Seasonal Modulation of Novel Brain Circuits Regulating Mood and Cognition

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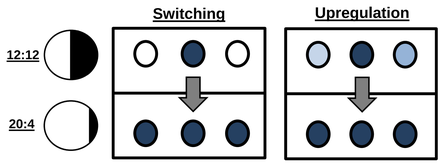
Introduction

- **Neurons in the brain are classified by peptide expression.**
  - Over 100 billion neurons in the brain
  - Based on these classifications, fixed identity assumed
- **Light alters the neurochemical profile of hypothalamic neurons[1].**
  - Rats exposed to long "summer" days:
    - Increased levels of Somatostatin (SST) in the hypothalamus
      - Changes seen in the paraventricular nucleus (PVN) and periventricular nucleus (PeVN)
    - The mechanisms for increased SST expression are unclear
      - *De novo* transcription of SST in reserve pool of cells (neurotransmitter switching)

        OR
      - Upregulation of peptide in existing SST neurons



- **The suprachiasmatic nucleus (SCN) processes light input from the environment.**
  - Receives direct light input from the eye via retinohypothalamic tract
    - Transmits light information to other areas of the brain
  - The SCN expresses SST, although its role is unclear

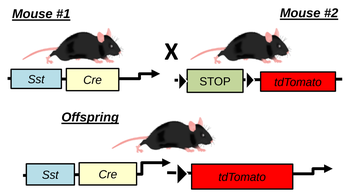
Research Questions:

Do long days activate SST transcription in a reserve pool of neurons?
Does this change happen in the SCN?
When does this change occur?
Is this change region-specific?

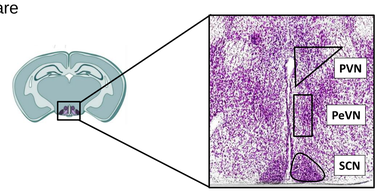
Methods

- **Lighting Conditions:**
  - Mice exposed to 2 different light conditions for 1, 2, 4, 8, and 12 weeks
    - Control = L12
      - 12 h of light/day
    - Long day = L20
      - 20 h of light/day

- **Genetic Model:**
  - Mouse #1 - Cre-recombinase driven by upstream *Sst* transcription
  - Mouse #2 - Fluorescent labeling by Cre-dependent tdTomato
  - Offspring - All SST neurons are labeled red by tdTomato



- **Regions of Interest:**
  - PVN
  - PeVN
  - SCN



1. Long "summer" days activate reserve pool of SST neurons in three distinct regions of the hypothalamus

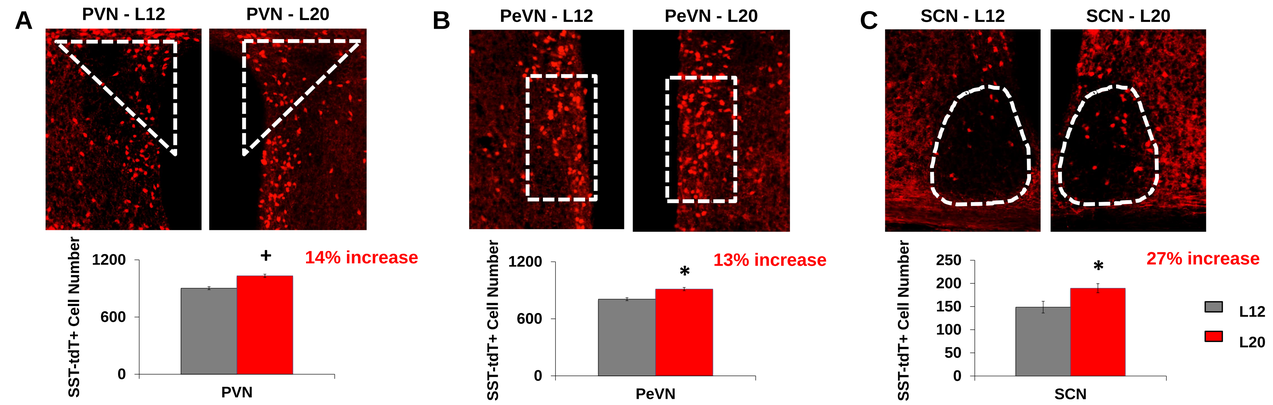


Figure 1. Long day length increases the number of neurons that express SST in the hypothalamus. (A-C) Representative images and quantification of tdT expression in the PVN (A), PeVN (B), and SCN (C) after exposure for at least 12 weeks. * Student's t test, $p < 0.05$ (+ one-tail Student's t test, $p < 0.05$).

2. SCN switch corresponds to time required for behavioral adjustment

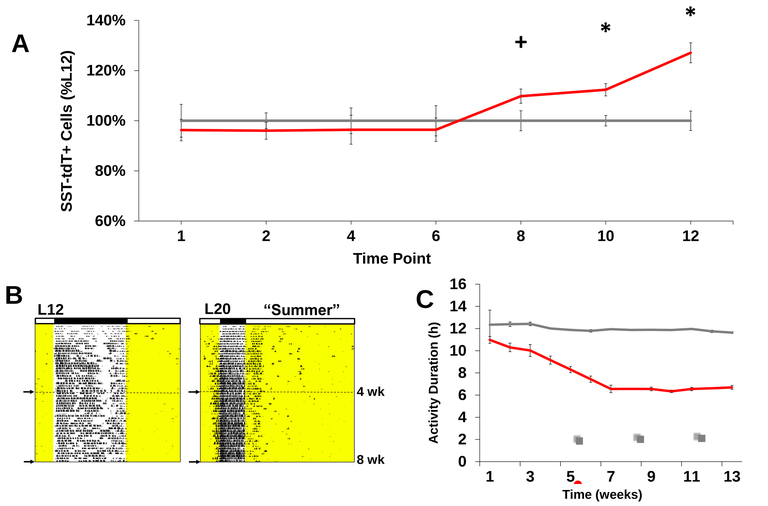


Figure 2. Changes in SST-tdT+ expression occur after at least 7 weeks of exposure. (A) 1, 2, 4, and 6-week time points show no difference in cell count. (B-C) Wheel-running actograms for L12 and L20 conditions (B) and quantification (C) show behavior adjusts to long day conditions after 5-7 weeks. * Differs from L12, Post-hoc contrasts, $p < 0.05$.

3. Larger SST-tdT+ increases in female SCN

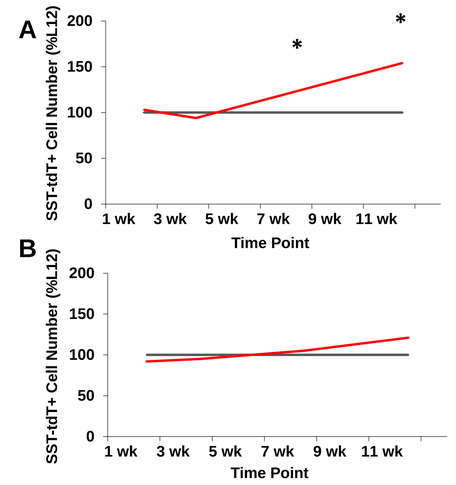


Figure 3. SST-tdT+ changes are more prominent in females. (A-B) Females show increase in cell number at 8 weeks (A) in comparison to the males at the same time point (B). * Differs from L12, Post-hoc contrasts, $p < 0.05$.

4. Region-specific dynamics of SCN switching may reflect network-level interactions

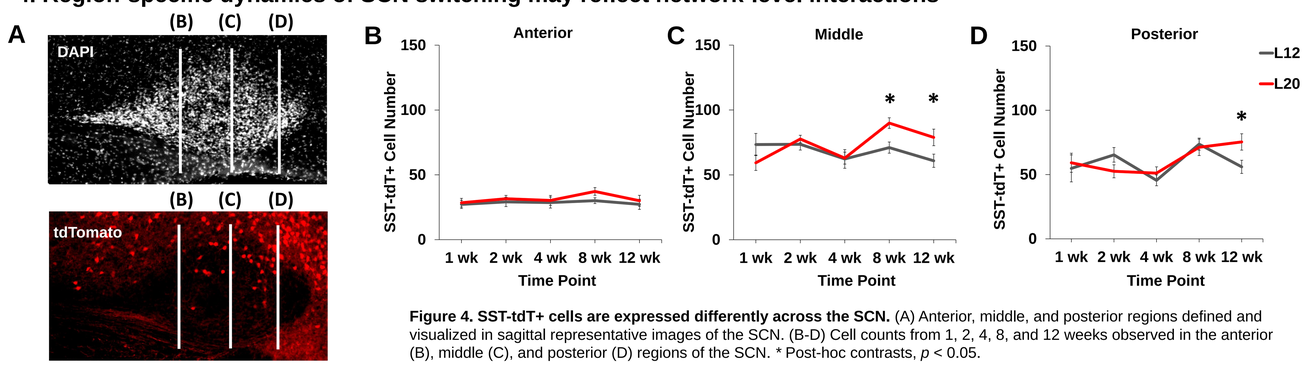


Figure 4. SST-tdT+ cells are expressed differently across the SCN. (A) Anterior, middle, and posterior regions defined and visualized in sagittal representative images of the SCN. (B-D) Cell counts from 1, 2, 4, 8, and 12 weeks observed in the anterior (B), middle (C), and posterior (D) regions of the SCN. * Post-hoc contrasts, $p < 0.05$.

Conclusions

- **Activation of reserve SST neurons occurs in the hypothalamus**
  - Findings consistent with studies done in rats[1]
    - Increases in the PVN and PeVN
  - Cell increase indicates neurotransmitter switching, not upregulation of peptide expression
    - Genetic model shows that increases occur in cells that have never previously expressed SST
- **Increase in SST-tdT+ cells also observed in the SCN and corresponds to changes in behavior**
  - Increase in SCN SST-tdT+ cells requires at least 4 weeks of long-day exposure
  - Behavioral adjustment to L20 takes about 6 weeks
    - Suggests that increase in SST-expressing cells and behavioral adjustment to long days may be related
- **Larger increase in SST-tdT+ in females suggests sex differences in light responsiveness**
  - Males and females exhibit similar cell number under L12 conditions
    - Larger increases in females after L20 suggest that brain plasticity may differ between sex
    - Females more sensitive to changes in lighting environment
- **Larger SST-tdT+ increases seen in the mid-SCN, corresponds to location of SCN core neurons**
  - Coincides with proximity of retinorecipient neurons

Future Directions

- **How does light cause neurotransmitter switching?**
  - Genetic model suggests switch is due to increase in *Sst* transcription
    - Result of change in chromatin or alteration of transcriptional machinery?
  - Do changes occur directly from light or as a signal from other cells?
- **Which SCN neurons respond to SST and the cellular mechanisms of SST signaling?**
  - What are the cellular and genetic components of the switch?
- **Why are neurotransmitters switching?**

Acknowledgements

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References

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