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FOXP2 Mutations and the Dorsal Striatum: FOXP2's Effect on Striatal Activity, Genetic Habit Formation, and Striatal Plasticity

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ABSTRACT

Habit formation, or the transitioning of behaviors into habits, is a phenomenon that has been a point of interest for many studies in recent years. The striatum, a key hub of habit formation, has been at the center of habit-related research, with the current consensus portraying the striatum as a crucial point in transforming learning into routine habits. The FOXP2 gene, a gene once known for its association with language learning and speech mutations, were found to have a profound impact on the striatum's ability to chunk and organize efficient habits. This review aims to put these various factors that contribute to striatal habit formation into conversation. We will also go over future possibilities regarding FOXP2 mutation application into drug addiction, as well as investigate potential reasons behind the effects of some FOXP2 mutations and the potentiation of habit formation.

Introduction

The striatum is a part of the basal ganglia, a region of the brain primarily associated with voluntary movement. The striatum itself is a hub for movement, behavior, and learning. The ventral side of the striatum specifically concerns itself with learning, and understanding the value of reward. The dorsal striatum is more procedural, and can be seen as the reward/outcome-independent, habit-driven section of the striatum [1, 3]. The striatum works through consolidating actions into chunks, and expediting actions once they have been repeated enough [2]. The moment of transition from learning to habit, from ventral to dorsal striatum, is a key focus of this review.

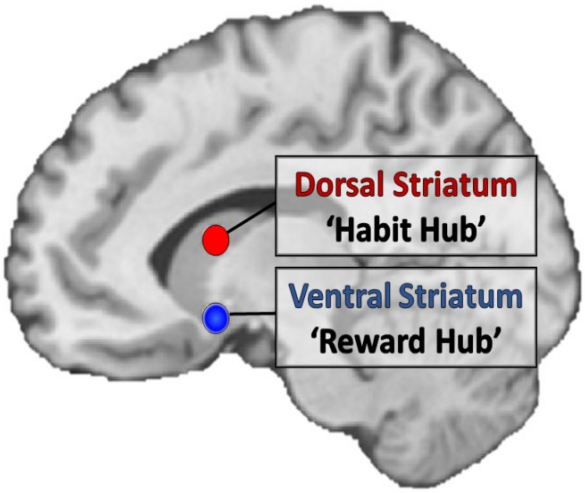

Figure 1. The relative location of the Dorsal and Ventral Striatum in regards to the overall brain.

FOXP2 is a transcription factor that encodes instructions for the protein Forkhead Box P2, which can in turn modulate many other genes' activities, particularly regarding speech and language. A particular series of studies on an extensive family named "KE" resulted in the discovery of FOXP2, where this gene was linked to language and speech [4]. A point mutation in the FOXP2 gene had resulted in cases of Developmental verbal dysphasia (DVD) and Childhood Apraxia of Speech (CAS) in the KE family [5, 15]. Later studies showed that FOXP2 has significant impacts on the striatum during language learning processes as well [4, 16]. FOXP2 was seen to have a profound impact on habit formation and behavior consolidation [5]. Thus, we will aim to link the exact effects of FOXP2 on striatal activity during habit formation, and address each component that is affected by FOXP2's interaction with the striatum. In this review, more light will be shed light on FOXP2's abilities within the brain, not just as a language-learning gene but as a gene that can potentially impact everyday habits.

Dorsal Striatal Modulations Regarding Habits and Learning

FOXP2 Mutations and Dorsolateral Striatal Activity

Various studies have shown the impact of different FOXP2 mutations on Dorsal Striatal activity, which has delineated a key pattern regarding FOXP2 and the striatum [5, 6, 13].

It has been established that the FOXP2 gene in humans is unique, separated by 2 substitution mutations to its closest resemblance [24]. There has been evidence suggesting that the idiosyncrasy of humanized FOXP2 could be traced to our immensely complex language structures.

Schreiweis & Bornschein, aimed to figure out the exact implications of human-specific FOXP2 on learning abilities of mice [6]. To do this, mice with homozygous humanized FOXP2 ($FOXP2^{hum/hum}$) were generated. These mice were found to prefer procedural decision making as opposed to declarative decision making. Specifically, mice that were administered humanized FOXP2 showed an enhancement in the transitioning from declarative/place-based learning to procedural/response-based learning during striatum-dependent habit learning (Fig 2).

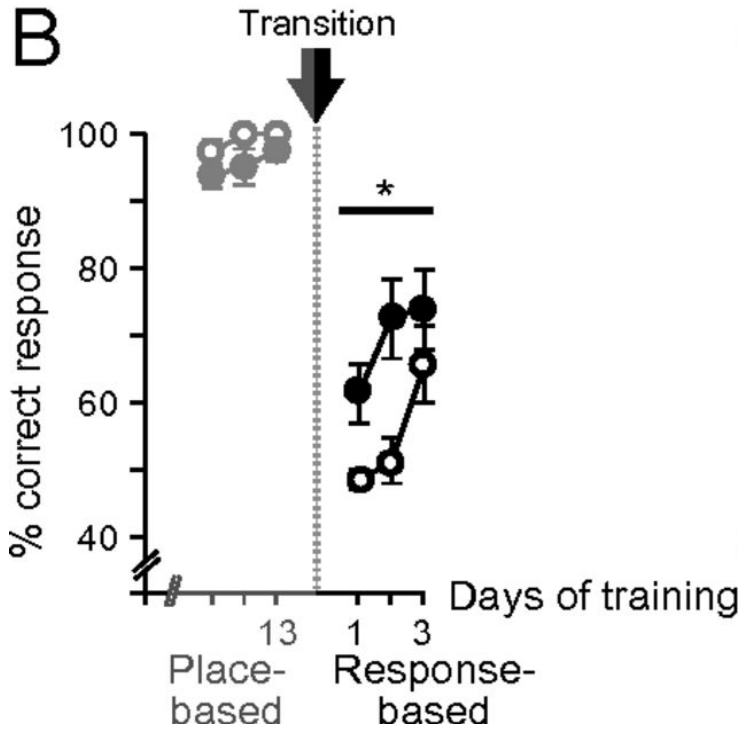

Figure 2. Foxp2hum/hum mice exhibit enhanced ability to make transitions from a declarative to a procedural mode of learning [6]. Average percent correct responses (±SEM) for Foxp2hum/hum (filled dots) and Foxp2wt/wt (open dots) mice successively trained on the two cross-maze task versions and tested on the switch to response-based/procedural learning.

Notably, the humanized FOXP2 was found to decrease the competition between the declarative and procedural learning centers in the striatum. This decrease in active competition induced by humanized FOXP2 facilitated the transition from declarative to procedural learning [19].

In another study by C. A. French and X. Jin, a mouse line named FOXP2-R552H/+ was generated with a point mutation in the FOXP2 gene identical to the one the KE family had [5, 4]. Mice in the FOXP2-R552H/+ line had an increase in striatal activity during acquisition of motor skills, which interestingly led to slower striatal functioning. Although the correlation is not completely certain, the increased firing rates in the certain neurons, known as Medium Spiny Neurons (MSNs), of the striatum is thought to result in collateral inhibition, resulting in an attenuation in plasticity [5].

These results suggest competition between areas and neurons of the striatum actually has a negative correlation with actual functioning. Furthermore, this shows that FOXP2 not only functions as a language-developing gene, but also has a profound impact on striatal activity that can influence motor skills and coordination within the brian. Further research regarding humanized FOXP2 in non-murine mammals may reveal additional insight on humanized FOXP2's idiosyncrasy, and give a clearer view on FOXP2's role in the human striatum.

The Genetic Promoters Regarding Habit Formation in the Dorsolateral Striatum

Histone deacetylase (HDAC) are enzymes that are known for their impact on gene expression [7]. HDAC works by removing the acetyl groups on the tails of histones, and this deacetylation results in a more compact chromatid, resulting in repressed transcription of genes. A greater insight into HDAC's role in the striatum could provide more understanding of FOXP2's underlying workings and correlations with HDAC.

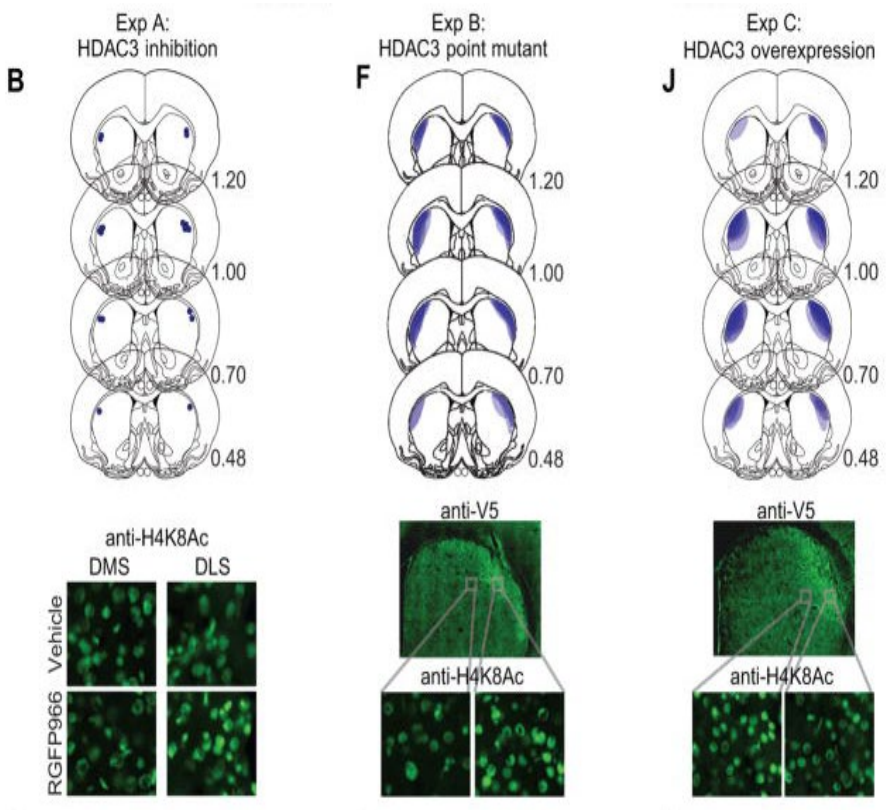

Figure 3. Effect of HDAC3 manipulation in dorsolateral striatum on habit formation [8]. *Top*, a sketch of where injections occurred. *Bottom*, representative immunofluorescent images of H4K8Ac in the Dorsomedial (left) and Dorsolateral (right) striatum.

In a study by M. Malvaez and V.Y. Greenfield, mice with inhibited HDAC3 (a class of HDAC found in the dorsolateral striatum) were found to have accelerated habit formation [8]. HDAC3 activity in the dorsal striatum, specifically the Dorsolateral Striatum (DLS), was observed to significantly impact its functions. Using histone marker H4K8Ac, researchers were able to track two important experimental groups: one of mice with a HDAC point mutation called HDAC(Y298H) given before instrumental conditioning, and another group of mice given Sodium Butyrate, an HDAC inhibitor, after the training process [18, 20] (Fig 3). In both cases, the mutation and the inhibition caused habits to form quicker and take over the learning process. It was found that deacetylation regulates the gene expression of certain specific points that encoded for a very specific type of long-term memory: habit [9, 11].

Specific genes were restricted from expressing when HDAC was engaged. HDAC acts as a regulator, or "brake", for habit formation during early learning when specific training is needed, but disengages when habits start to form with overtraining [21]. The inhibition of HDAC allows the DNA to be expressed without repression, which can lead to habit takeover early in the learning process.

The genetic promoters and habit-driving genes found through HDAC3 could help reveal a future area of study regarding FOXP2 and these habit-potentiating genes. Further research into other Lysine Deacetylases (KDACs), which HDAC is a part of, could also shine more light onto the results.

Overall, the HDAC findings show how specifically the Dorsolateral Striatum accounts for much of habit formation. The genes of interest that potentiate habit formation early on in the learning stage are also a very noteworthy area of research.

FOXP2 Mutations and Long-Term Depression in the Dorsolateral Striatum

Long Term Potentiation (LTP), and its inverse Long Term Depression (LTD), are two processes crucial for neuroplasticity. FOXP2 has been consistently shown to have a profound effect on AMPA and NMDA receptors involved in LTP and LTD [14]. As communication across a synapse potentiates NMDA receptors to increase the number of AMPA receptors, the neural communication is further facilitated. Yet LTD, the attenuation of this process, is induced significantly in both FOXP2$^{hum/hum}$ and FOXP2$^{S321X/+}$.

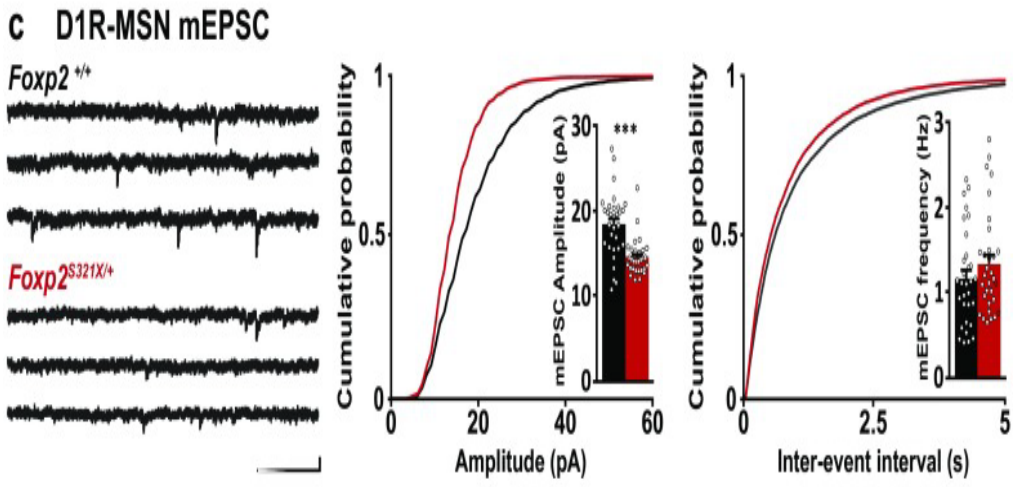

Figure 4. Foxp2 is predominantly expressed in D1R-MSNs in dorsolateral striatum and affects synaptic activity [13]. D1R-MSN mEPSC amplitude is decreased with FOXP2$^{S321/+}$.

In a crucial study on FOXP2 and GABA by J. v. Rhijn and S. E. Fisher, it was found that a mouse line with reduced FOXP2, FOXP2$^{S321X/+}$, had a decrease of LTP [12, 13]. Researchers were able to measure AMPA receptor activity by the tiny current mEPSC. Newborns with the mutation displayed reduced current amplitudes on excitatory receptors D1R-MSNs. Furthermore, the FOXP2$^{S321X/+}$ mice were found to have NMDA receptor currents also reduced within the D1R-MSNs. FOXP2$^{S321X/+}$'s attenuating effect on both of their currents shows that FOXP2 reduction has a negative effect on excitatory synaptic communications in the D1R-MSNs (Fig 4).

Interestingly, the humanized FOXP2 discussed in previous sections, was also found to have an effect on the experimental mice in terms of LTD within the MSNs as well [6]. Researchers used two different levels of depolarizations to induce LTD [23]. These depolarizations act on the DLS to induce LTD, and it was observed that when given severe depolarization, both FOXP2$^{hum/hum}$ mice and the genotypes had a similar level of LTD. However, when given mild depolarization, the FOXP2$^{hum/hum}$ mice displayed a greater amount of LTD. This suggests that FOXP2$^{hum/hum}$ mice can induce LTD more easily than genotype mice within the DLS.

When given a D2R antagonist, the inducible LTD disappeared from the FOXP2$^{hum/hum}$ mice, suggesting the inhibitory D2 receptors are the main receptors in FOXP2$^{hum/hum}$'s inducible LTD mechanism, contrasting FOXP2$^{S321X/+}$ mice's D1R modulations.

The FOXP2$^{S321x/+}$ and FOXP2$^{hum/hum}$ line's roles in inhibitory modulation within mice's dorsolateral striatum, especially in the facilitation of LTD and the inhibition of LTP, draws a key parallel between these two mutations. However, the difference between reduced FOXP2's effect on D1 receptors versus humanized FOXP2's effect on D2 receptors is important to note. Overall, the results of these studies reveal FOXP2's crucial role in the biological aspect

of neuroplasticity within the brain. This showcases an even further extension into how deeply correlated FOXP2 and learning are. LTD and inhibition of striatal habit formation could also be put into research regarding addiction.

Discussion

We have established that there are many different factors that influence the striatum and habit formation, including a vast number of FOXP2 mutations and HDAC. FOXP2 has been shown to not only be a language-learning gene, but a gene that can change levels of striatal activity, induce LTD, and control habit formation through the Dorsal Striatum. The implications around FOXP2's effect on habits and learning are great, as it could lead to a greater understanding of human learning phenomenon within the brain. In addition, FOXP2's influence on LTD of certain receptors shines light on possible research regarding dopamine circuits and neuroplasticity.

However, perhaps most importantly, the discussion of FOXP2's effect on habit formation brings up a point of possible research regarding addiction. It has been shown that in research, severe addictions rely on the same striatal chunking habits as regular routine [10, 22]. For example, heroin addiction and nightly tooth brushing can use similar striatal pathways and patterns. FOXP2's role in habit formation may lead to further possible discoveries on severe addiction within the brain. Specifically, certain FOXP2 mutations that have been shown to decrease or inhibit transition into habit could possibly be used as medical interventions against drug addictions. Mouse line $FOXP2^{S321X/+}$ has shown that a decrease in FOXP2 can affect inhibitory drive and induce LTD. Therefore, future research regarding a reduction of FOXP2 in dopamine pathways could have significant findings regarding possible therapeutic solutions to addiction. HDAC's role as a negative regulator for habit-forming gene expression also presents itself as a promising area of possible study regarding addiction.

The reason behind FOXP2's impact on learning and habit still remains unclear. However, in this review it has been demonstrated that humanized FOXP2 was able to give mice more efficient learning strategies and a faster transition into procedural learning. FOXP2's impact as a language-learning gene in humans is a key point to consider, as language learning is perhaps the most habitual form of learning humans can undertake [4, 17]. Language is learnt through countless repetition and simulation of others, a behavior that epitomizes habit. Therefore, FOXP2's implications with learning and habit may stem back to its ties to language learning within the brain. This can provide a greater understanding of a uniquely human learning phenomena within the brain.

We would like to comment before the conclusion that some analyses confirmed there was no evidence of recent positive evolution selection of *FOXP2* in humans, even if the language development and related habit formation discussed in this review are specific traits of Homo Sapiens. In the sections explored above, it has been detailed that there are many factors that may influence and collide with FOXP2's influence on the striatum and habit formation, resulting in some striatal modulations being hard to attribute completely to FOXP2. These gaps in knowledge demonstrate vast room to improve our understanding on the topic.

Conclusion

From a gene originally thought to relate only towards language, FOXP2 has proven itself to have a much broader area of influence. As the world approaches a more habit-influenced lifestyle, the impact of FOXP2 and striatal activity will be ever greater, and we hope this review has introduced a new perspective and possible courses of action for this fascinating phenomenon.

Limitations

This review focused on the specific topic that expect of FOXP2 gene mutation on habit formation. We acknowledge that there are extensive research and literatures of habit formation in general. We also understand that there are several counter arguments against the claims we reviewed in this paper. These topics are out of scope for this review.

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