**Intranasal insulin enhances functional connectivity of the default mode network and reduces subjective feeling of hunger**

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**Background:** Enhancing brain insulin action has beneficial effects on eating behavior and cognition. Studies in dementia suggest that intranasal insulin can enhance functional connectivity within the default-mode-network to improve cognition. Behavioral studies have shown that intranasal insulin can reduced food intake. Little is known, however, if intranasal insulin can influence brain functional connectivity in young healthy individuals to influence human eating behavior.

**Methods:** We performed resting-state functional magnetic resonance imaging (rsfMRI) of the brain (3 Tesla scanner; Tim Trio Siemens), on two separate days, in 47 healthy participants (26 men, 21 women; age range 21-36 years). We measure rsfMRI before and 30 min after intranasal insulin or placebo application. Functional connectivity maps were acquired of the default mode network using a seed based approach (REST toolbox version 1.8). Functional connectivity maps of each subject were corrected for the baseline measurement and entered into a second level analysis in SPM8, to determine the effect of insulin versus placebo. Additionally, participants rated subjective feeling of hunger on a visual analogue scale before, 60 as well as 120 min after spray application.

**Results:** We identified a significant increase in functional connectivity between the prefrontal regions of the default-mode-network and the hippocampus after intranasal insulin compared to placebo (p<0.001 whole-brain uncorrected; p\(_{\text{FWE}}\)<0.05 small volume corrected for the hippocampus). Moreover, this enhanced functional connectivity correlated with the change in hunger after intranasal insulin application. Hence, participants with a stronger increase in functional connectivity revealed a decline in hunger 120 min after intranasal insulin. No such relationship was observed after placebo administration.

**Conclusions:** Taken together, we were able to show that the functional connectivity of the default mode network can be enhanced by intranasal application of the hormone insulin in healthy young adults. This may explain the beneficial effects of brain insulin action on eating behavior and cognition.