Congratulations to IMCB's latest PhD graduate – Lucy SHARPLES

Tuesday, 23 Jun 2020

Thesis Title: Disrupted-in-schizophrenia 1 (disc1) regulates development of the hypothalamus and its associated behaviours

Neuropsychiatric disorders constitute a devastating disease spectrum characterised by social withdrawal and high suicide rates. Understanding how the genetic risk factor Disrupted-in-schizophrenia-1 (Disc1) contributes to schizophrenia, bipolar disorder and major depression will help direct therapeutic efforts. Disc1 functions in neurogenesis and neuronal migration. Defects in early neurodevelopment are believed to be a contributing factor in neuropsychiatric disorders.

Previous data from our group demonstrated disc1 mutant zebrafish larvae had alterations in hypothalamic development. Critically, behaviours associated with the hypothalamic-pituitary-interrenal (HPI) axis such as stress were also perturbed. We have generated a novel disc1 CRISPR knock out zebrafish line, with a mutation lying closer to the human-equivalent breakpoint. After mutant validation, we investigated

cellular markers and behaviours relating to hypothalamic functions. disc1 mutants exhibited hypophagia relating to deficits in hunting behaviour, altered sleep regulation, arousal and stress-response.

Whole-brain activity revealed that loss of disc1 led to significant increases and decreases in activity in different neuronal populations. Regions of interest (ROIs) with increased activity included the forebrain and cerebellum, while ROIs with decreased activity included hypothalamic and connected regions. Finally, GSK-3β inhibition during a critical time window, normalised the expression of hypothalamic markers and had sustained effects on neuronal activity and feeding. This study demonstrates the validity of zebrafish in neuropsychiatric disease research and shows the potential of intervention during a critical time window in neurodevelopment.

Supervisor
Prof. Sudipto ROY

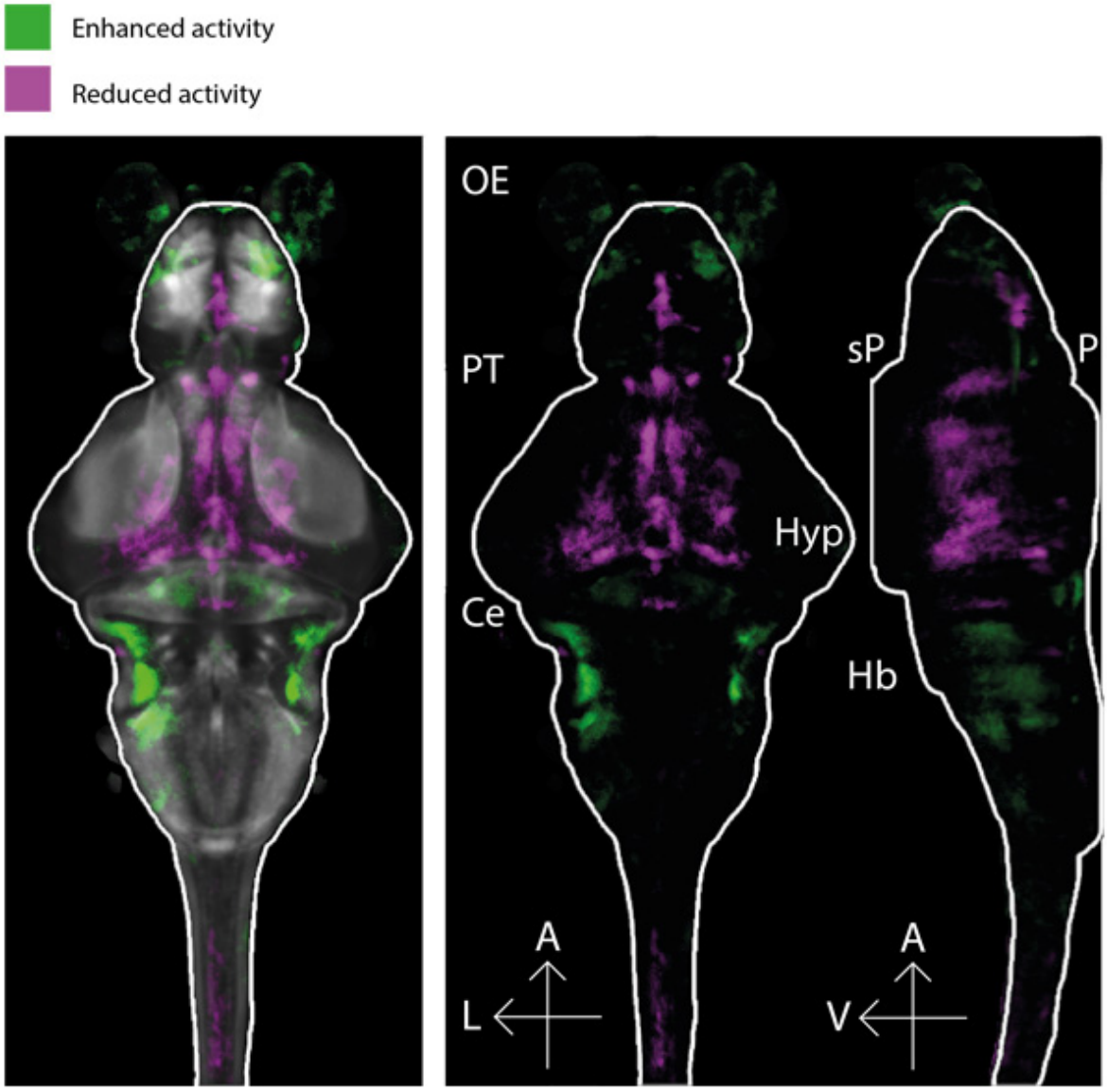

Figure legend: Brain activity maps from *disc1*$^{-/-}$ mutants. Wholemount dorsal view of Z-projection (Z=137). $N_{+/+}$= 76, $N_{-/-}$= 88, image representative of 2 experimental repeats. Activity increases are indicated in green and localise to the olfac tory epithelium (OE), pallium (P), subpallium (sP), cerebellum (Ce) and hindbrain (Hb). Activity decreases are indicated in purple and localise to posterior tuberculum (PT) and hypothalamus (Hyp). Orientation shown by arrows at the bottom right. A: anterior, L: lateral, V: ventral