal hypotheses which relate specific neurons' activities directly to behaviors operationalizing specific cognitive phenomena, experimenters need the capacity reliably to intervene into the hypothesized neuronal mechanisms: to activate and inhibit specific neurons. (Bickle 2018)

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The tungsten microelectrode is a case of "a specific tool developed for a specific experimental purpose", even though the motivating problems guiding Hubel and Wiesel's exploration are far more limited in scope than would be causal hypotheses about the underlying mechanisms of visual processing (although they will not shy away from hypothesising mechanisms eventually). The electrophysiological recording of single neurons in the visual cortex provides evidence for testing claims about the receptive field of neurons or the columnar architecture of the cortex. Testing claims about the receptive field or the columnar organisation of the cortex provide experimental purposes that may precede and guide microelectrode engineering. These purposes not only turn salient which experimental variables (e.g., individual neurons) and ranges of values for these variables (e.g., discharges bursts or silence) are relevant but also provide fairly precise guidelines to help orientate the development and use of the new tool. When there is an experimental (theory-driven o exploratory) purpose, such as detecting a neuron's activity in the visual cortex, experimenters may anticipate many things they need: they need low-impedance, tiny wires made of some metal hard enough to penetrate the cortex; they also need the surface of the wire to be insulated except at its tip, so that signal from other neurons that cross its path will not contaminate the recording; they need a device allowing them to fix and vary the position of the electrodes. Laboratory tinkering would probably be scattered in useless or unnoticed findings without the guidelines that these motivating problems provide.

4. Data's reliability as a guiding source for the tungsten microelectrode development and use

Once the information experimenters want or need has been defined, it remains to be seen, no less, how they succeed at obtaining it. Laboratory tinkering needs to develop the means to obtain reliably useful information, and for this purpose, the general guide of pre-existing concepts and theories is of limited use. Laboratory tinkering follows - so I argue - the guidelines that derive from the very structure of what we recognise as reliable experimentally produced information. The idea of reliable information guides the atheoretical laboratory tinkering and helps to make it productive.

In this section, I describe the structure of reliable information at three different levels. First, experimentalists must produce the phenomena they want to observe and study. To do so, they design and run experiments. These experiments allow the testing of specific claims, but these claims do not guide experimenters directly. What guides experimenters directly is the causal process through which the experiment produces the phenomenon under study (section 4.1). Secondly, experimenters need to ensure the functioning of the apparatus that collects information about each of the relevant variables in an experiment. At this level, experimental work concentrates more specifically on developing tools (especially detection tools, such as microelectrodes). Tools are devices for producing data about well-isolated variables (section 4.2). Finally, it should be noted that tools' functioning and experimentation always occur in situated contexts. This local or situated character of experimentation provides pretty precise guidelines to experimenters for the development and application of tools (section 4.3).

4.1. Experimental paradigms as ways of producing phenomena

In exploring the visual cortex with a new tool, Hubel not only moved within a realm laden by pre-existing concepts or theoretical intuitions concerning visual perception, but he also adapted to existing ways of doing and experimenting, that is, to standard practices of knowledge production in the discipline. Scientific mentors such as Haldane Hartline, Stephen Kuffler and Vernon Mountcastle were not only a source of intellectual inspiration and their experimental work not only bequeathed results, research questions and motivating problems. They also provided models of experimental practice; they exemplified ways of doing, of producing experimental knowledge.

In the philosophy of neuroscience, the idea of experimental model or experimental paradigm has been extensively discussed by Jacqueline Sullivan in relation to the neurobiology of memory (Sullivan 2007, 2009, 2010; 2015; 2018). An experimental paradigm is the set of procedures that neuroscientists implement to produce and study specific phenomena. In the case of visual neuroscience, the standard or classical paradigm for producing visual processing phenomena consists of activating some relevant component of the visual system (retina, optic nerve, visual cortex) using simple, parametrised stimuli controlled by the experimenter. This method dates back at least to the mid-nineteenth century. In 1866, the Swedish physiologist Frithiof Holmgren published a paper with his discoveries about retinal currents (Holmgren 1866; Kantola, Piccolino, and Wade 2019), but the author's main interest seemed to lie in the fact that he had come up with a method or "way of doing" for experimentally producing relevant information. To discover that light on the retina caused electrical activity in the visual pathways was at the same time to discover an experimental device that would make it possible to produce the phenomenon of vision and to intervene in it. The title of Holmgren's paper was "Method to obtain objective evidence of the effect of light on the retina", and the second paragraph reads: "it would be of great importance to find a method that would give, if possible, a direct and objective expression for the effect of light on the retina. The following is an attempt to solve this problem" (Holmgren 1866, 178; Kantola, Piccolino, and Wade 2019, 4).

Experimenters seek to install, with the help of tools, experimental processes allowing them to control and intervene into vision pathways. The causal control of the system not only makes it possible to reproduce a result or to foresee contexts for its reproduction; it also makes it possible to produce controlled variations. Controlled variations are intrinsic to the functioning of experimental systems. The experimental process generates a space for differentiation that

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allows for discovering and identifying reproducible effects under defined conditions. Controlled variation of the experimental variables and their values allows experimenters to produce new knowledge. Experimenters vary the properties of stimuli (size, shape, distance, light intensity, etc.) as well as the exposure time during trials, the receptor (dissected eyes or living models, animals free to move or deprived of movement, awaken or anaesthetised), the recording loci (retina, optic nerve, cortex), the recorded entity (one cell or the summated activity of several cells), and so forth. Even if experimenters' goal consisted of reproducing the same known effect (for instance, in order to calibrate an instrument), this reproduction will succeed and have epistemic value if and only if it reproduces the same effect in *a different* instance, for example, in a different trial using a different subject. Even the reproduction of the same involves the controlled production of variations[1].

To Hubel's and Wiesel's eyes, it could not but be promising to record single neurons in the cortex in situations comparable to those previously designed by Stephen Kuffler. Undoubtedly the discoveries of light bars as stimuli suitable for activating the response of neurons and orientation selectivity were largely fortuitous (see section 2). However, these findings derived from a (voluntary or involuntary, directed or exploratory) controlled variation of experimental variables and their values. For instance, a group of scientists in Freiburg and another in Montreal succeeded in developing devices to project vertical and horizontal bars on the retina. However, the devices were unable to vary bars' orientation. This technological limitation prevented these groups of experimenters from discovering orientation selectivity:

> To vary orientation and speed of movement we had to tilt and move the entire projector by hand, and we produced our line stimuli by cutting out slits in pieces of cardboard that we stuck to a frame with masking tape. We turned the stimulus on and off by interposing our hand in front of the lens. We later learned that two competing groups had attempted to activate cortical cells by using more elaborate methods: the Freiburg group led by Jung had built a device that somehow projected horizontal lines onto the retina, whereas a group in Montreal had built a projecting device that was limited to vertical lines. Both methods were presumably used to locate receptive fields efficiently, but neither was capable of varying orientation, so that it was impossible to stumble on orientation selectivity. Our methods, though crude, were flexible, and paid off. (Hubel and Wiesel 2005, 80)

It is improbable that Hubel's atheoretical tinkering did unfold as capricious inventing. On the contrary, this tinkering relied on historically determined ways of doing or ways of producing reliable information. Experiments (or "experimental paradigms") possess a history that

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[1] The philosophical literature on this topic is very extensive. As a relevant reference, I have in mind Hans-Jörg Rheinberger's idea of “differential reproduction” (Rheinberger 1997). See also more recent discussions in Jutta Schickore (2018) and Stephan Guttinger (2019, 2020)

transcends their implementation in particular research programmes. Experiments bequeathed knowledge only insofar as they are repeated and varied (Schmidgen 2014). The novelty of results find their opportunity when inscribed as controlled variations of known procedures. The great challenge Hubel decides to face – the "motivating problem", in Bickle's terms - is to shift the recording of single cells in the retina (Kuffler) and the somatic sensory cortex (Mountcastle) to single cells in the visual cortex.

Being guided by the production of reliable information does not imply being guided by causal claims about the visual system and its underlying mechanisms. Conversely, searching for relevant information to test causal claims does not ensure the ability to produce reliable information. Data "relevance" and data "reliability" are different things - as "explanation" and "observation" are different things -, to the extent that it may well happen that an experimental system produces reliable yet artefactual information, i.e. information about the experimental system itself rather than information about a target system. Suppose it is revealed that neural responses to simple and parametrised stimuli play no relevant role in visual processing. In other words, suppose that the "receptive field" of neurons is artifactual - the artifactuality of single-cell recording is, in fact, one of the main features and challenges of "classical paradigms" in visual neuroscience (Maldonado 2007; Yuste 2015). In that case, if the artifactual recording is reliable, then no matter how irrelevant the recording may be as evidence for some theory: the experimental process can make other uses of it (e.g., the classical receptive field of a neuron can be used to calibrate an eye-tracker). When studying visual processing mechanisms, it seems far better to count on artifactual yet reliable information than be unable to count on reliable information production processes at all. Information whose causality cannot be determined has no use or is not information in any sense of the word. Instead, we can always try to find better ecological conditions to control the relevance of our experimental data to provide evidence for hypothesised explanations (Rust and Movshon 2005).

4.2. Tools as causal devices for data-production

In developing the microelectrode, experimenters lose sight at times of the phenomenon of visual processing. They need to concentrate on producing a device capable of detecting reliable information about one particular experimental variable: the activity of single neurons in the visual cortex. This variable is considered independently of the other variables to which it is experimentally connected. The activity of the other variables to which it is connected may "explain" variations in its recorded values. However, experimenters must first ensure they properly register this variable activity (single neurons' activity). As the experimenters focus on one variable, it is expected that the causality of the phenomenon as a whole will no longer guide decision-making. The causality of the electrophysiological signal guides decision-making. Experimenters need to ensure that the signal variations reflect the activity of single neurons, regardless of whether this activity exhibits a particular connection with the other relevant variables from the point of view of the experimental production of the phenomenon.

An electrophysiological recording is reliable and usable to the extent that it allows experimenters to recognise variations of the neural tissue's electrical activity in the electromagnetic signal modulations. For this to be possible, the signal needs to refer to the set of technical and experimental conditions that produce it. Neural activities of very different kinds cohabit in the same electrophysiological signal, as much as noise from different sources is superimposed. But suppose we ignore the impedance, the sensitive area, and the size and location of the implanted terminal. In that case, we could hardly manipulate the recordings further to deconfound variables at stake (for example, to distinguish the noise from neural activity and, in neural activity, to distinguish single from multiple cells activity). Experimenters may not be able to hypothesise about the mechanisms that are ultimately responsible for the behaviour of the neurons they record (e.g., the timing and rate of discharges), nor about the role these neurons play in visual processing. However, they need to know the circumstances responsible for the signal's production. They could hardly use a signal if they were unable to decode the information this signal carries, and to decode this information implies understanding the causality underlying its technical production.

The reliability of the information depends on the traceability of the electromagnetic signal. This traceability involves understanding the type of signals the implanted terminal detects according to the physical and geometrical properties of the wire (for instance, the metal impedance and the sensitive area). It involves, in general, indirect control over current flow variations as causes of the variations in the electromagnetic signal. What guides laboratory tinkering in this sense is the causality of data-production processes. The tungsten microelectrode development and use aim to install an invariant causal correlation not between physical stimuli and the receptive fields of neurons but more basically between the activity of neural tissue in the cortex and the electromagnetic signal. Here, causal reasoning is not oriented towards inferring causal claims about the mechanism of visual processing but towards the device's productivity. Through the microelectrode, experimenters isolate the neuron's activity from other unknown or uncontrolled circumstances and factors that are presumed to affect current flow changes. Along with isolating the activity of the neuron, the microelectrode channels or straightens the concatenation of events that culminates in the signal (for the concept of "straightening" (*Begradigung*), see Tetens 1987). Experimenters can observe, in the variations of the effect, sc. variations in the waves' frequency and amplitude, the variations of the cause, i.e. the behaviour of neurons. Microelectrodes implanted in the cortex function as "channelers" or "straighteners" that convert the current emitted by the neurons' activity into a cause of signal fluctuation. It is not the experimenter who "makes" something here but the tool itself. Microelectrodes allow experimenters to set (indirectly) the variables and ranges of values causally relevant to signal amplitude and frequency variations.

Experimenters aim to develop productive devices whose functioning they can account for. To understand how a tool works and what it produces, and in the long run, what experimenters can do with the information this tool generates, one does not need to presuppose, for example, what a neuron's receptive field is. To understand how the microelectrode works and what information it produces, experimenters need to understand the concatenation of events triggered when they implant the terminal in the cortex. The electromagnetic signal informs primarily and immediately about the causality of its own production. Whether the signal confirms a prediction about a phenomenon is a different matter. Its value as confirmatory evidence would require connecting the signal to other experimental variables suspected to explain its modulations. For example, suppose I want to confirm a claim about neurons' receptive field or the columnar architecture of the cortex. In that case, I must analyse the interaction of the signal's modulations with other variables (e.g. the physical stimulus or the position of the microelectrode).

4.3. The contextualised development and use of tools

The project of recording neurons in the cortex occurred to Hubel in the mid-1950s during his three-year stay at the Walter Reed Army Institute of Research. The Italian-born neurophysiologist Michelangelo Fuortes introduced him to electrophysiological recording techniques in a project on the cat spinal cord. Fuortes suggested that Hubel fabricate electrodes and place them on the cortex of cats. The idea was to see whether he could capture single neurons.

> The time came to select a project of my own. Mike [Michelangelo Fuortes] listed a few ideas for me to consider, one of which was to take fine insulated wires, cut them off with scissors, poke them into cat cortex, sew up the cat, and hope to record single cells when the animal recovered. I thought it worth trying, and so I began a project that was to last three years. (Hubel and Wiesel 2005, 18)

Needless to say, pre-existing concepts and theories about what a "neuron" is, about the cortical tissue and its electrical properties, surely guide a project of this kind. However, the central technical problems become apparent once the experimenter attempts to develop and use the tool in the specific context of its application: the cat's visual cortex. The tool's expected functioning is not theoretical but localised. And the local character of the experimenters' interventions presents specific challenges that guide the engineering and development of new technologies.

> The first experiments were utter failures, and I soon realised that I would have to develop an electrode fine enough to record from single cells and stiff enough to push into the brain, and some way of advancing it in fine, controlled steps. So I began to

> work on developing a new electrode and a means of holding and positioning it. (Hubel and Wiesel 2005, 18)

The challenges that laboratory tinkering faces are revealed in the contexts of the tool's application because these challenges concern the tool's functioning in those contexts. The 1957 paper reports the challenges of size (less than 1 µm for intracellular recording and less than 5 µm for extracellular recording), insulation and position. As Bickle notes, "the nature of these initial problems and solutions, as reflected in Hubel's word choices, 'becomes too fragile,' 'requires too thick a shaft,' 'stiffest, easily available.' He confronted engineering problems that required practical solutions" (Bickle 2022, 16). It should only be added that these engineering problems are defined in the context of concrete, specific data production processes (and through concrete, specific "utter failures").

The production of reliable and useful information guides the situated engineering of experimentation. Laboratory tinkering pursues the correct and, at the same time, materially contextualised functioning of tools. For instance, the hardness of cortical tissue, through which the wire needs to pass without breaking or bending, is a relevant factor to consider when searching for a suitable material for building the wire. And the microelectrode's size needs to reach the proximity of single neurons. One of the main problems that arise when using a hard metal such as tungsten is finding the proper technique for sharpening the tip (a problem that Hubel solves with electropolishing techniques). The microelectrode's position is defined by the relatively stable position of the neuron in the cortex with respect to the mobility of the wire. Head movements (in the case of non-anesthetised animals) or simply (in the case of anesthesised animals) the movements of the cortex resulting from respiration or vascular pulsations may critically change the wire's position (Hubel and Wiesel 2005, 39). At the same time, the stability of the wire should not inhibit precise repositioning. Hubel designed an "advancer" that he attached to the animal's skull. This device allowed him to fix the electrode and move it forward in small and controlled steps. The whole procedure involved drilling a hole over the visual cortex, cutting the dura mater, placing a guide tube, waxing the surrounding space and lowering the piston that held the microelectrode (Hubel and Wiesel 2005, 59). Without an apparatus of this kind, it would not have been possible to record the activity of different neighbouring neurons and thus collect evidence concerning the columnar organisation of the cortex.

Tools are first and foremost means of intervening in localised material systems. The information they generate immediately refers to the singular circumstances of their application. For instance, reliable information about the behaviour of neurons entails multiple localised recordings: recordings of the receptive field of the same cell at different times in the presence or absence of the stimulus, recordings of multiple single cells obtained during the same session or in different sessions using the same or varying the light bar's orientations, and so on. Suppose the measurements did not concern single events each time. Then it would most likely be impossible to accumulate data points and thus obtain statistically significant information. The material singularity of a spike or a neuron is essential when accumulating different recordings from the same or different neurons. In a year's work, Hubel and Wiesel recorded about 300 neurons in the cat's visual cortex. Researchers could listen to and study the behaviour of these neurons for periods ranging from a few minutes to a few hours (Hubel 1958; Hubel and Wiesel 1961).

Nevertheless, the situated functioning of tools does not limit the recordings' epistemic validity. Recordings provide information about causal processes and not about isolated or erratic events without general meaning. The design and engineering of Hubel's and Wiesel's recording system ensured a stable functioning and application to more than a dozen cats during one year of work. However localised and situated, every recording is an effect or result of the causal devices (the tools) with which the experimenters intervene in the cortex. The functioning of the intervention devices confers a general meaning to each localised recording process. The isolation of 300 units needs both the localised application and the regular causal functioning of the intervening tools. The stability of the recording system is a fortiori a necessary condition for the experimental production of the phenomenon under study, for the exploration of causal connections between different experimental variables (e.g. receptive field and stimulus) and for the testing of claims about the phenomenon's underlying mechanisms (see above, section 4.1).

The main challenge of experimenters is to transform the circumstances in which they develop and use their tools into parameterised procedures with general import. An experiment materialises not only concrete actions or singular facts but also "ways of doing", "modes of proceeding", in a word: "methods" of observation and detection. The details of the process of obtaining information are "methodological". They allow information to "transcend" the local circumstances of its production. For that reason, detailed information about the conditions under which data are initially obtained should only facilitate their storing, transferring or modelling and reuse across different epistemic contexts (Goodman et al. 2014; Boyd 2018; Leonelli 2016; 2020; Garrido Wainer, Fardella, and Espinosa Cristia 2021). It is thus the "local" character of the electrophysiological signal that ensures its "mobility" (its potential use in other unforeseen contexts as evidence of other unforeseen phenomena).

5. Conclusive remarks: the reciprocal determination of theory and tools in laboratory tinkering

Tools development and use in neuroscience are doubly guided. On the one hand, research goals, pre-existing theory and concepts determine which information might be relevant to obtain (section 3); on the other hand, experimenters' decision-making and the search for engineering solutions follow requirements for reliable information production (section 4). One remarkable feature of this double conditioning of laboratory tinkering is that both requirements of relevance and reliability, although different, are neither contradictory nor conflicting. On the contrary, they seem to converge productively.

On the one hand, clarity about information's relevance is a valuable asset for planning research. As seen in section 3, however fortuitous and exploratory the project of studying the behaviour of single neurons in the visual cortex may have been at its inception, experimenters' decision-making was largely based on pre-existing theories and concepts. For example, the neuron doctrine defines single cells as relevant experimental variables, thus guiding the experimenter in designing and testing the microelectrode and the advancer. Another example is the concept of "column", which was not a major factor in developing the microelectrode, but it did lead to one of its most productive uses. It led experimenters to record specific zones and to vary the electrodes' position through the advancer device.

On the other hand, data-production processes allow experimenters to assess what to expect from an experimental system in terms of concept- and theory-generation and confirmation. I think that the analyses in sections 3 and 4 offer a strong endorsement of Bickle's thesis about the tertiarity of theory. It is not a question of minimising the role of theory, which philosophers of neuroscience traditionally propose to enhance (Gold and Roskies 2008; Churchland 1986; see also Levenstein et al. 2020). It is about situating our expectations of explaining phenomena in relation to the real capacities to generate and test experimental predictions. According to the view defended in this paper, only experimental systems can develop these capacities. For instance, the concept of "receptive field" pre-exists the tungsten microelectrode, but only once the microelectrode is developed experimenters will be able to operationalising it and generate testable predictions about neurons in the visual cortex. Similarly, the concept of "orientation selectivity" is not analytically contained in the pre-existing concept of "receptive field", but is a result of the "ingenious use" of stimuli. The same should be said about the distinction between simple, complex and hypercomplex cells. Properly testable predictions about the orientation selectivity in columns make sense as long as the experimental system allows investigators to observe correlations between the position of the stimulus on the retina and the controlled advance of the microelectrode obliquely through the cortex. Testable predictions do not precede but result “from the development and ingenious uses of experiment tools” (Bickle 2019; for a case in visual neuroscience see Garrido Wainer et al. 2020).

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