

## BRAIN FOUNDATION RESEARCH REPORTS

Author: Dr Tim Aumann

Qualification: BSc (hons), PhD

Institution: Florey Institute of Neuroscience and Mental Health

Title of Project: "Can our environment or behaviour change the number of dopamine brain cells?"

Summary:

Background. In rodents we had shown that the number of tyrosine hydroxylase immunoreactive (TH+) or dopaminergic neurones is altered up or down by  $\pm 10-15\%$  following 1-2 weeks exposure to environmental or behavioural stimuli, including length of light:dark cycle (photoperiod), sex pairing, or environment enrichment. Furthermore, this appears to involve activity-dependent changes in expression of genes and proteins necessary for dopamine synthesis and handling, and as such it is likely to be a new form of long-lasting (days-weeks) brain plasticity.

If the same occurs in humans it might provide new opportunities to help treat symptoms associated with not enough dopamine (e.g. Parkinson's disease, ADHD) or too much dopamine (e.g. addiction, schizophrenia).

Hypothesis. Salient stimuli in our environment cause the activity of midbrain neurons to change resulting in altered expression of genes and proteins necessary for dopamine neurotransmission.

Aim. To determine whether photoperiod alters the number of dopaminergic neurons in the human midbrain.

Findings. Brains of people who had lived at high latitude but died in mid-summer (long-day photoperiod) or mid-winter (short-day photoperiod) were obtained from the Edinburgh Brain Bank. Sections were cut through the midbrain and immunoreacted against TH, the dopamine transporter (DAT), and TUNEL (a marker of cell death). There were ~6-fold more TH+ and ~2-fold less TH- midbrain neurons in summer compared with winter (Figure 1 & Figure 2B). There were also ~2-fold more DAT+ and ~2-fold less DAT- midbrain neurons in summer compared with winter (Figure 1 & Figure 2C). In contrast there were no seasonal differences in the number of glia, or in TUNEL+ cells. TH immunoreactivity was also higher in the hypothalamus in summer compared with winter.

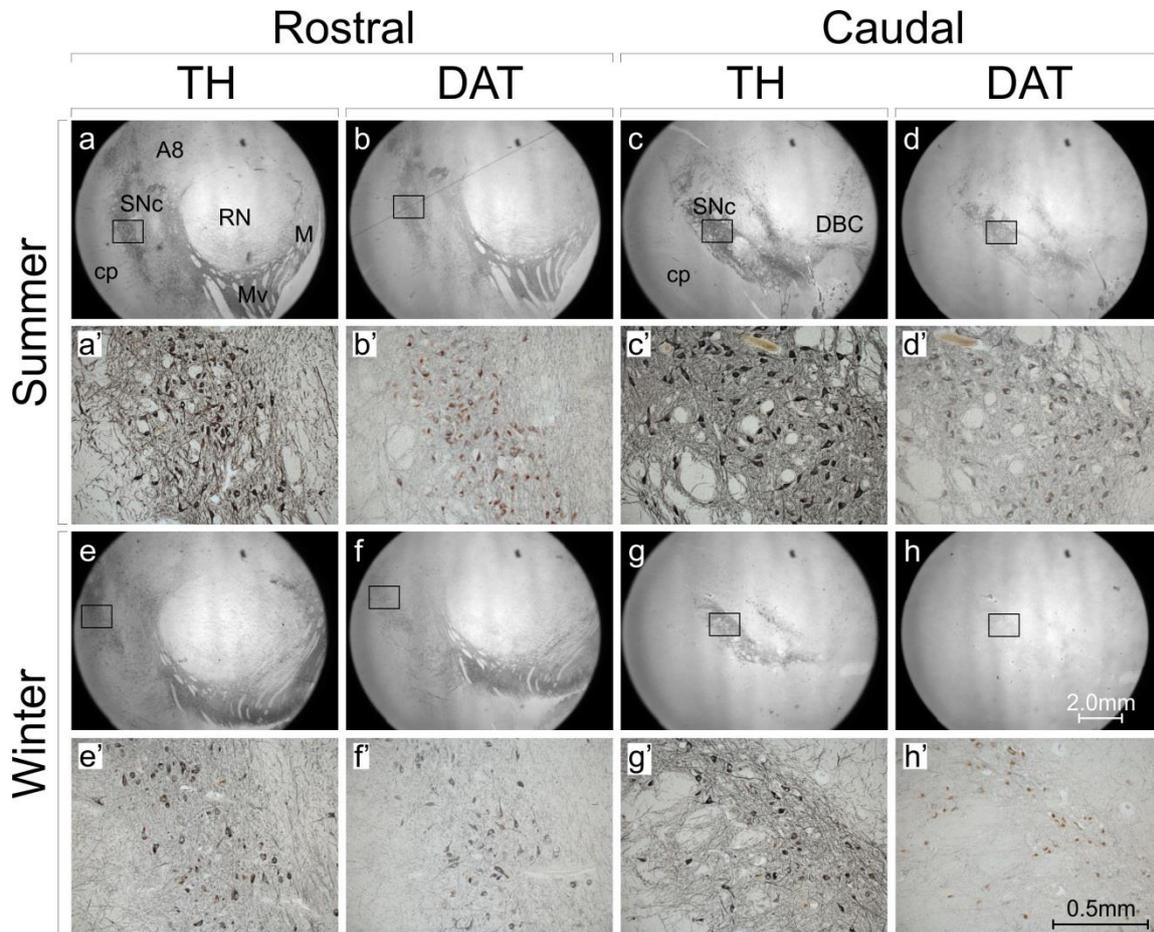
Thus, in humans in summer there are many more midbrain neurons immunoreactive for markers of dopamine synthesis and handling than in winter. This occurs with smaller or no differences in the total number of neurons, and with no difference in number of glia or a marker of cell death. These data suggest we have more midbrain dopamine in summer, and that this occurs at least in part through environmental induction of dopamine gene and protein expression in extant neurons, as opposed to cell birth and cell death.

Unanswered questions. Do these differences in number of midbrain TH+ and DAT+ neurons in summer versus winter translate to altered midbrain dopamine and ability to learn new movements (the subject of the current grant application)?

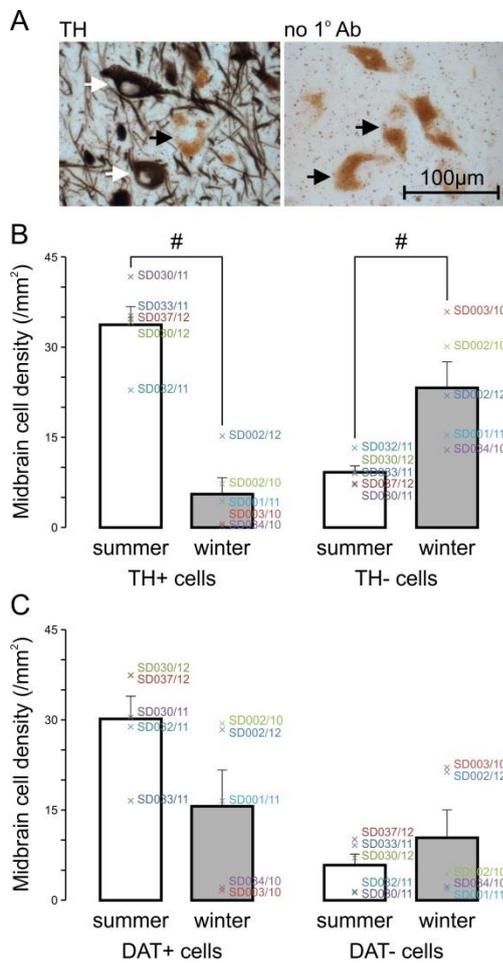


What these research outcomes mean. That our findings in rodents probably occur also in humans, which means environment-induction of differences in midbrain dopamine neurons may lead to novel therapies for treating symptoms of midbrain dopamine imbalances such as in Parkinson's disease, ADHD, addiction, OCD and schizophrenia.

These data are being presented at the International Society for Neurochemistry and Australasian Neuroscience Society joint meeting in Cairns 2015, and are submitted for publication in the Journal of Neuroscience.



**Figure 1.** Midbrain tyrosine hydroxylase (TH) and dopamine transporter (DAT) immunoreactivities are higher in summer than in winter. Shown are photomicrographs of immunoreacted (black DAB reaction product) and Nissl-counterstained (red) human post-mortem sections at rostral (**a,b,e,f**) and caudal (**c,d,g,h**) levels of the midbrain in subjects who died in summer (**a,b** = SD033/11; **c,d** = SD030/11) and winter (**e,f** = SD002/10; **g,h** = SD034/10). The regions outlined with squares in **a-h** are shown at higher magnification in **a'-h'**. Note the increased density of immunoreactive (black) cell bodies and neural processes in summer compared with winter, more obvious for TH than DAT. A8 = dopaminergic group A8; cp = cerebral peduncle; DBC = decussation of the brachium conjunctivum; M = medial dopaminergic group; Mv = medioventral dopaminergic group; RN = red nucleus; SNc = substantia nigra pars compacta.



**Figure 2.** The density of tyrosine hydroxylase immunoreactive (TH+) midbrain neurons is higher in summer than in winter. **A** Cell-type classifications were made during cell density measurements. Only large (neuronal) cells with a visible nucleus were counted. TH+ neurons contained black TH immunohistochemistry reaction product (e.g. white arrows), whereas TH- neurons (e.g. black arrows) had no black reaction product but contained brown clusters of neuromelanin granules around the nucleus and/or Nissl counterstain (red staining). The photomicrograph on the left is of a section processed with the primary TH antibody, the photomicrograph on the right is of a negative control section processed without the primary TH antibody (no 1° Ab). **B** Mean  $\pm$  SE density of midbrain TH+ (left) and TH- (right) neurons in the summer (white bar) and winter (gray bar) groups (n=5 in each case). Individual subject means are indicated by colored crosses. TH+ neuron density is significantly higher in summer compared with winter (#,  $p=0.0001$ , unpaired two-tailed t-test), and TH- neuron density is significantly lower in summer compared with winter (#,  $p=0.01$ , unpaired two-tailed t-test). **C** Mean  $\pm$  SE density of midbrain DAT+ (left) and DAT- (right) neurons in the summer (white bar) and winter (gray bar) groups (n=5 in each case). Individual subject means are indicated by colored crosses. Although seasonal differences in both DAT+ and DAT- neurons show the same trends as TH+ and TH- neurons, the differences are not statistically significant (DAT+,  $p=0.08$ ; DAT-,  $p=0.39$ , unpaired two-tailed t-tests).