Humanized FoxP2 and the timing of habits

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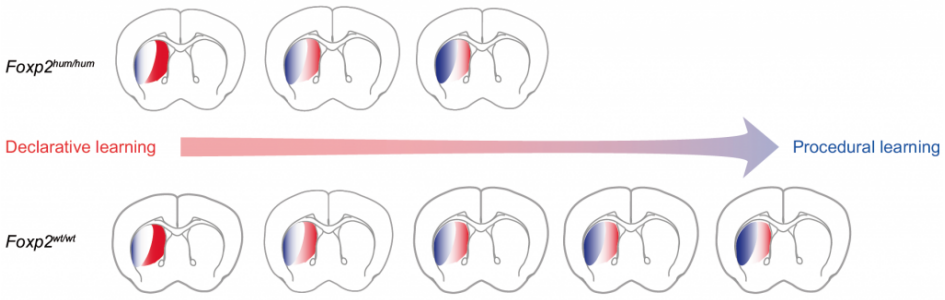


Last week, Elizabeth Pennisi asked me to comment on the recent paper from Schreiweis *et al.* entitled "Humanized FoxP2 accelerates learning by enhancing transitions from declarative to procedural performance". Since I don't know how much, if anything, of my answers to her questions will end up in her article, I thought I might expand my answer into a post about this very interesting work.

As the title implies, Schreiweis *et al.* have tested transgenic mice in which the mouse version of the language-related gene FoxP2 was replaced with the human version. They found that the timing of when repeated behaviors become stereotypic is altered, such that the behaviors become stereotypic earlier in the humanized mice than in the unaltered animals.

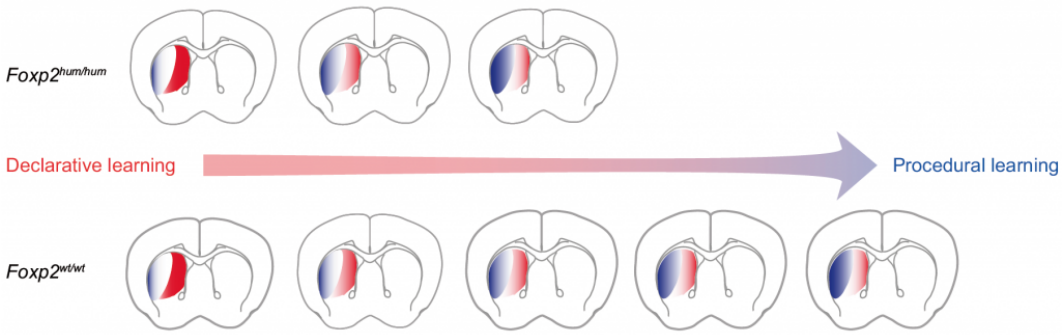
Importantly, this was only observed in tasks where two learning systems were engaged simultaneously. In the literature, there are several accounts of how to label these learning systems. In vertebrate learning they are often referred to as procedural vs. declarative (also in Schreiweis *et al.*), in animal navigation many authors refer to them by allocentric vs. egocentric, and in *Drosophila* fruit flies we have coined the terms world- vs. self-learning. The gist behind these word pairs is that brains as different as those from insects and mammals seem to adhere to a common functional organization that makes a very fundamental distinction between self and non-self on various levels. Of relevance to the current research is that external cues are treated by different brain regions and learning of relationships among external cues is mediated by different molecular processes than the internal processes controlling behavior. Hence our distinction between world- and self-learning.

In situations where both world- and self-learning can occur simultaneously, world-learning commonly dominates in the first phases of training, while self-learning kicks in later. There is converging evidence from vertebrates and invertebrates suggesting that this staggering is probably accomplished by inhibitory connections from circuits engaged in world-learning slowing down the circuits involved in self-learning. Thus, it is this negotiation between self- and world-learning which provides us with time to practice our skills before they become automatic. One may also say that this negotiation is the reason why it takes time (and how much time it takes) to form habits. I've written a longer account of this negotiation on occasion of the poster publication of some of the Schreiweis *et al.* work in 2011.

The recently published work by Schreiweis *et al.* now contains both molecular genetic and physiological results in addition to the behavioral data. It adds weight to the so-called 'motor-learning hypothesis' that came up some time around 2006/7 or thereabout. This hypothesis posits that FoxP2 is mainly involved in the motor, or speech component of language, i.e., learning to control the muscles in the lips, tongue, voice chords, etc. in order to articulate syllables and words.The movements of these organs have to become stereotypic in order to reliably produce understandable language and the main experimental paradigms for this stereotypization of behavior (independent of language) have been procedural learning and habit formation. This work provides further evidence that indeed FoxP2 is an important component of the learning process that leads to automatic, stereotypic behavior.

In particular, it suggests that FoxP2 is involved in the control of the process of stereotypization, i.e., at what point the behavior shifts from being flexible, to becoming more rigid. Until this work, the evidence from vertebrates and invertebrates has pointed to FoxP genes to be involved in the automatization of behavior. Now, this evidence is extended to also – at least in mammals – include the negotiation process, which I don't think anybody had on the radar thus far.

One of the most interesting mechanistic questions that derive from the fact that these mice only showed an effect on the negotiation between the two learning systems (and not on the individual systems when isolated), is how this negotiation takes place. Again, converging evidence from invertebrates and vertebrates points towards inhibitory connections from the world-learning processes keeping a break on the self-learning processes. Is FoxP directly affecting these inhibitory connections, or is it just subtly increasing the relative strength of the procedural/self mechanism, such that it cannot be detected in individual experiments where the components have been isolated, but only in experiments where the negotiation actually takes place? The physiological results by Schreiweis et al. point towards the latter: induction of long term depression (LTD) in the dorsolateral, but not the dorsomedial striatum is enhanced in the humanized mice – and the dorsolateral striatum is the region thought to be involved in self-learning, while some world-learning processes have been localized to the dorsomedial striatum.



Mice with the humanized version of FoxP2 form habits earlier and this might be due to earlier formation of LTD in the dorsolateral striatum. (Fig. S7 in Schreiweis *et al.*)

The generation of these humanized mice was a particularly cool aspect of the work. Compared to other, more common transgenic manipulations (e.g. knock-outs), this humanization of FoxP2 is a rather sophisticated and subtle alteration with rather nuanced but nevertheless very exciting consequences. Many of the more drastic FoxP manipulations are homozygous lethal and since there is evidence for positive selection of the human variant, it was very straightforward to try and see what the human variant would do in an organism that doesn't normally express this version. Moreover, such a subtle alteration may uncover more subtle roles of FoxP than the cruder manipulations have been able to. In fact, the most specific behavioral consequences of any gene manipulation have commonly been the most subtle of genetic manipulations. Therefore, the scientific value of this manipulation extends far beyond the fact that it mimics the human gene.

One needs to keep in mind, though, that it was only the structure of the protein that was humanized, the regulatory region of the gene was not altered, i.e., the putative expression pattern of the humanized FoxP2 gene is still that of the mouse version (and I don't know how different the human regulatory region is from the mouse one – in fact, I'm not sure if we have full knowledge about the regulatory region of FoxP2, yet).

Thus, it is quite amazing that these mice showed any difference at all to WT mice, subtle as these differences may be perceived to be.

On a wider perspective, this work adds to our growing understanding of the relation between learning and language acquisition. Schreiweis *et al.*'s results fall very nicely within a string of recent work suggesting that a major component of language acquisition is based on a form of learning called operant conditioning. The debate about the relevance of this form of learning for language is at the core of the idea history of neuroscience and psychology. In 1957, BF Skinner published "Verbal Behavior" in which he made the sweeping claim that language was essentially acquired via operant learning.

Two years later, Noam Chomsky took Skinner to task in what would become one of the cornerstones in the fall of behaviorism and the rise of cognitive neuroscience and with it, of course, Chomsky's rise to fame as one of the US' leading intellectuals.

If one can summarize Chomsky's massive (32 pages) book review in a single sentence, it might be: "it may look like operant learning, but you don't have any evidence". Instead, Chomsky went on to famously propose that we all have inborn language acquisition devices as well as 'universal grammar'. Of course, Chomsky also did not provide any evidence, either.In the absence of any evidence on either side, Chomsky's outstanding rhetorical skills prevailed and changed nearly all of psychology and neuroscience for the coming 5 decades until this day (I'm simplifying and exaggerating somewhat, for the sake of brevity and argument).

In the last few years, evidence has accumulated not only that the concept of universal grammar likely is untenable, but also that indeed operant learning (and especially the form of operant learning called motor learning) is an important if not crucial component of language acquisition, in particular the speech component of language. For instance, *FoxP* manipulations in flies specifically affect operant self-learning, but not other forms of learning. Thus, the currently available evidence points towards an ancestral FoxP function in self-learning, a function that is not only conserved in humans, but one that has been further honed by evolution to allow for the acquisition of language.This work by Schreiweis *et al*. falls neatly within this last string of publications tilting the outcome of this long-standing debate more and more in Skinner's favor.

As we don't know the exact mechanism by which the negotiation between self- and world-learning processes takes place, one can only speculate what advantage the current human version of the FoxP2 gene might have conferred. One interesting aspect here might be that it may have been critical for the evolution of language to speed up the stereotypization of certain orofacial movements during the first attempts to articulate.

A further, even more tentative speculation might be that this speeding up was adaptive, because it allowed more effective communication between parents and their infants, at an earlier time point in the development of the child, when it was beneficial for the vulnerable infant to convey its status in a more nuanced way than just crying to its caregivers. In this way, children which were able to speak earlier may have had a survival advantage over those that spoke later.But then again, at this time point, such speculations are merely just so stories.

On a personal note, being so used to data mostly falsifying my hypotheses over the last 20 years, it makes me quite nervous that now in this particular research field, everything seems to fit so well together. If something fits so well to one's ideas, one should be especially cautious and (beware of confirmation bias!), think hard to make doubly sure that the next experiments are designed such that they can easily yield results that contradict the current hypothesis, more so than usual.

And on a side note, it is quite an irony that three years ago a reviewer (for the same journal that now published his work, PNAS) heavily criticized our essentially analogous conclusions. Now, three years later, PNAS is finally ready to publish work that supports the motor hypothesis.

Schreiweis, C., Bornschein, U., Burguiere, E., Kerimoglu, C., Schreiter, S., Dannemann, M., Goyal, S., Rea, E., French, C., Puliyadi, R., Groszer, M., Fisher, S., Mundry, R., Winter, C., Hevers, W., Paabo, S., Enard, W., & Graybiel, A. (2014). Humanized Foxp2 accelerates learning by enhancing transitions from declarative to procedural performance *Proceedings of the National Academy of Sciences* DOI: 10.1073/pnas.1414542111