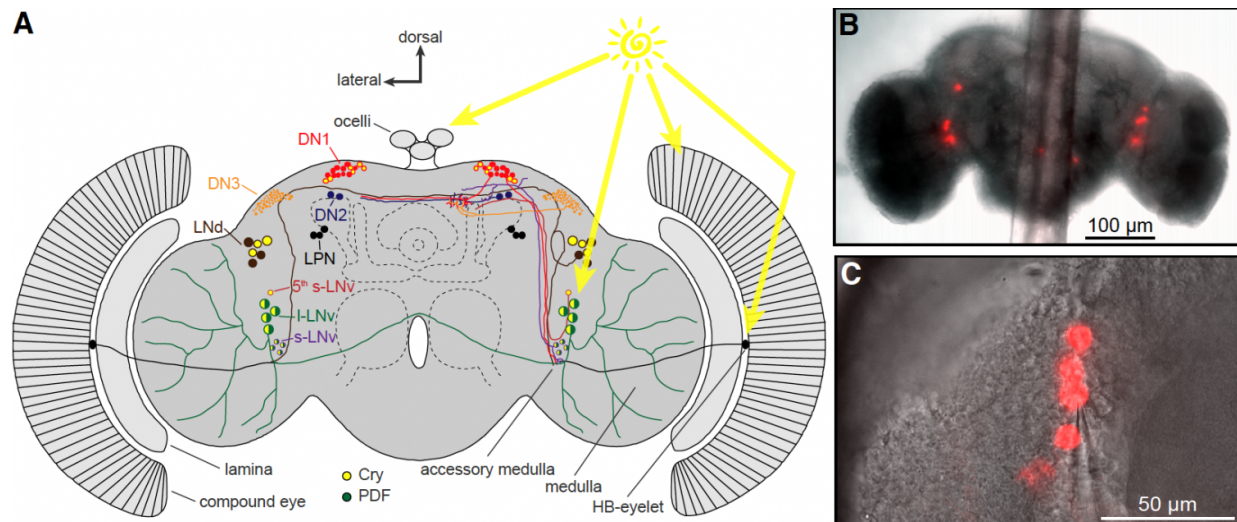


Quasimodo illuminates the secret to the ticking of our internal clocks

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A, Cartoon of the front of the *Drosophila* brain showing the ~100 clock neurons. The current study recorded from the 4 large pigment dispersing factor (PDF)-expressing ventral lateral neurons (LNV) clock neurons that receive several light inputs. B, The whole brain preparation used in the study showing the PDF::Red Fluorescent Protein labelled clock neurons for recording (the band in the middle is a nylon thread holding the brain down in the recording chamber) and C, detail of a clock neuron with recording electrode (from below and middle). Credit: University of Bristol

Drosophila fruit flies are so named after the Latin for "dew loving" because they are more active at dawn and dusk. This strong sense of circadian rhythm (the 24 hour time cycle) is generated by a clock that

ticks in the brain of all animals including humans.

The fly's clock consists of about one hundred neurons in its 100,000-neuron brain, which can fit on a pin head. Inside each clock neuron is a "[molecular clock](#)" that consists of [clock genes](#), which switch each other on and off every night and day.

Writing in the journal *PNAS* today, a team of researchers, led by Dr Edgar Buhl and Dr James Hodge from the University of Bristol in collaboration with Professor Ralf Stanewsky's group at UCL, explain how they identified three novel proteins that act together on the surface of clock neurons to make the clock light responsive.

"To be useful for an organism, circadian clocks need to be synchronized (or reset) to the natural environment cycles of light and temperature, much like you need to reset your [alarm clock](#) or watch when you change time zone," said Dr Hodge from Bristol's School of Physiology, Pharmacology and Neuroscience.

The findings could ultimately have implications for identifying novel membrane drug targets for sleeping disorders and jetlag, while furthering scientific understanding of the relationship between body clocks and health, as well as ageing and neurodegenerative disease.

The research builds on one of Professor Stanewsky's earlier discoveries regarding the Quasimodo gene, named after the fact that some mutant versions of the gene caused *Drosophila* to have hunched backs.

Using a red fluorescent protein to illuminate the clock neurons and record [electrical activity](#) in the brain, the authors showed that Quasimodo regulates light responses in the fly's clock neurons, thereby controlling the circadian rhythm.

Recordings from the fly clock neurons were taken at different times of the day, showing that they were more excitable in the day as opposed to at night. Using fly genetics to alter the amount of Quasimodo in the clock neurons, the researchers found that increasing Quasimodo caused the clock neurons to be less active as they would be at night, while decreasing Quasimodo had the opposite effect.

The Quasimodo protein is localised at the cell surface and electrical activity is generated in the membrane by small pores called ion channels. Therefore attention was turned to ion channels that were known to be active in clock neurons and that could potentially interact with Quasimodo to form a "membrane clock", which could control these day-night differences in electrical activity.

The first component of the membrane clock was a potassium channel called Shaw (dKv3.1), which Dr Hodge and Professor Stanewsky had previously shown to be important for circadian rhythms. The second component was the ion transporter NKCC, which also plays an important role in the day/activity changes in the mammalian brain clock. This latest study shows that Quasimodo interacts with Shaw and NKCC to form a membrane clock that controls daily changes in electrical activity of [clock neurons](#), which allows the clock to respond to light.

More information: Quasimodo mediates daily and acute light effects on *Drosophila* clock neuron excitability, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1606547113

Provided by University of Bristol

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