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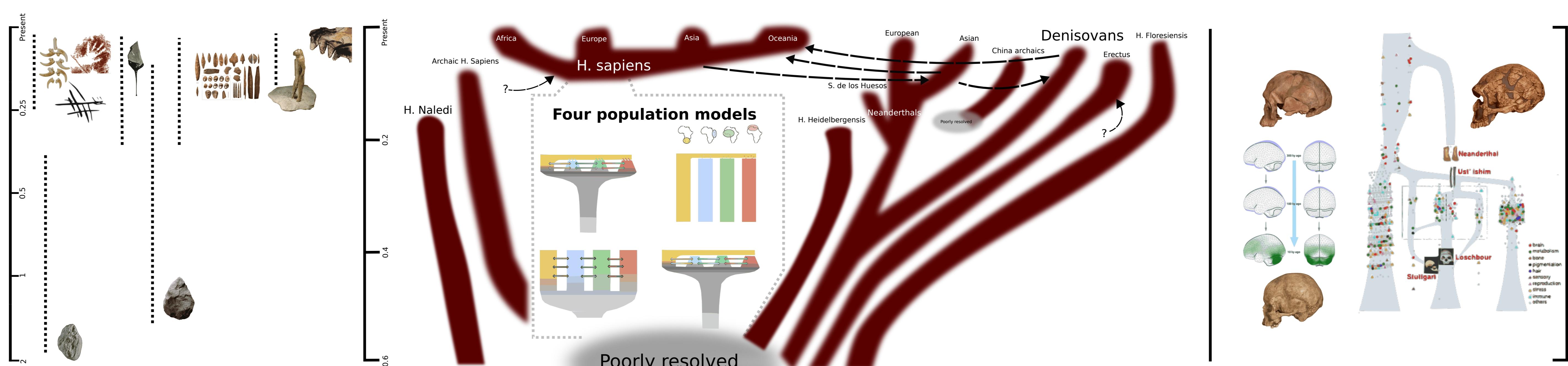
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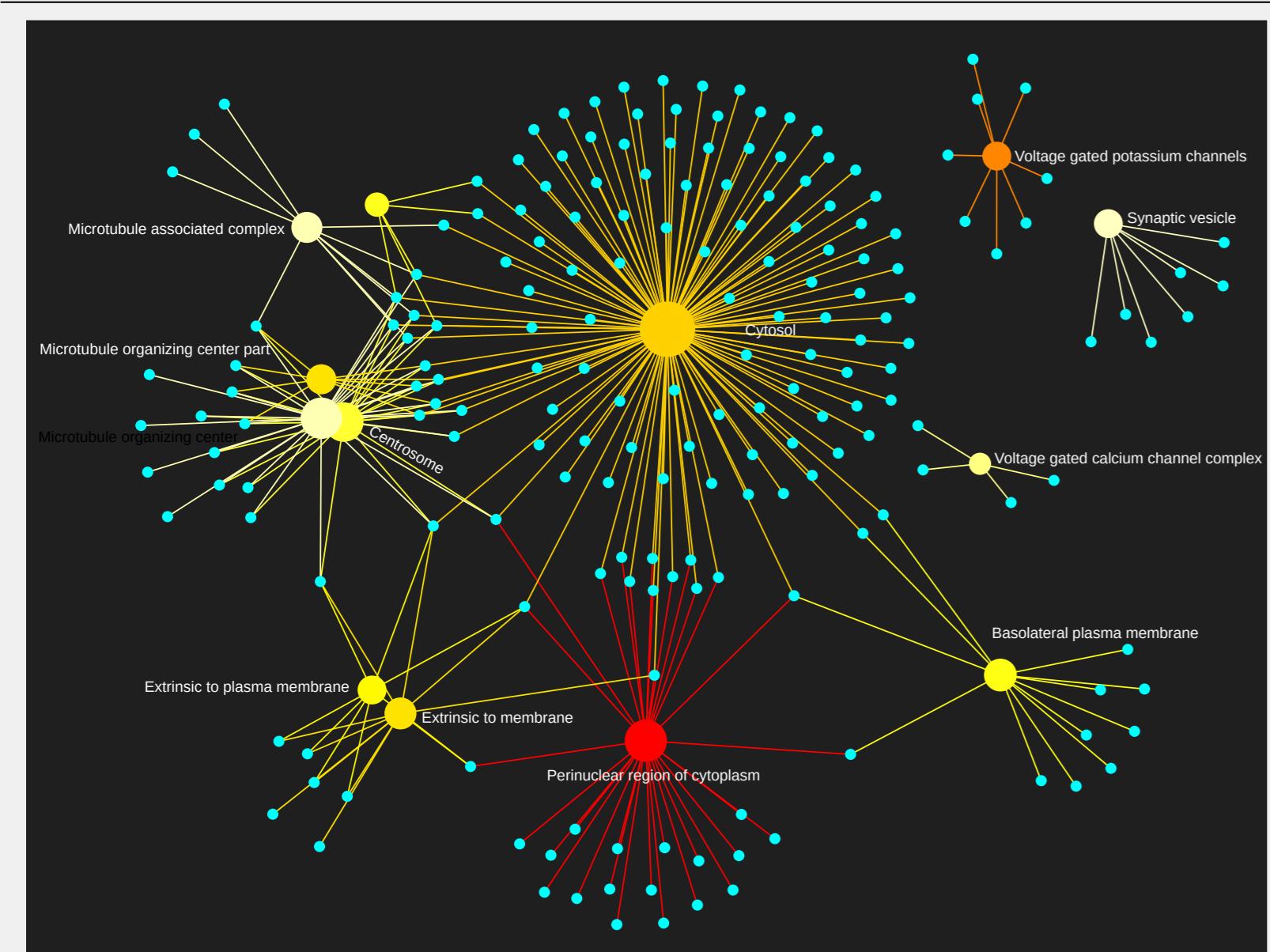
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## 1. Recent developments in human evolution

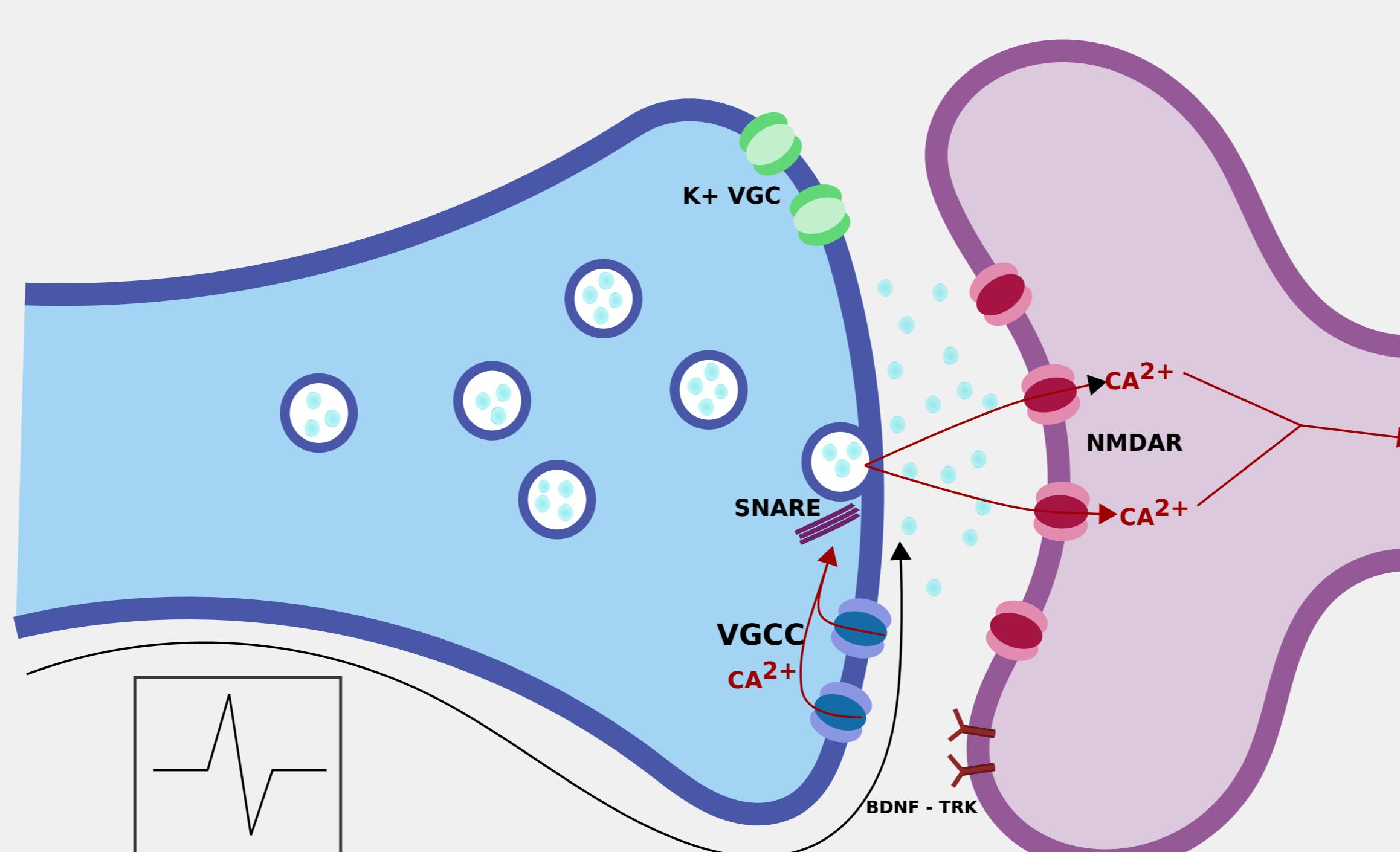


## 2. Changes in *H. Sapiens* cytoarquitecture



- Genes that show signals of **positive selection** or lying in **deserts of introgression** can tell us about the *Homo Sapiens* cognitive profile
- Here we propose a mechanistic hypothesis for how these genes might affect **brain metabolism** through changes in **calcium signalling**, with potential behavioral consequences
- Can any of these cellular properties be recapitulated through model organisms?

## 3. Changes in neuronal calcium circuitry in *Homo Sapiens*

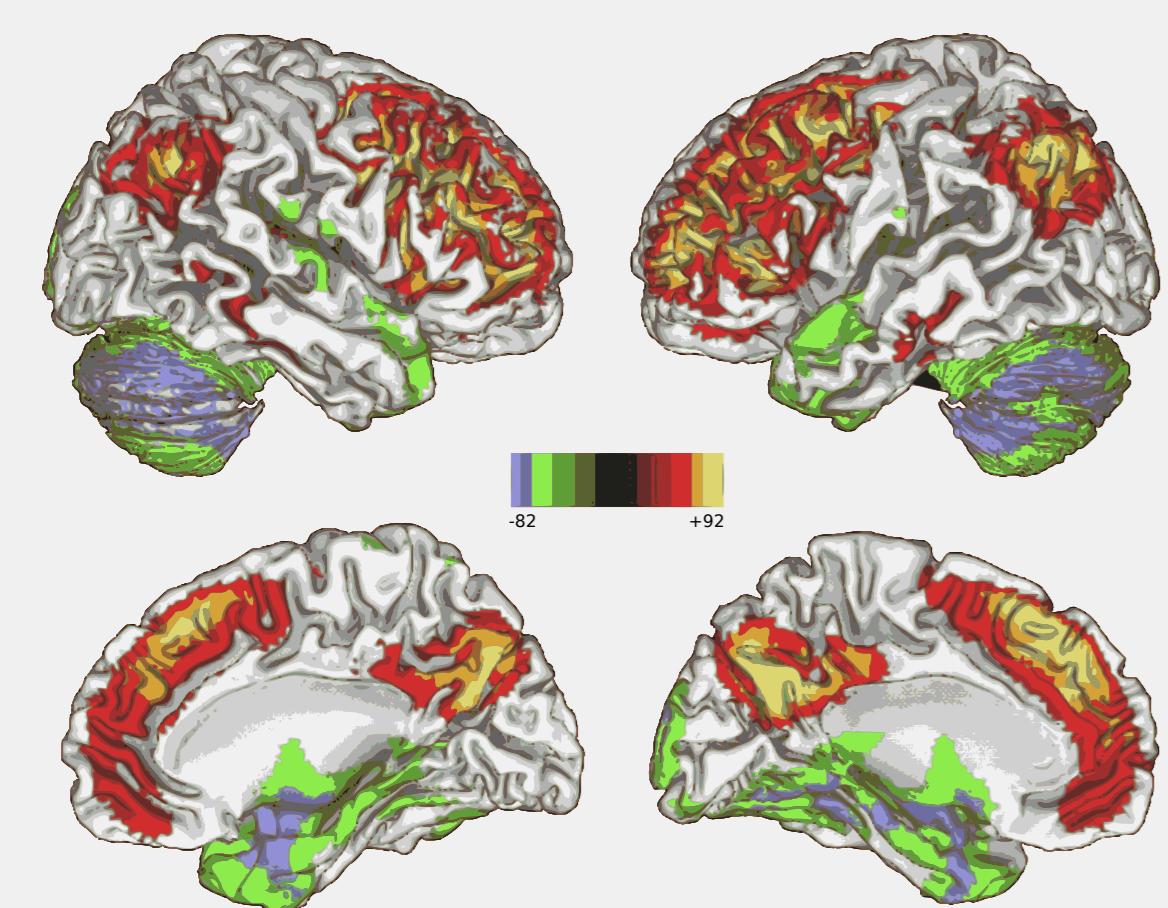


Genes affecting **cytoskeletal** properties of neurons are statistically enriched in the GO analysis ( $p < 0.05$ ). In the presynaptic and postsynaptic button these genes are expressed in:

- Voltage gated calcium and potassium channels
- The SNARE complex
- NMDA glutamate receptors

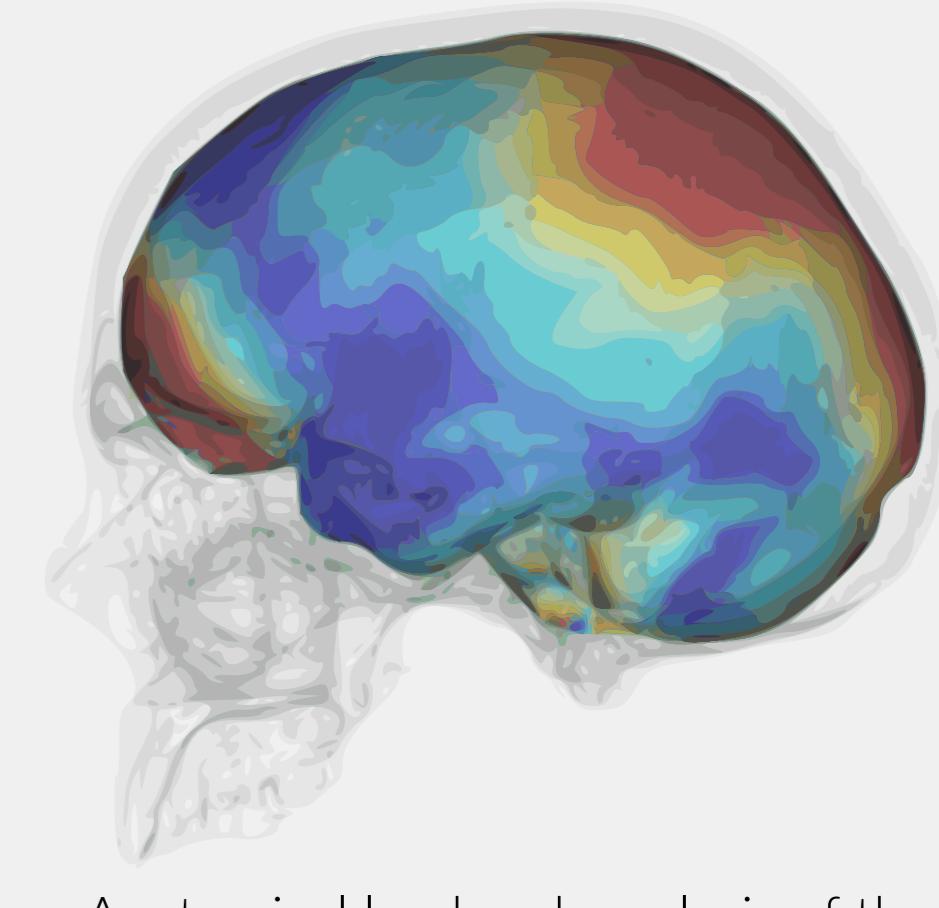
We hypothesize that changes in the calcium signaling could have downstream effects in the mitochondrial respiration chain, favoring a reliance on **aerobic glycolysis**, following a trend that is thought to have started at the emergence of the *Homo* clade (Bauernfeind et al 2014.).

## 4. Aerobic glycolysis



Distribution of aerobic glycolysis (adapted from Vaishnavi et al. 2010)

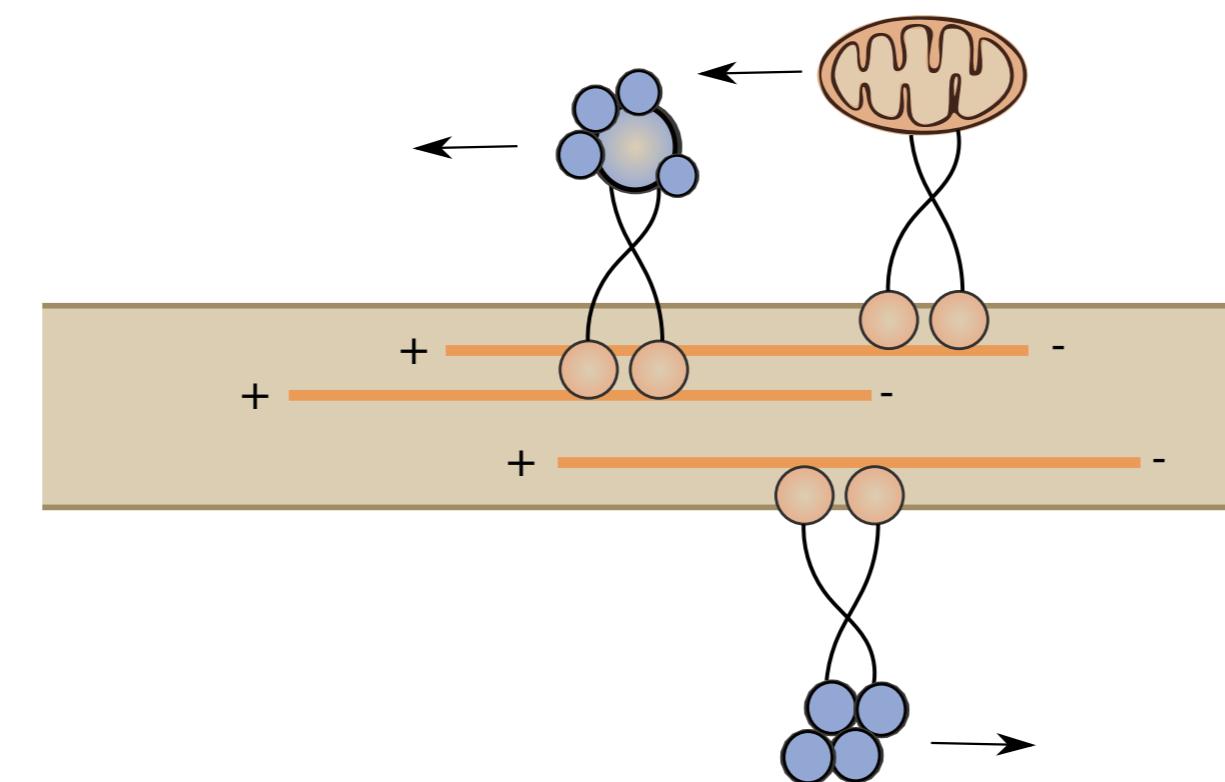
- Two metabolic programs to generate ATP: **aerobic glycolysis** and **oxydative phosphorylation**
- Aerobic glycolysis is less efficient in terms of ATP productivity, but it correlates in ontogeny with **key developmental milestones** (synaptogenesis, myelination), and it's necessary for local dosing of ATP where mitochondria can't reach
- Calcium impairs the mitochondrial respiration chain by gene expression modulation (Bas-Orth et al. 2017), promoting aerobic glycolysis metabolism
- Calcium signaling also plays a role in microtubule formation, actin invasion of filopodia in the growth cone and **BDNF** signaling (a brain growth factor), maybe accounting for a part of the correlation we observe between synaptogenesis and aerobic glycolysis
- NMDA receptors**, the gateway of calcium into the neuron, are upregulated by a byproduct of aerobic glycolysis, suggesting a positive feedback loop. Some NMDAR subfamilies are under positive selection (for more on NMDAR check T. O'Rourke's poster in slot 86)



Anatomical landmark analysis of the modern human skull (adapted from Bruner et Ogiwara 2018)

## 5. Cytoarchytecture

- Positive selection and desert of introgression genes related to axonal transport
- Ca2+/calmodulin-dependent protein kinase II (**CaMKII**) acts downstream in the calcium signalling pathway regulating microtubule growth cycle
- Fast (vesicular) axonal transport is dependent on aerobic glycolysis
- An interaction with synaptic calcium changes?



## 6. Future directions

- Test the hypothesis using model diseases
- Alzheimer's disease** is specially suitable: metabolic disease that disregulates calcium signaling
- Are Alzheimer's DEG genes overrepresented in human evolution studies? Can that tell us something about the evolution of *Homo Sapiens* brain areas?

You can download this poster here:



## Bibliography

A selected bibliography can be found in [andirko.eu/posts/EMBL19/](http://andirko.eu/posts/EMBL19/)