ACTA NEUROBIOLOGIAE EXPERIMENTALIS

Review Acta Neurobiol Exp 2013, 73: 1–9

Gnostic cells in the 21st century

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In this short review, I revise the notion of gnostic cells posited by Konorski, together with similar arguments by James, Lettvin and Barlow – namely, the idea of pontifical, grandmother and cardinal cells, respectively. I then discuss whether the characteristics of the recently discovered concept cells, i.e. neurons in the human medial temporal lobe with a very high degree of specificity and invariance, fit the conjecture of gnostic or grandmother cells and then discuss the key role of concept cells in memory formation.

INTRODUCTION

More than 40 years ago, in front of a crowded audience of MIT undergrad students, Jerry Lettvin told the fictitious story of Akakhi Akakhievitch, a brilliant though unknown Russian neurosurgeon, who completely erased the concept of "mother" from a subject's brain by ablating each and every single of the several thousand neurons representing it (Barlow 1994, Gross 2002). However, after a first moment of exultation, Akakhievitch reasoned that the concept of "mother" was too subjective and prone to critics among his peers. He then though that grandmothers are more ambiguous and formless and, a patient man, he decided to go for grandmother cells… Hence the name that became popular among neuroscientists for the conception that single neurons can encode concepts like "grandmother", "cat", or "Luke Skywalker".

Lettvin's story ended up triggering a hot debate in neuroscience, but the idea of grandmother cells goes a long way back to the late XIX century. In his acclaimed "Principles of Psychology" (James 1890), William James set the ground of modern psychology and with notable insight described some of the main principles that rule neuroscience nowadays. Among these visionary ideas, and following the principles of "Monadology" by Gottfried Leibniz (according to Leibniz monads are entities that cannot be divided into parts), James wondered how units of thoughts, that are formed of parts, are represented in the brain (James 1890). He speculated that (vol. 1, p. 179):

"(…) among the cells there may be a central or pontifical one to which our consciousness is attached. But the events of all the other cells physically influence this arch-cell; and through producing their joint effects on it, these other cells may be said to 'combine'(…). The physical modifications of the arch-cell thus form a sequence of results (…) the conscious correlates to these physical modifications form a sequence of thoughts or feelings (…)"

Nowadays, the thought of a single "pontifical" neuron as the locus of our consciousness is generally agreed to be blatantly wrong, but James should be given credit for conceiving the idea of a hierarchical representation of brain cells encoding both the whole and the particulars of thoughts, notably, even before Cajal neuron's doctrine. Not least surprising is the fact that shortly after James, Sigmund Freud, most known for his theories that gave rise to psychoanalysis, conceived the idea of "Psy" and "Phi" cells, correlating to perception and memory, respectively (Freud 1953). Cajal himself also saw pyramidal cells in neocortex as the substrate of high level mental functions and called them "psychic cells" (DeFelipe and Jones 1988).

Departing from Cartesian dualism and the division of mind and body, after Cajal's breakthroughs there is no dispute among scientists that behavior is the result of the activity of neurons; but how many are involved in the awareness of a certain concept? James idea of pontifical neurons remained unnoticed but was retak-

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Received 03 June 2013, accepted 11 June 2013

en, to be demolished, in 1940 by Nobel laureate Sir Charles Sherrington (Sherrington 1940). Sherrington wondered whether the convergence of sensory inputs may end up in pontifical nerve-cells, but quickly dismissed this conception and argued instead for a million-fold democracy, or what in our days we know as coarse population coding.

KONORSKI'S VIEWS

The idea of pontifical cells, completely dismissed by Sherrington, was, however, taken very seriously by Polish neurophysiologist Jerzy Konorski in the 1960's, just before the time of Lettvin's famous parable (Konorski 1967). These were quite exciting days in neuroscience, after Hubel and Wiesel's discovery of neurons in primary cortical visual cortex (V1) that fire to local orientations (Hubel and Wiesel 1959) – for example one such neuron would fire to a line at a given orientation in some particular location– and their proposal of a hierarchical organization of visual processing (Hubel and Wiesel 1962, 1965, 1968): neurons in the retina fire to local pixel intensity and connect through the lateral geniculate nucleus of the thalamus to neurons in V1 that fire to oriented lines and these, in turn, connect to neurons in higher visual areas that fire to conjoint features.

Konorski reasoned that this hierarchy of visual processing could carry on to more complex shapes in higher areas, culminating in cells that could represent unitary perceptions, what he called "gnostic neurons" (from the Greek *gnosis*, meaning knowledge) (Konorski 1967). He argued that (p. 74):

"We perceive people, human faces, animals, small objects from nearby, large objects from afar (…). However, neither humans nor animal notice lines, edges, corners, "tongues", or "rods," which were the adequate stimuli for the units so far investigated."

"Having at our disposal the recent data derived from Hubel and Wiesel's experiments, we can extrapolate their findings and explain the origin of perceptions according to the same principles which were found to operate on the lower levels of the afferent systems. In other words, we can assume that perception experienced in humans' and animals' lives, are represented not by the assemblies of units buy by single units in the highest levels of particular analyzers. We shall call these levels gnostic areas and the units responsible for particular perceptions, gnostic units."

Konorski's reasoning was far from a wild guess. It was not only based on an extrapolation of Hubel and Wiesel's hierarchical processing idea, but also on evidence of specific dysfunctions generated by lesion studies in animals and agnosias in humans, which he postulated were generated by lesions or pathologies in the "gnostic area" – i.e. the area in which the Gnostic neurons corresponding to the impaired function reside. He even postulated the existence of neurons in high visual areas that could respond to faces and limbs, which, following his premonition, were found a few years later in the monkey infero-temporal cortex by Charles Gross and colleagues (Gross et al. 1969, Bruce et al. 1981, Gross 2002, 2008).

Face cells in monkeys were indeed taken by Konorski as gnostic neurons (Gross 2002), or in Lettvin's terms, a grandmother cell representation. Moreover, single neurons in the frog retina that acted as feature detectors (which are used by the animal to detect bugs) were previously described by Horace Barlow and Lettvin himself in the 1950's (Barlow 1953, Lettvin et al. 1959, Gross 2002). In the early 70's, Barlow revisited Sherrington's views and offered a more refined version of James' pontifical cells (but far from Sherrington's million-fold democracy), arguing that rather than a single pontifical neuron the brain may use a "college of cardinals" (Barlow 1972) – i.e. a few "cardinal neurons", but not just one – to code for different percepts, what in our days we call a sparse representation (Olshausen and Field 2004) (actually, though seldom recognized, Lettvin and Konorski's conceptions of grandmother or gnostic cells were not that far from Barlow's, as they also explicitly argued that there should be more than 1 such neuron per concept).

Following the discovery of face cells in IT, the challenge was out there; now the quest was to find the gnostic or grandmother cells. Face cells were indeed a good start, but since we can distinguish between different faces that in fact correspond to different people or concepts, now the goal was to find neurons that fire selectively to a particular face, no matter how it is presented. In other words, a grandmother neuron should fire to grandma – seen in front view, in profile, wearing a red hat or weaving a scarf – and not to other people or objects. This quest proved to be unsuccessful and it became generally accepted that face cells fire to several different faces (Gross 1992, 2008, Rolls 1992, Young and Yamane 1992). Furthermore, although it remained

unaltered by simple image transformations (e.g. a change in scale or position of the image), their firing changed dramatically when using different views or 3D rotations of the same face (Logothetis and Sheinberg 1996, Tanaka 1996). It is possible though to distinguish different faces from the activity of a population of these cells (Hung et al. 2005, Kreiman et al. 2006) (e.g. if cell 1 fires to face A and B but not C, and cell 2 fires to B and C but not A, analyzing the firing of both cells together can tell us which face it is) but each individual cell cannot tell on its own which face is presented. The representation is given by the million-fold democracy, it is a coarse population code.

At about this time, very elegant distributed memory models started to emerge (the most popular being the Hopfield network, which, in analogy with a spin glass in statistical mechanics, encodes a given memory by the state of all the neurons) (Hopfield 1982), together with evidence for distributed representations (McClelland et al. 1986, Rumelhart et al. 1986), and the role of oscillations as a way of communication between areas that encode in parallel different aspects of percepts (Gray et al. 1989, Singer and Gray 1995, Engel and Singer 2001). Straw man arguments, together with other seemingly paradoxical inferences, helped to discredit the idea of gnostic or grandmother cells even further (Barlow 1996, Page 2000, Bowers 2009): how can one and only one neuron encode a concept and if so, how we would ever be able to find it? What if this neuron dies? How can we represent different variations of a concept? Moreover, we can clearly distinguish grandma from front view and profile, but there are not enough neurons for all possible variations we can be aware of (an argument known as combinatorial explosion) Harris 1980). So, in spite of descriptions of neurons with very specific responses in different species and areas (for reviews see Barlow 1972, 1994, Page 2000, Bowers 2009), the fate of gnostic or grandmother neurons seemed to be sealed.

CONCEPT CELLS

Epileptic patients with seizures that cannot be controlled with medication may be candidate to epilepsy surgery, a procedure aimed at removing the epileptic focus to cure their epilepsy. The prognosis of the surgical intervention depends on the location of the focus and other clinical factors, but particularly for seizures triggered in the hippocampus and surrounding cortex (what it is known as the medial temporal lobe), this procedure is quite successful (Wieser et al. 2001). The success of these surgeries clearly relies on an accurate delineation of the epileptic focus and in some cases, when the evidence about its localization is not conclusive, these patients may be implanted with intracranial electrodes to record the brain activity during the seizures and then localize the focus (Quesney and Gloor 1985). Patients examined with intracranial recordings may remain in the hospital ward for about a week or two, until a sufficient number of seizures is recorded. This has provided the extraordinary opportunity to record directly from single neurons in the human brain – through electrodes developed at University of California Los Angeles (Fried et al. 1999, Engel et al. 2005) – while the patients do various tasks, like watching different images in a computer screen. First studies showed neuronal responses to words, faces and conjoint stimulus features, such as gender and facial expressions (Fried et al. 1997), and later studies showed responses to the category of the stimuli (animals, places, etc.) (Kreiman et al. 2000a), even when the subject imagined the particular stimulus that triggered the cell's responses (Kreiman et al. 2000b) (e.g. a single neuron fired when the subject viewed or imagined the picture of a person). Several technical improvements then allowed recording many more neurons (Quian Quiroga et al. 2005, 2007, Quian Quiroga 2012), particularly those that are silent at baseline and fire very strongly when a specific stimulus is shown. For example, one such neuron in the hippocampus of a patient fired very strongly to a picture of actress Jennifer Aniston (Quian Quiroga et al. 2005). But was this neuron really firing to Jennifer Aniston or to something specific about the particular picture used? The experiment was then repeated but now using 7 different pictures of Aniston. The result was striking: the neuron fired to all pictures of Jennifer Aniston and to none of the other 80 pictures displayed (including several images of other actors, celebrities, places, animals, etc.) (Quian Quiroga et al. 2005). An hippocampal neuron in another patient fired to different pictures of actress Halle Berry and even to her name written in the computer screen (and did not respond to other persons, objects or names); another neuron fired selectively to different pictures of Oprah Winfrey and to her name written in the screen and also pronounced by a

computer synthetized voice; and yet another one fired to pictures of Luke Skywalker (the character of the movie "Star Wars") and to his written and spoken name (see Fig. 1), and so on (Quian Quiroga et al. 2009, Quian Quiroga 2012).

GNOSTIC CELLS REVISITED

The finding of "Jennifer Aniston" neurons in the human hippocampus brought back to light the issue of gnostic cells. Were these the long awaited gnostic (or grandmother) cells, that means, single neurons firing to individual concepts? To address this question we should first consider possible definitions of what these cells are (Quian Quiroga and Kreiman 2010a,b). The first, extreme version of grandmother cell coding is that one and only one neuron encodes one and only one concept. But neither Konorski, Lettvin or Barlow ever say that it was only one neuron per concept. On the contrary, they explicitly said that there should be many. Indeed, just a bit of redundancy avoids critics as: what would happen if this neuron dies? (Nothing, because they are other neurons encoding the same concept.) In the case described above, if a neuron firing to Jennifer Aniston was found, then there had to be more because the chance of finding the one and only among billions is neglectable (Waydo et al. 2006, Quian Quiroga et al. 2008). Discarded this extreme version, we can consider a second definition, namely, that many neurons fire to one and only one concept. This is in principle possible, but very difficult (if not impossible) to prove. The problem is that if a neuron fires only to Jennifer Aniston during an experiment, we cannot rule out that it could have also fired to some other thing that was not shown in the experiment. In other words, it is not possible to try every possible concept to prove that the neuron fires to Jennifer Aniston and nothing else. In fact, the opposite is often the case, as some of these neurons tend to fire to more than one concept (Quian Quiroga et al. 2009, Quian Quiroga and Kreiman 2010a, Quian Quiroga 2012). For example, in an experiment performed the next day, the neuron that fired to Jennifer Aniston also responded to Lisa Kudrow (Quian Quiroga et al. 2005), a costar in the TV series "Friends" (that catapulted both to fame). The neuron that responded to Luke Skywalker also fired to Yoda, another Jedi from "Star Wars" (see Fig. 1); another neuron fired to two basketball players; another one to the author of this article and three other colleagues that interacted with the patient at UCLA, and so on (Quian Quiroga et al. 2009, Quian Quiroga and Kreiman 2010a, Quian Quiroga 2012). But even then, one can still argue that these neurons could be taken as gnostic or grandmother cells. It is just that they respond to broader concepts, namely, the two blond girls from "Friends", the Jedis from "Star Wars", the basketball

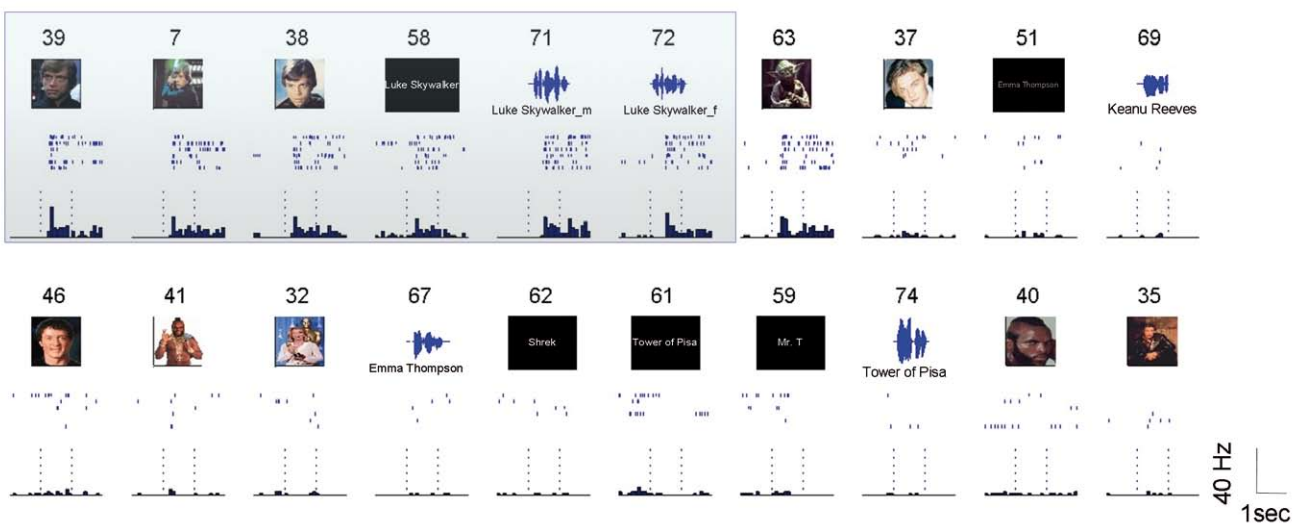

Fig. 1. A neuron in the entorhinal cortex of a patient that responded to different pictures of "Star Wars" character "Luke Skywalker" and even to his name written in a computer screen (stimulus 58) and pronounced by a male and female synthetized voice (stimuli 71 and 72, respectively). Note that the neuron also responded to a picture of Yoda (stimulus 63) – the only picture of Yoda presented in this experiment – another character of "Star Wars". For space reasons the largest 20 (out of 76) responses are shown. Vertical dotted lines mark stimulus onset and offset, 1 s apart.

players, or the scientists doing experiments with the patient. However, the discussion of whether these neurons should be taken as gnostic cells or not then turns into a semantic issue.

So, let's then leave aside for now Akakhievitch's lore and James notion of pontifical cells, and highlight a few aspects of these "Jennifer Aniston neurons" or "concept cells", which are key to understand their function. First, their responses are very selective, or in other words, these neurons fire to a very small proportion of the presented stimuli (Quian Quiroga et al. 2007). Second, they show invariance, in the sense that the neuron firing to a person or object does not fire to visual features of a particular picture, but to different pictures of the same person or object and even to its written or spoken name. Third, these neurons can fire to more than one thing, but if this is the case, these things are closely related (the two Jedis, the experimenters, etc.) (Quian Quiroga and Kreiman 2010a, Quian Quiroga 2012).

FROM DISTRIBUTED TO SPARSE CODING

As we move along the pathway of brain areas that lead to the recognition of what is in front of us, neurons tend to fire selectively to more complex features (Barlow 1972, Logothetis and Sheinberg 1996, Tanaka 1996). A neuron in early visual areas fires to the localized details that compose the image. This neuron does not know if this detail is part of a face, a cat or the Tower of Pisa. For this, we need to consider the activity of many of these neurons and put together the information of many details. The information in each neuron is implicit. Moreover, if we slightly change the picture, the local features, and therefore the firing of these neurons, will change. A neuron in higher visual areas, in turn, may fire to faces and not to local details (Logothetis and Sheinberg 1996, Tanaka 1996, Gross 2008). So, this neuron will indeed tell us that we are seeing a face and not the Tower of Pisa. Now the information is explicit. Moreover, if we slightly change the picture, we will change some local features, but these neurons don't care about this and, within some limits, their firing will remain more or less the same (Logothetis and Sheinberg 1996, Tanaka 1996, Gross 2008). Neurons in high-level visual areas send their information to the medial temporal lobe (the hippocampus, amygdala, and the entorhinal, perirhinal and parahippocampal cortices) (Saleem and Tanaka 1996, Suzuki 1996, Lavenex and Amaral 2000), which develop this process even further. A neuron in the hippocampus does not fire to any face, but to a particular person, irrespective of visual details and even to the person's name (Quian Quiroga et al. 2005, 2009, Quian Quiroga 2012).

As we argued above, we cannot assert that one-and-only-one neuron fires to a particular concept. Granted, it is not one, but will they be dozens, thousands or perhaps millions? In other words, how sparse is the representation in the medial temporal lobe? Clearly we cannot measure this directly, as we don't record from all neurons in this area, but using some statistical arguments we can provide a good estimation (Waydo et al. 2006). Considering that there are approximately a billion neurons in the medial temporal lobe and that in a given experiment we record from up to hundred, of which about 15 will respond to at least one of the approximately hundred pictures presented, it can be estimated that a given concept is represented by about a million neurons or less, maybe much less… This number should indeed be taken as an upper estimation because typically pictures of things that are very familiar to the patients are used, for whom there is a higher probability of finding responses (Viskontas et al. 2009) – i.e. they are represented by more neurons compared to non-familiar things. Moreover, the neurons with the highest degree of sparseness are less likely to be detected (unless we happen to show the right stimulus).

Let's now get back to the problem of combinatorial explosion. Given the specificity of the responses in the medial temporal lobe, do we have enough neurons to represent all possible concepts and their variations? The key aspect here is that along the pathway processing visual information there is not only an increase of selectivity but also of invariance (Ison and Quian Quiroga 2008, Quian Quiroga 2012). Neurons in the medial temporal lobe just don't care about different instances of the same concept, they fire to the concept no matter how it's presented, being a particular picture or its name (Quian Quiroga et al. 2009).

Intelligence is expensive. Our brains hardly weights 2–3% or our total body mass but use 20% of the total oxygen consumption and hence of body energy (Raichle and Gusnard 2002). It was estimated that due to these metabolic constrains, only less than 1% of our brain can be active at a given time (Lennie 2003). So, the

best the brain can do is to represent each concept with a relatively low number of neurons (Levy and Baxter 1996, Attwell and Laughlin 2001, Olshausen and Field 2004). However, the information about complex sensory stimuli, like a face, has to be encoded in a distributed manner in early sensory areas, given the way that external physical stimuli impinge on sensory receptors (Barlow 1972, Barlow et al. 2009): the sight of the face triggers the firing of relatively large number of neurons in the retina and early visual areas, encoding local details of the received information. So, the nature of sensory stimuli imposes a more distributed representation in early sensory areas and metabolic constrains push towards a sparser representation in higher areas, which indeed has several advantages, as we will see below.

WHY DO WE HAVE CONCEPT CELLS?

We now focus on the function of concept cells and why they fire in such a remarkable way. Are they involved in visual perception; are they instead storing memories? Evidence from patient H.M. (Scoville and Milner 1957, Milner et al. 1968, Squire 2009) and lesion studies in animals (Squire and Zola-Morgan 1991, Squire et al. 2004) have clearly show that the medial temporal lobe is not necessary for these two functions, but it is rather critical for transferring short-term memories (things we remember for a few minutes) into long term memories (things we remember for hours, days or years). Therefore, concept cells give an explicit representation of what is in our awareness –the flow of the present, whatever is triggered by visual perception or internal recall processes – to create long-term memories that will later consolidate into cortical areas. In particular, the Jennifer Aniston neuron found in one patient was not necessary to recognize her or to remember who she is, but it is critical to bring Jennifer Aniston into awareness for creating new links and memories, such as remembering seeing her picture in the hospital ward.

Why then such a sparse and invariant representation? We tend to abstract concepts and forget details. We don't need or want to remember every detail of whatever happens to us. If we fortuitously meet somebody we know in a café, weeks later we will likely remember this encounter but not exactly how this person looked like that day or what he was wearing. The level of abstraction is subjective and it depends on the relevance that the concept has and how we would like to store it in memory: our dog may be just another dog for somebody else but it is a specific individual for us. Not surprisingly, concept cells tend to fire to familiar things (Viskontas et al. 2009), those that the subjects mind to store in memory. Surely, when we met the person we knew in the café we would have seen many other people, but we won't remember any of them because they were not relevant; we didn't have concept cells firing to them. Memories are based on creating this type of abstractions and links between different concepts. Weeks after the encounter, we will remember the person we met, the café, perhaps the topic of some conversation and few other things; a handful of concepts that we will link together for later remembering the salient facts of this encounter (Quian Quiroga 2012).

More than a century ago, James noticed that memories are based on associations, links between concepts (James 1890). Therefore, it makes perfect sense that concept cells sometimes fire to associated concepts (see example in Fig. 1). These are represented by different cell assemblies, and if some are related, part of the neurons encoding one concept may also fire to the other one, thus giving a neural substrate for how things can be associated and how we can go for one concept to the other (Quian Quiroga 2012). This simple mechanism could be the neural substrate for the creation of episodic memories (memories of events) or the flow of consciousness, going spontaneously from one concept to the other. A similar process may also create the link between aspects of the same concept stored in different cortical areas, bringing together the *qualia*, like the smell, shape, color and texture of a rose.

It is then clear the advantages of a conceptual representation for memory functions, but why does it have to be sparse and explicit, so close to a grandmother cell coding? Modeling studies give a compelling answer. The general idea is quite simple. Imagine a distributed representation for the person we met in the café with neurons coding for different minute features, and another distributed representation for the café itself. Making a link between these two concepts would require making links between the different details representing each concept, but without mixing them up with others. Creating such links with distributed representations is very slow (it requires several presenta-

tions of the stimuli) and leads to interference (mixing up memories) (Willshaw et al. 1969, Rolls and Treves 1990, McClelland et al. 1995, McClelland 1996, O'Reilly and Norman 2002). Establishing such links with sparse networks is, on the contrary, very fast and easy to implement (Marr 1971, McClelland et al. 1995, 1996, O'Reilly and Norman 2002) – as it is in real life – and it just requires creating a few links between the assemblies representing each concept, through synaptic plasticity (Hebb 1949).

Distributed representations are very good for feature extraction and generalization, which are key ingredients for visual perception. So, this may explain why the brain uses a distributed coding for visual perception and a sparse one for memory functions (McClelland et al. 1995, O'Reilly and Norman 2002).

CONCLUSION

Concept cells are the link between perception and memory; they give an abstract and sparse representation of semantic knowledge that constitutes the building blocks for declarative memory functions (Quian Quiroga et al. 2008, 2013, Quian Quiroga 2012). So, concept cells may then be the neural base for our thoughts, for leaving aside countless details and extracting meaning, for creating new associations and memories. They encode what is critical to retain from our experiences. As Jorge Luis Borges, the acclaimed Argentinean writer, once said: "to think is to forget differences, to generalize, to abstract (...)". (Borges 1944). Concept cells are not quite like the gnostic cells that Konorski once envisioned but they may be a key neural substrate for the power of human reasoning.

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