Investigating brain connectivity and sleep changes following melatonin treatment in children with persistent post-concussion symptoms

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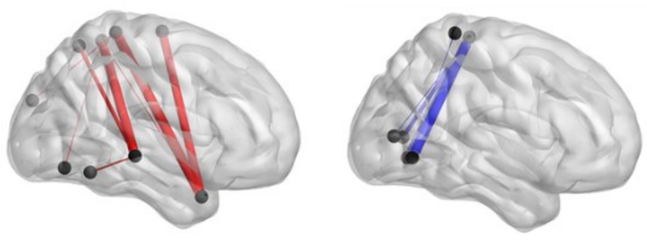
Introduction

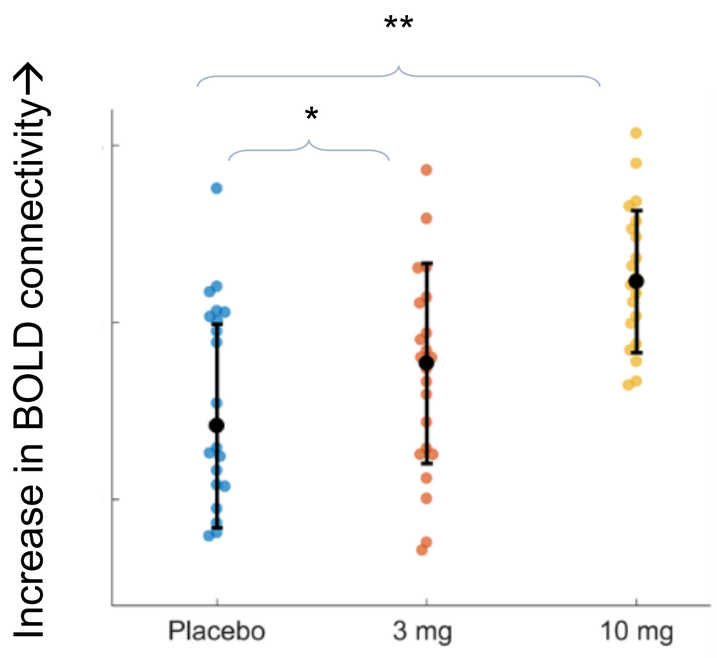
- Sleep-wake disturbances affect over 70% of children with persistent post-concussion symptoms (PPCS)
- Evidence-based treatments for children with PPCS are few and limited
- Common sleep-wake complaints could be ameliorated via the supplementation of melatonin, which has significant neuroprotective and anti-inflammatory properties
- The present study investigated the neural effects of melatonin as a treatment for children with PPCS
- Functional brain (fMRI BOLD connectivity) and anatomical (T1 grey matter) markers observed before and after treatment in 62 children were assessed alongside clinical recovery and improvement in sleep parameters

Key Results

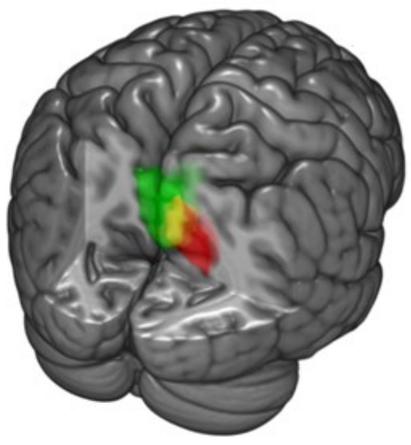
Functional (BOLD) connectivity



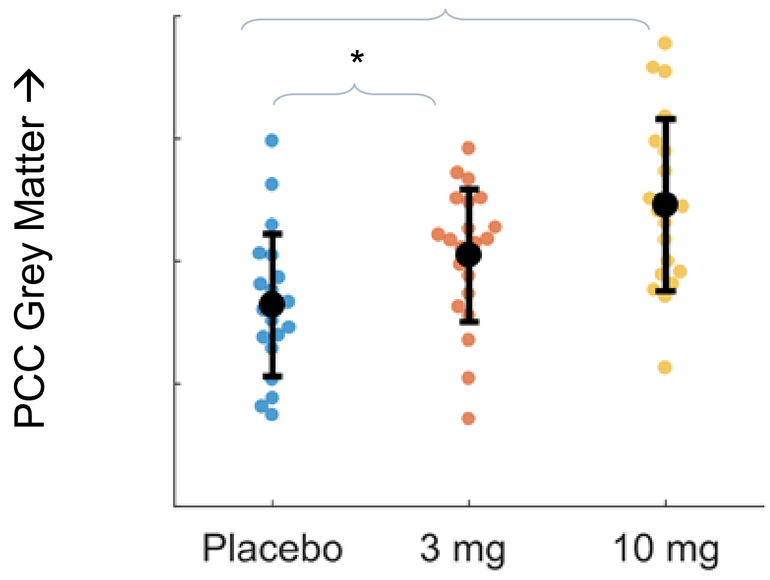
Red and blue areas highlight which brain connections increased with melatonin



Anatomy (Grey matter changes in T1 scans)



Green and yellow areas indicate where grey matter increased post-melatonin



Highlights:

- *Dosage-related improvements in brain functions and grey matter were localised within the default mode network (ANCOVA, significant interaction and main effect over time)*
- *Connectivity of BOLD signals and grey matter linearly increased as dosage of melatonin increased, when compared across placebo, 3 mg melatonin and 10 mg melatonin groups.*
- *Localised changes suggest that children with PPCS taking melatonin benefitted from a compensation of brain functions that may have been temporarily lost due to injury.*

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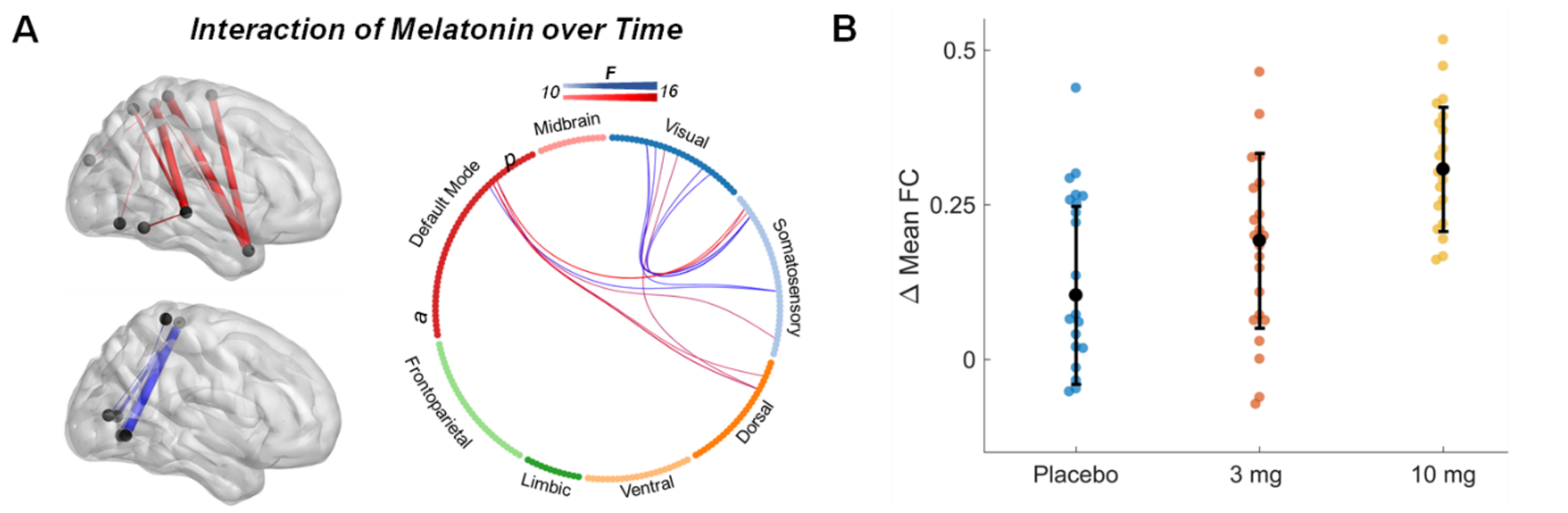
Results (cont'd)



Changes to whole-brain FC following melatonin treatment in pediatric PPCS.

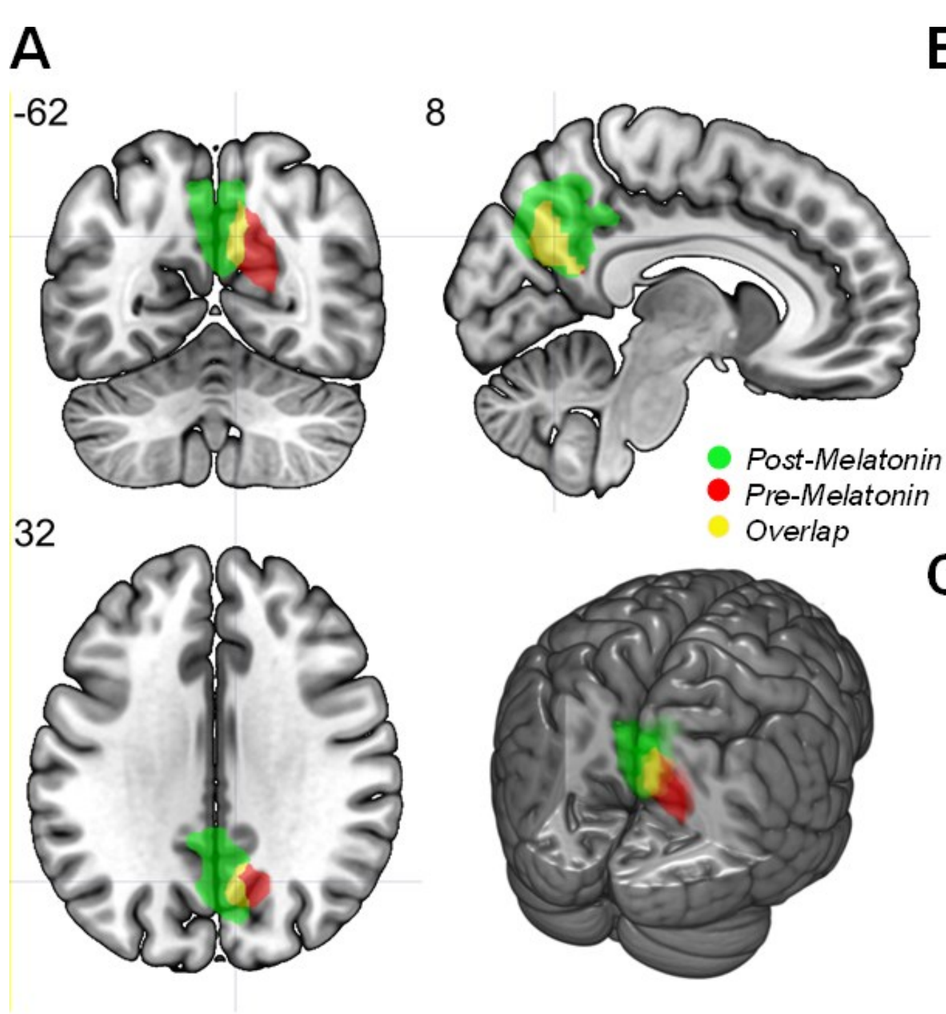
A) Brain networks showing a melatonin over time interaction. Labels 'a' and 'p' indicate anterior and posterior regions of the DMN.

B) Change in mean FC (post minus pre) of all network edges across all subjects in each treatment group, where black error bars indicate the mean ± standard deviation (SD). Individual subjects are allocated by treatment groups indicated by specific colors where placebo = blue, 3 mg = orange and 10 mg = yellow.

C) Change in mean FC values negatively correlated with WASO measures, where higher FC post-treatment corresponded with reduced WASO.

D) PPCS patients who did not recover (n = 39) had higher FC in anterior DMN and limbic nodes versus patients who did recover (n = 23) following the treatment period ($p_{FWE} < 0.05$, $T_{2,61} = 4.3$).

Whole-brain grey matter (GM) and intra-regional connectivity (ReHo) changes following melatonin in pediatric PPCS.



A) Pre-melatonin GM clusters in the posterior cingulate (PCC) were identified from whole-brain analyses to be negatively correlated with sleep and fatigue disturbances. The main effect of group of whole-brain GM post-melatonin in this study is also shown (indicated in bright green). The overlap (indicated in yellow) highlights a mutual region of change.

B) Changes in PCC GM contrasted across melatonin treatment groups, where black error bars indicate mean ± SD.

C) ReHo estimates across pre and post treatment periods

D) PCC GM changes negatively correlated with change in WASO, with higher GM corresponding with reduced WASO.

E) Higher PCC GM change positively correlated with increased sleep from the PCSI scale post-treatment.

N.B. Individual subjects are allocated by treatment groups indicated by specific colors where placebo = blue, 3 mg = orange and 10 mg = yellow. All contrasts adjusted for age and gender.

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Methods

Structural and functional neuroimaging (MRI) analyzed in 62 children with PPCS in a randomized, double-blind, placebo-controlled trial of 3mg or 10mg of melatonin (NCT01874847). Neuroimaging conducted at 4-weeks post-injury and 8 weeks post-injury time points. Melatonin dosage was administered daily for a 28-day period, between study timepoints, one hour before usual bedtime.

Clinical outcomes

- Primary outcome was change in Post-Concussion Symptom Inventory (PCSI-Y) score. Recovered (n=23) and unrecovered (n=39)
- Melatonin groups: Placebo (n=20), 3 mg (n=22), 10 mg (n=20)
- Sleep-wake disturbance scores using the sleep/fatigue domain questions of the PCSI were used to assess increases/decreases in sleep
- Actigraphy data over the treatment period was used to assess the change in
  (i) Wake After Sleep Onset (WASO): this measure constituted the total number of estimated minutes between sleep onset and the end of a sleep period that was scored as “wake” by the sleep/wake analysis; and
  (ii) total sleep time: this was the calculated period of time in minutes from sleep onset and sleep end.

Neuroimaging outcomes

- Whole-brain analyses of functional connectivity (FC) of resting-state fMRI
- Structural grey matter (GM) volumes via voxel-based morphometry
- Both measures assessed immediately before and after melatonin treatment and compared to placebo

Summary

- Following a 4-week course of melatonin treatment in children with PPCS contributed to dosage-related modulations of functional connectivity and grey matter in defined brain networks

- Children with PPCS that reported better sleep and reduced wake periods following sleep onset demonstrated a net increase in grey matter within the posterior cingulate (PCC) and improvements in brain functions of the PCC network including connections to visual and somatosensory areas

- Those that did not recover from PPCS post-treatment had significantly increased functional connectivity between anterior default mode and limbic network regions

- Despite the absence of a direct clinical benefit, neural evidence examined via brain mapping provides evidence supporting a protective effect of melatonin on brain function and structure in children presenting with PPCS

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