HORMONE REPLACEMENT THERAPY INSULIN, and HIPPOCAMPAL VOLUMES in POSTMENOPAUSAL WOMEN A LONGITUDINAL STUDY

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Introduction

The hippocampus is a structure within the brain that is vital for memory and spatial cognition.

Pathological hippocampal atrophy in ageing can result in memory, goal setting, and mood regulation dysfunction[1].

Impaired insulin metabolism is a risk factor for hippocampal atrophy[2].

Hormone replacement therapy (HRT) in postmenopausal women can be protective against hippocampal atrophy[3].

There is some evidence that HRT can also be beneficial for insulin function, though there are some studies that find the opposite effect[4,5].

It is possible that the relationship between HRT and hippocampal atrophy occurs, at least in part, due to the impact of HRT on insulin function in postmenopausal women.

It remains unclear whether insulin function is a mediator of the longitudinal association between hormone replacement therapy and age-associated hippocampal atrophy.

Methods

Participants were 327 post-menopausal community-living women, aged 40-65 (*M*=45) at baseline, followed over 12 years.

Participants were Canberra and Queanbeyan residents, drawn from the Personality and Total Health (PATH) Through Life study[6]. Participants were interviewed on two or more (of a total of four) occasions, each four years apart. Of 3813 females in the PATH study, participants were included if they had undergone menopause, and MRI and HRT data available for two or more time points. The selected sample was significantly older (mean age 52, vs 42), and were significantly more likely to have undergone HRT (χ^2=37.43, p<0.01) than the wider PATH sample.

Hormone replacement therapy information was obtained from self-report (**HRT-SR**). **Hormone replacement therapy and medications which include sex hormones** (e.g. estrogens, progesterones) were obtained from both self-report and Pharmaceutical Benefits Scheme prescription data for two months prior to interview (**HRT-PBS**).

Hippocampal volume and change of volume was drawn from Magnetic Resonance Imaging (MRI) data.

Insulin function was obtained via the homeostatic model assessment (HOMA2[7]) drawn from venous blood measures plasma insulin, glucose, and creatinine) at the final wave of data collection.

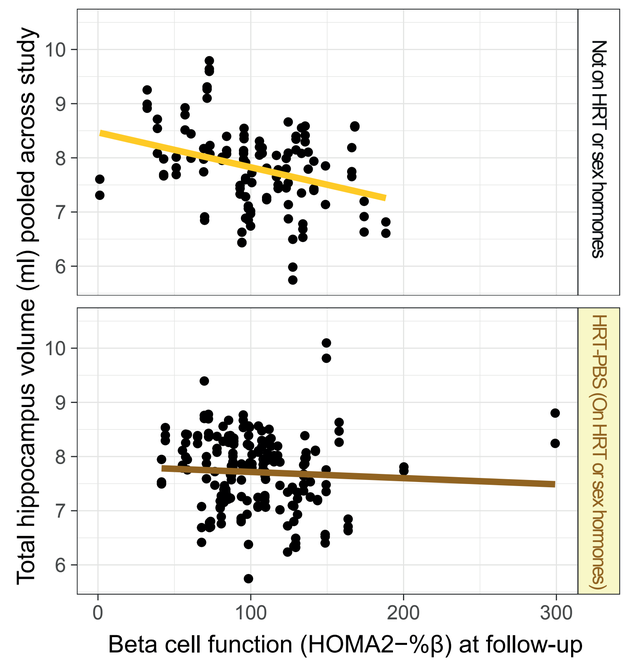
Analyses were hierarchical models, with repeated MRI and medication measures nested by participant. All models controlled for participant age and intracranial volume.

Results

Fourty two percent (*n*=138) of participants had undergone **HRT-SR**, and approximately half (*n*=155) of the current sample had undergone HRT or taken medications which include sex hormones during the study (**HRT-PBS**).

Total hippocampus volume averaged 7.98ml at baseline, and decreased by 0.025ml/year (*b*=-0.025, 95%CI[-0.029,-0.22]).

Neither hippocampus volume, nor hippocampal atrophy, were significantly associated with insulin function (HOMA2-IR, HOMA2-%β, or HOMA2-%S; exemplified in the figure below). There were no significant interactions between **HRT-SR** or **HRT-PBS** and insulin function as predictors of hippocampus volume.



Individuals with HRT-SR had 0.089ml significantly smaller hippocampus volumes (*b*=-0.089, 95%CI[-0.156,-0.022]), but not significantly greater hippocampus atrophy over time (*b*=0.022, 95%CI[-0.012,0.056]), than those not on HRT.

Conversely, **HRT-PBS** was not significantly associated with hippocampus volumes (*b*=-0.032, 95%CI[-0.097,0.032]), but was associated with significantly less hippocampus atrophy over time (0.015ml less atrophy per year; 95%CI[0.006,0.025]), than those not on HRT.

Conclusions

HRT-SR was associated with smaller hippocampal volumes, while **HRT-PBS** was protective against hippocampal atrophy.

It may be that HRT earlier in life (e.g. prior to the study) is associated with hippocampal atrophy, but becomes protective due to biological changes later in life (e.g. in the duration of this study).

There was no significant association between insulin function and hippocampus volume and atrophy, so HRT could not mediate the association.

This discrepancy with previous findings[2] may be due to methodological differences, e.g. a female-only sample, and use of HOMA2 (rather than the earlier HOMA) model in the current study.

This study did not support the hypothesis that insulin function mediates the effect of hormone replacement therapy on age-associated hippocampal atrophy.

References

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