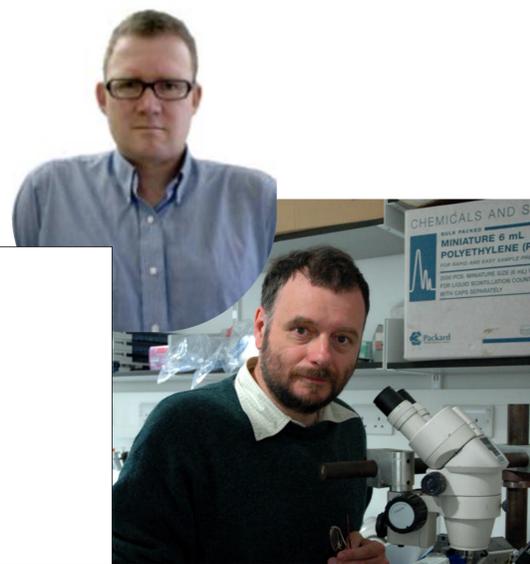


Visual abnormalities caused by non-autonomous actions of LRRK2-G2019S in a fly model of Parkinson's Disease

Farinaz Afsari, Alex R. Wade & Chris Elliott

Departments of Biology and Psychology



Introduction

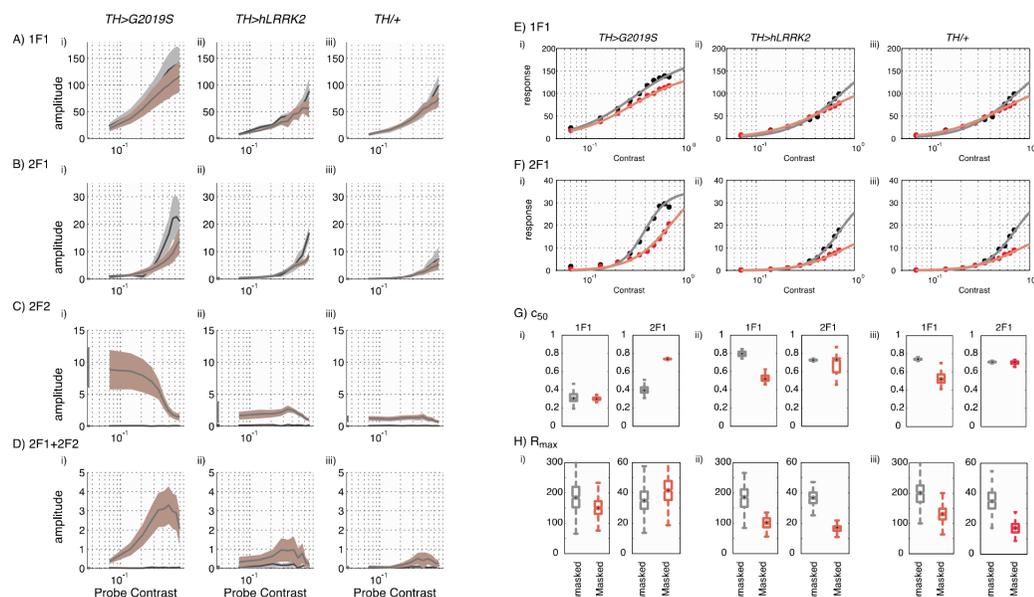
The most common cause of PD is a mutation (*G2019S*) in the LRRK2 kinase. This affects dopaminergic neurons leading to movement disorders. Dopaminergic neurons are also found in the retina, and some PD patients report defects in contrast perception.

As noticed in 1913 by Cajal, the network of neurons in the retina is similar in both flies and mammals; importantly, both contain dopaminergic neurons.

Aim: to develop the SSVEP visual recording technique for flies, and use it to quantify the neuronal effect of the *LRRK2-G2019S* mutation.

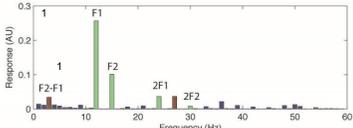
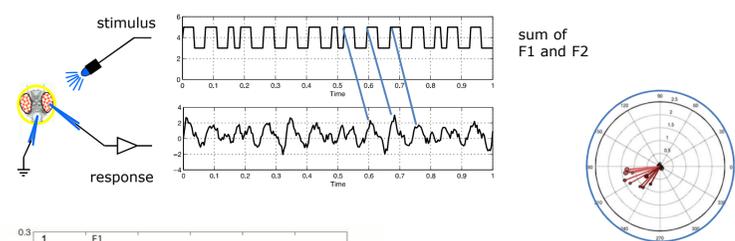
TH>G2019S makes visual signalling stronger...

Here we compare the expression of the mutant (*G2019S*) and wild-type (*hLRRK2*) genes in the dopaminergic neurons, along with a control in which no transgene is expressed. On the left (A-D) is the raw data, on the right the best-fit curves (E,F) with parameters c_{50} and R_{max} (G,H). Control flies had responses very similar to humans, while the *G2019S* flies had stronger responses. All data form 1 day old flies – long before any movement disorder has been seen!



Technique

SSVEP recording

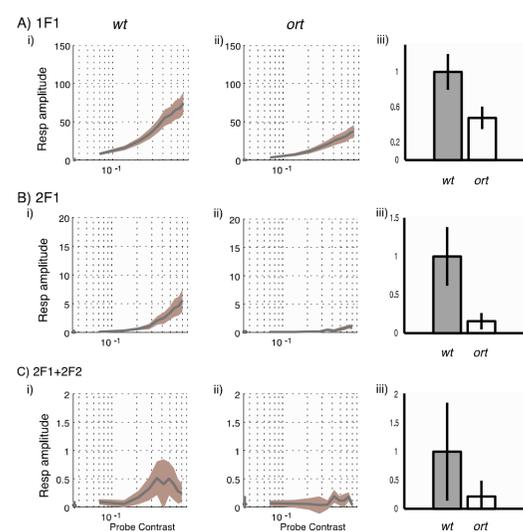


Fourier analysis
 → amplitude of 1F1, 1F2
 → amplitude of 2F1, 2F2
 → amplitude of F2-F1

Steady State Visual Evoked Potential

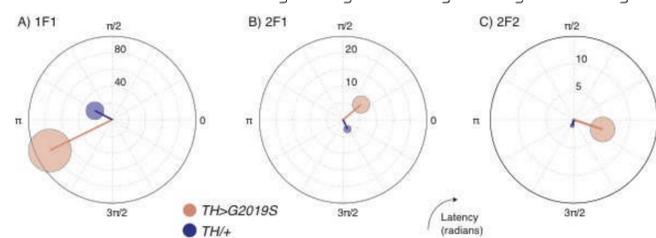
Flies were illuminated with a two component (1F1 and 1F2) flickering blue light. The response was divided into frequency components, corresponding to the two inputs and their harmonics. We also determined the phase of the response.

Validation of SSVEP using genetic tools

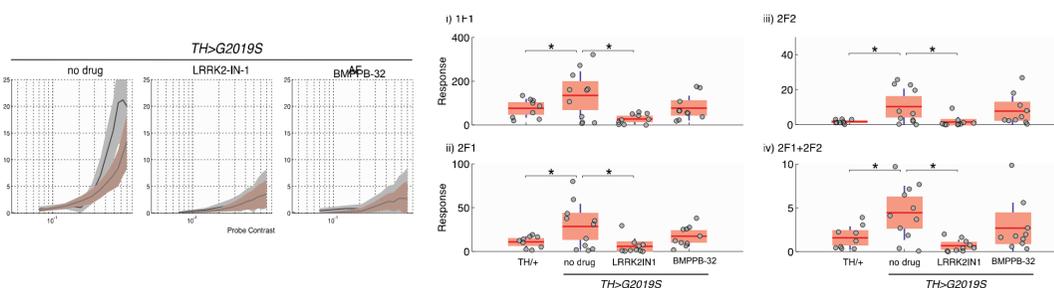


We tested our SSVEP system with the *ort* mutant, which blocks signalling by histamine. The *ort* mutant produces a known lesion, blocking the output of fly photoreceptors. We found the *ort* flies had normal photoreceptor (1F1) response, but the 2F1 and 2F1+2F2 components were severely reduced. We conclude these components are generated in the lamina or medulla.

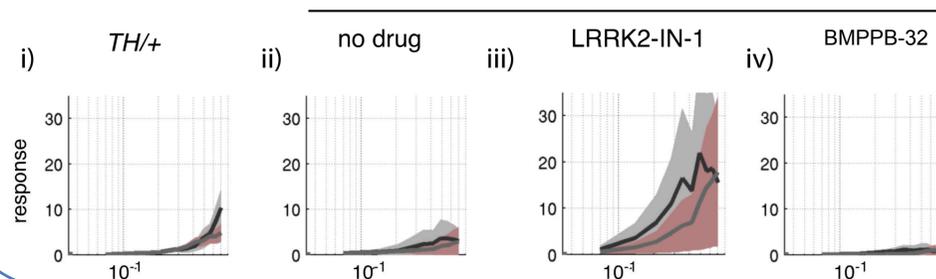
... and faster



Kinase inhibitors rescue the *TH>G2019S* effect



Off-target effects of kinase inhibitors seen in *dLRRK*^{-/-} knockout



Conclusion

- ◆ SSVEP shows fly vision is functionally similar to human vision
- ◆ SSVEP + genetics identifies neuronal pathways
- ◆ Dopaminergic expression of mutant LRRK2-G2019S leads to visual defects due to increased kinase function
 - this is a non-autonomous effect
- ◆ Off target effects are readily identified
- ◆ We hypothesize that this is the cause of...

