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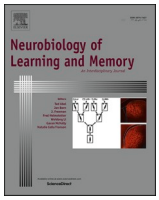

Short communication

A possible mechanism of neural read-out from a molecular engram

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ABSTRACT

What is the physical basis of declarative memory? The predominant view holds that stored information is embedded in the structure of a neural net, that is, in the signs and weights of its synaptic connections. An alternative possibility is that storage and processing are separated, and that the engram is encoded chemically, most probably in the sequence of a nucleic acid. One deterrent to adoption of the latter hypothesis has been the difficulty of envisaging how neural actively could be converted to and from a molecular code. Our purpose here is limited to suggesting how a molecular sequence could be read out from nucleic acid to neural activity by means of nanopores.

1. A molecular engram?

The physical substrate of memory remains unknown. Gold and Glanzman (2021) give a succinct survey of the several theories of the engram that are currently in play. The majority view is that all forms of memory depend on the growth and attenuation of synaptic connections in a neural net, although there is little agreement on whether the unit of memory is a dendritic spine, a cell or a cell assembly (e.g. Abdou et al., 2018; Asok et al., 2019; Choi et al., 2018; Langille and Brown, 2018; Mayford et al., 2012; Roelfsema and Holtmaat, 2018; Ryan and Frankland, 2022). There is, however, an alternative view, that the engram is held in a molecular code (Akhlaghpour, 2022; Gallistel, 2021; Gallistel and Balsam, 2014; Gershman, 2023; Langille and Gallistel, 2020).

The extensive body of experimental evidence that supports the synaptic account is predominantly drawn from studies of fear conditioning and other forms of implicit memory. For the case of human *declarative* memory, however, there is much to recommend a molecular code. Particularly attractive is the possibility that the declarative engram is encoded in nucleic acid, RNA or DNA. The code could be represented by the nucleotide sequence itself – as in the hereditary DNA code – or it could, say, be represented by a pattern of methylation.

The advantages of storage in a molecular code would be several:

(i) The volume occupied by a given engram would be many orders of magnitude smaller than it would be if it were stored in the synaptic connections of a neural net. The compactness of storage in synthetic DNA has independently been exploited in computer science: 10^{18} bytes of information can be stored in one cubic millimeter of DNA (Ceze et al., 2019; Erlich and Zielinski, 2017; Ezekannagha et al., 2022; Hao et al., 2021; Neiman, 1965; Stanley et al., 2020).

(ii) The energy costs of duplicating and maintaining the engram would be much lower.

(iii) Molecular storage, especially in DNA, would be very stable. DNA can survive for thousands of years if it is protected from humidity, irradiation, and air. Allentoft et al. (2012) give a half-life of 521 years at 13.1 °C, on the basis of an analysis of Moa bones that were of varying age but had been preserved under similar circumstances. Conditions are very different in a living cell, but here enzymatic repair mechanisms are present.

(iv) The storage and the processing of information could be separated. This is not the case if memory is embedded in a neural net, that is, in the signs and weightings of the connections between neurons (Gallistel and Balsam, 2014; Langille and Gallistel, 2020; Mollon et al., 2022).

(v) Owing to the complementary nature of DNA, specific engrams could be readily addressed by an oligonucleotide probe if the target DNA carried a unique index sequence (and *similar* memories could be identified by hybridisation if their similarity were reflected in the similarity of the nucleotide sequence.).

2. The problem of conversion between neural and molecular codes

Two traditional problems that face a molecular account of the engram – problems that might be thought almost insuperable – are those

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of how information is encoded and how it is rapidly read out. We here confine ourselves to the problem of read out. Richard Semon, who first introduced the term 'engram', called the hypothetical read-out process 'ecphory' (Schacter et al., 1978; Semon, 1904; 1921). How can the stored information be rapidly retrieved and converted into the neural activities – action potentials or graded potentials – that we believe underlie sensory, cognitive and motor processes?

In the models of Gallistel (2021) and of Akhlaghpour (2022), the storage and the processing are both performed at a molecular level. In a hybrid model, the storage – the passive engram – could be molecular while the cognitive manipulation of the material could be neural. In either case, the problem arises of how the conversion between neural and molecular representations is achieved. Our purpose in this paper is limited to proposing a class of cellular mechanism that could read out a nucleic-acid code and generate a neural representation. The class of model we propose may not prove to correspond to reality, but the example serves to show that a biological read-out from a molecular engram to neural activity is certainly conceivable.

3. A technological analogue

We propose that nature might have developed an analogue of the nanopore technology that is now widely used to sequence DNA (Deamer et al., 2016; Wang et al., 2021) – not only DNA of biological origin but also synthetic DNA that encodes images or text (Lopez et al., 2019).

The man-made system – as developed by Oxford Nanopore Technologies – uses a nanometer-sized protein aperture, or 'nanopore', embedded in a thin, electrically resistant, polymer membrane (Fig. 1, left panel). The channel through the protein has a width of < 1.5 nm. A voltage bias (typically 180 mv) between electrodes on either side of the membrane produces a baseline ionic current through the pore. Single-stranded DNA is driven through the pore from the negative charged side to the positive. A motor protein that binds DNA is used to 'ratchet' the movement of the DNA molecule in steps and at a controlled speed. The motor protein has the secondary function of unwinding double-stranded DNA and allowing only a single strand to be drawn through the nanopore.

The ionic current during the 'translocation' depends on the string of nucleotides that are currently present in the narrow section of the pore (Fig. 1, right panel). So the changes in this current can be decoded (by complex software) to read the nucleotide sequence of the DNA molecule. This is not a trivial task since several bases (~5) may concurrently be contributing to the attenuation of the baseline current. The modulations of current are typically measured in nA.

The nanopore technology allows rather long sequences (>2 megabases) to be sequenced in a continuous read. To improve the accuracy of the sequencing, a so-called 1D method may be used. The two strands of the DNA (called for this purpose the 'template' and the 'complement') are each ligated separately to a so-called 'adapter' molecule and are sequenced independently.

4. Biological nanopores for read-out from a molecular engram?

In the course of evolution, nature has developed a rich variety of biological nanopores, and it is indeed such 'biopores' that have most often been exploited in man-made sequencing systems. Typically, biotechnologists alter the natural protein structures by replacing, adding or deleting amino acids so as to tune the dimensions, charge, hydrophobicity etc. (Deamer et al., 2016; Howorka, 2017). The biopores most often used in man-made systems are pore-forming toxin proteins secreted by pathogenic bacteria: an example is α-hemolysin (α-HL), which causes the cell death of erythrocytes by producing pores on the membrane of the cell that allow uncontrolled movement of critical molecules.

Membrane channels that specifically transport DNA have been studied in detail in prokaryotes (Burton and Dubnau, 2010). For example, in *Bacillus subtilis* and other bacteria, during the natural process of transformation, extracellular DNA is imported and is integrated into the bacterium's genome (Dubnau and Blokesch, 2019). A single-stranded DNA molecule can be moved across the cytoplasmic membrane by the aqueous channel protein ComEC (Burghard-Schrod et al., 2022).

Is there any evidence in mammals for membrane channels that transport nucleic acid? In brain slices from rat, Shi et al. (2007) demonstrated the presence of a channel, previously identified in rat kidney cells, that transports oligonucleotides across a lipid membrane (Hanss et al., 1998; Hanss et al., 2002). The channel consists of two protein subunits: a 45-kDa component that forms the pore and a 36-kDa

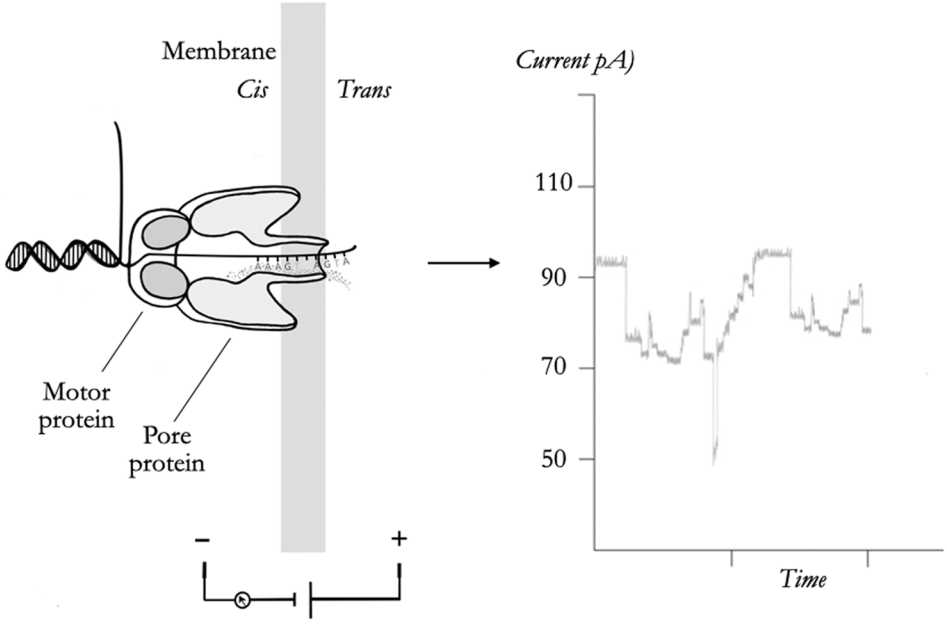

Fig. 1. A generic nanopore. *Left*: Double-stranded DNA is unwound and one strand is drawn through the nanopore. *Right*. The current flowing through the pore varies with the set of nucleotides that are present within the narrow part of the pore at a given time.

regulatory subunit. Antibodies to this channel blocked the uptake of oligonucleotides by brain cells. *In vivo* injection of fluorescein-labelled oligonucleotides into the nucleus accumbens of rats showed clear evidence for uptake by brain cells in the local region.

The 36-kDa regulatory subunit of the channel identified by Hanss *et al* is known to be malate dehydrogenase, and has been shown to be critical for the channel's specificity to oligonucleotides. However, the identity of the 45-kDa protein that forms the pore is not yet known. The channel has been of interest to those working on the therapeutic use of antisense RNA, but the natural function of the channel remains unknown.

The rate of translocation of single-stranded DNA in typical man-made systems is of the order of 450 bases per second. A critical limitation is the temporal resolution of the variations in current. To account for the bit rates that must characterise the recall of human episodic memories, we might suppose that read-out occurs in parallel through multiple channels, distributed between cells or cell processes – and of course, nature has had a long time to optimise both the speed and the signal size. Our default assumption is that the nanopores would be embedded in the cell membrane, but there are other possibilities such as the nuclear envelope (Matzke et al., 2010). The nuclear membrane contains ion channels and transporters, as well as the nuclear pore complexes, which transport RNA to the cytoplasm. In some neurons, fluctuations of the nuclear envelope can induce synchronous spike discharges, probably via Ca^{2+} signalling (Yamashita, 2011).

We conclude that it is not biologically implausible to envisage a nanopore channel that reads out an engram encoded in nucleic acid, converting the molecular sequence to electrical signals.

5. The advantage of single-stranded reading

The nucleic-acid channels underlying transformation in bacteria, and the channel identified in mammals by Hanss *et al*, are specific for single-stranded sequences. If memory were stored in DNA, then single-stranded read-out would have an advantage analogous to the advantage of genetic coding by DNA – the advantage immediately apparent to Watson and Crick (1953): The single-strand that is left behind after read-out, i.e. the strand that does not pass through the pore, can be rebuilt with complementary nucleotides to reconstitute the stable double-stranded engram.

6. DNA or RNA?

Our discussion above has predominantly been in terms of DNA rather than RNA. The greater stability of DNA recommends it as the ultimate seat of the long-term engram, and non-chromosomal DNA is abundantly available, both in cytoplasm and outside the cell (Aucamp et al., 2018). Cytosolic DNA usually serves as a marker of infection, inflammation or aging (Miller et al., 2021), but of interest in the present context is 'brain metabolic DNA', which is modulated when animals learn or are exposed to novel environments (Giuditta et al., 2017; Giuditta et al., 2023).

However, RNA can subserve memory functions in *Aplysia* (Bedecarrats et al., 2018); and mammalian brain cells contain a wide range of types of non-coding RNA, in linear or circular forms, in short or long lengths, and in single- and double-stranded state (Morris and Mattick, 2014; Xu et al., 2021). The circular forms in particular may be relatively stable (Jeck et al., 2013). The exponentially increased abundance of long non-coding RNA in primates and man suggests a critical role in the evolution of the human brain (e.g. Grinman et al., 2019; Mattick, 2011). Many types of RNA are known to affect biological processes by complementary binding to specific DNA or RNA regulatory sites (e.g. Zhang et al., 2019), but for other RNAs the functional role, and the molecular mechanism of action, remain unknown.

If declarative memory is encoded in RNA, there is certainly no shortage of potential codes, since as many as 170 natural modifications of RNA are known, including A-to-I editing (the conversion of adenosine to inosine) and N6-Adenosine methylation (e.g. Boccaletto et al., 2018; Schaffer and Levanon, 2021). However, our limited purpose here is not to consider specific codes, but to propose a generic mechanism for read-out. We note that the Oxford Nanopore technology can be used for direct sequencing of RNA, not only DNA (Garalde et al., 2018). Moreover, man-made nanopore technology has been used explicitly to detect *modifications* of RNA (Leger et al., 2021; Smith et al., 2019; Wang et al., 2022), although complex algorithms are needed in the analysis. Nature has had the advantage of aeons to select modifications and a pore that give strong and unambiguous signals.

The fact remains that RNA is much more labile than DNA: the half-life of RNA is typically measured in hours (Schwanhausser et al., 2011). Circular RNA is more stable (Jeck et al., 2013), but would presumably need to be broken to be read by a nanopore (unless the pore forms around the nucleic acid). However, cells are able to secrete exosomes, the lipid bilayer extra vesicles containing DNAs, mRNAs and non-coding RNAs, protecting them from degradation (e.g. O'Brien et al., 2020; Silva and Melo, 2015). Exosomes circulate in biological fluids and mediate cell communication. It is conceivable that a form of RNA serves as a messenger, carrying information held permanently in a DNA engram. In this case, its nucleotide sequence would be translated not into the amino-acid sequence of a protein but into a specific pattern of signals that could be read-out by a nanopore reader.

7. Is an empirical test possible?

It would be difficult to use the contemporary methods of brain imaging to test a molecular model of declarative memory. For the engram itself must be almost completely passive, requiring little energy expenditure for its maintenance and thus being invisible to imaging methods; and even our proposed read-out mechanism would generate only tiny, and local, signals that would be masked by conventional action potentials and graded potentials. The optogenetic methods that have been so successful in recent animal studies (e.g. Abdou et al., 2018; Liu et al., 2012) are more suited to analysing implicit forms of memory, such as fear conditioning. We suggest, however, that the engram for human declarative memory might be experimentally approached via a genome-wide association study (GWAS) of performance in long-term memory tasks.

There are large individual differences in long-term declarative memory (e.g. LePort et al., 2017; Luria, 1968; Unsworth, 2019). Such variations cannot, of course, all depend on a single polymorphic protein, since performance in long-term memory tasks must depend on many processes of strategy, encoding, storage and retrieval (Jenkins, 1979). Factor analyses of performance have suggested several underlying factors, including one corresponding to retrieval ability or retrieval fluency (Unsworth, 2019). By means of a GWAS in which genomic associations were assessed not only with individual memory tasks but with the factors that emerge from a factor analysis of the phenotypic data, it should be possible to identify genetic polymorphisms that are associated with variations in memory; and these in turn may point to the proteins that underlie declarative memory, including perhaps those used in our postulated nanopore mechanism.

8. Conclusions

Conversion from a molecular signal to an electrical one is intrinsic to nanopore technology. If it proved to be the case that nature long ago invented this method of converting between molecular and electrical signals, then many specific questions would arise: Where are the nanopores located? What is the direction of translocation of the nucleic acid? How is the electrical signal amplified to yield action potentials or graded potentials? What indeed is the actual molecular code? In order to obtain clear electrical signals, are the elements of the code larger than a single nucleotide? Has the code evolved for efficient conversion between neural and molecular representations (Mollon et al., 2022)? And of

course, what is the process of encoding?

Our purpose in this paper is very limited: to remove one salient objection to theories that postulate molecular storage for declarative memory. We hope to have shown that a plausible mechanism can be envisaged for read-out from a molecular storage. Richard Semon in *Die Mneme als erhaltendes Prinzip im Wechsel des organischen Geschehens* (1904; translated 1921) emphasised the identity of the basis of inherited memory and of acquired memory; and he was much criticised for this view (Schacter et al., 1978). If engrams were indeed encoded in nucleic acid, Semon would be vindicated.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data were used for the research described in the article.

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