

Effects of intranasal insulin as adjuvant on fear extinction in healthy humans: a randomized, double-blind, placebo-controlled experimental study

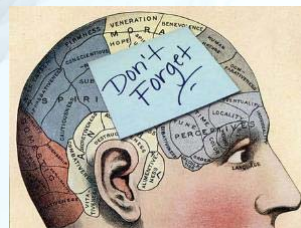


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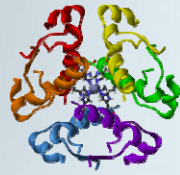
How to make treatments more effective?

- Use of endogenous hormones and pharmacological agents that enhance extinction learning and memory
 - Cortisol (Soravia et al., 2006, Lass-Hennemann & Michael, 2014; Yehuda et al., 2015)
 - D-cycloserine (Hofmann et al., 2006; Otto et al., 2009)
 - Oxytocin (Acheson et al., 2013)
- Insulin?
 - modulates learning and memory processes (Stockhorst et al., 2004)



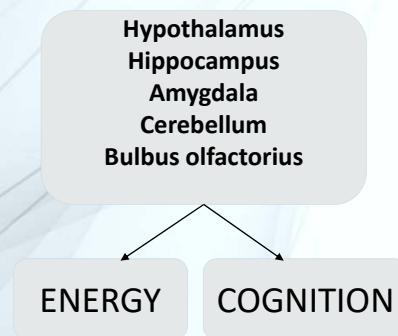


Insulin



- Peptide hormone produced in the pancreatic β -cells
- Main function: glucose homeostasis

- Potential to cross the blood-brain barrier \rightarrow reach the CNS components of the insulin signaling pathway



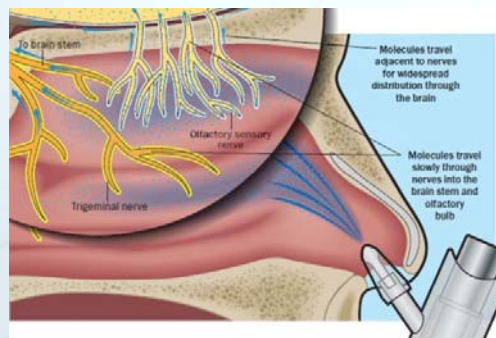
Intranasal application of Insulin

Insulin crosses the nose mucosa

Diffuses into the cerebrospinal fluid (CSF) through olfactory epithelium

Reaches brain receptors

Enables the study of central insulin under **euglycemia** (less invasive)





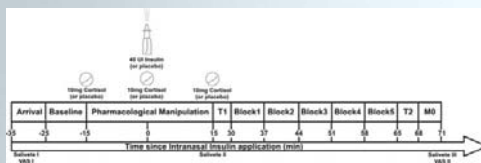
Beneficial effects of central insulin on memory processes

- Better memory performance in patients with Alzheimer's disease and mild cognitive impairment (Freiherr et al., 2013; Claxton et al. 2015)
- Better declarative memory in healthy participants, chronic and one time application (Benedict et al., 2004; Benedict, Kern, Schultes, Born, & Hallschmid, 2008; Hallschmid, Benedict, Schultes, Born, & Kern, 2008; Krug, Benedict, Born, & Hallschmid, 2010)
- Evidence for sex differences in central insulin signaling: greater improvement of memory functions in women (Benedict et al., 2008)

Hum Brain Mapp. 2013 Aug 1. doi: 10.1002/hbm.22304. [Epub ahead of print]

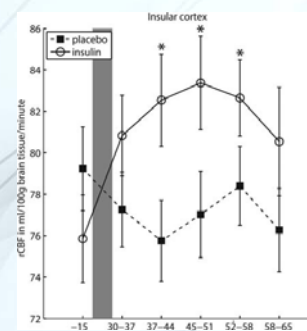
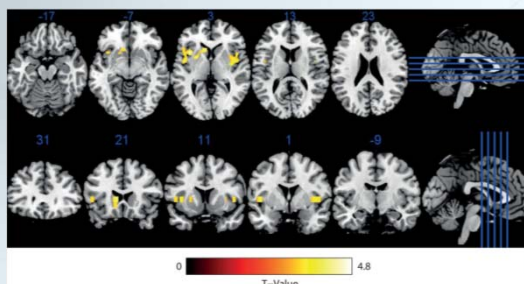
Intranasal insulin increases regional cerebral blood flow in the insular cortex in men independently of cortisol manipulation.

Schilling TM, Ferreira de Sá DS, Westerhausen R, Strelzyk F, Larra MF, Hallschmid M, Savaskan E, Oitzl MS, Busch HP, Naumann E, Schächinger H. Institute of Psychology, Division of Clinical Psychophysiology, University of Trier, Trier, Germany.



37-58min Ins: rCBF increase in the
insular cortex

Region relevant for
fear extinction



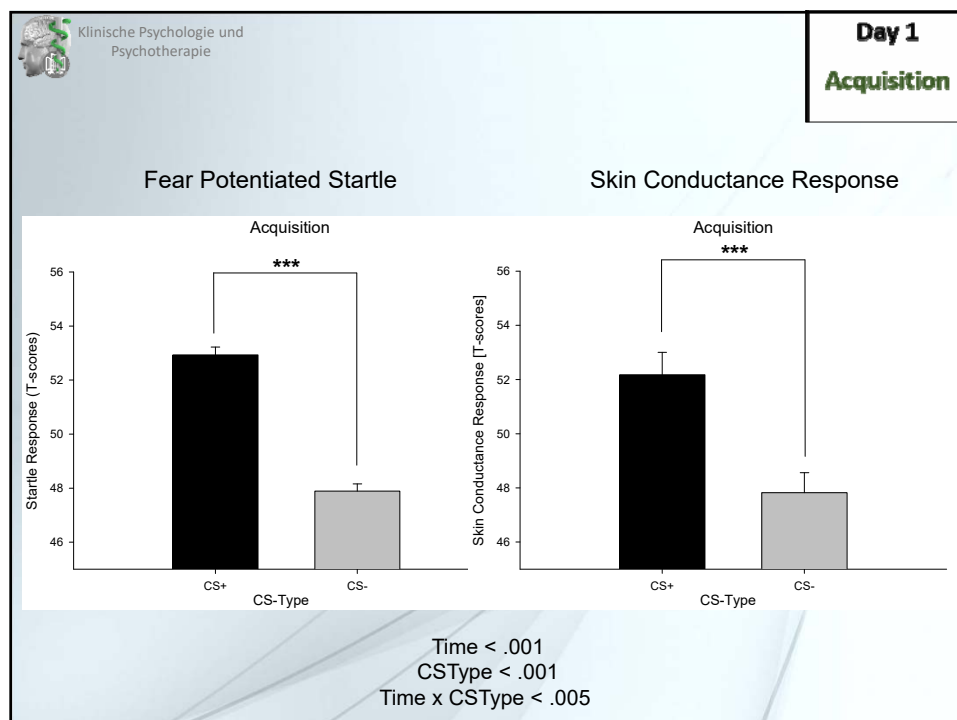
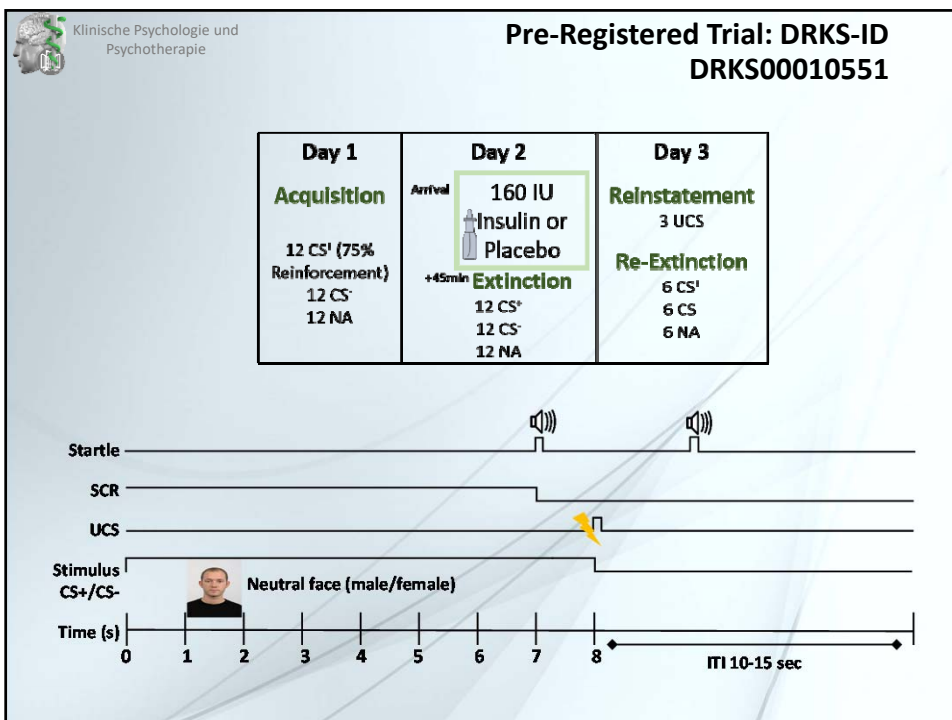


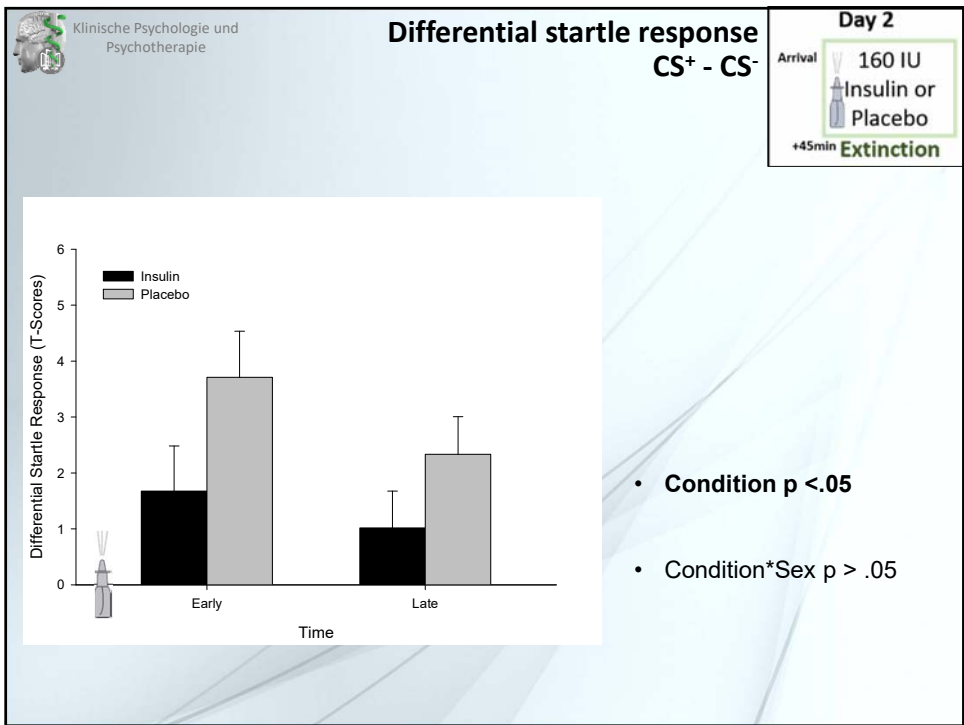
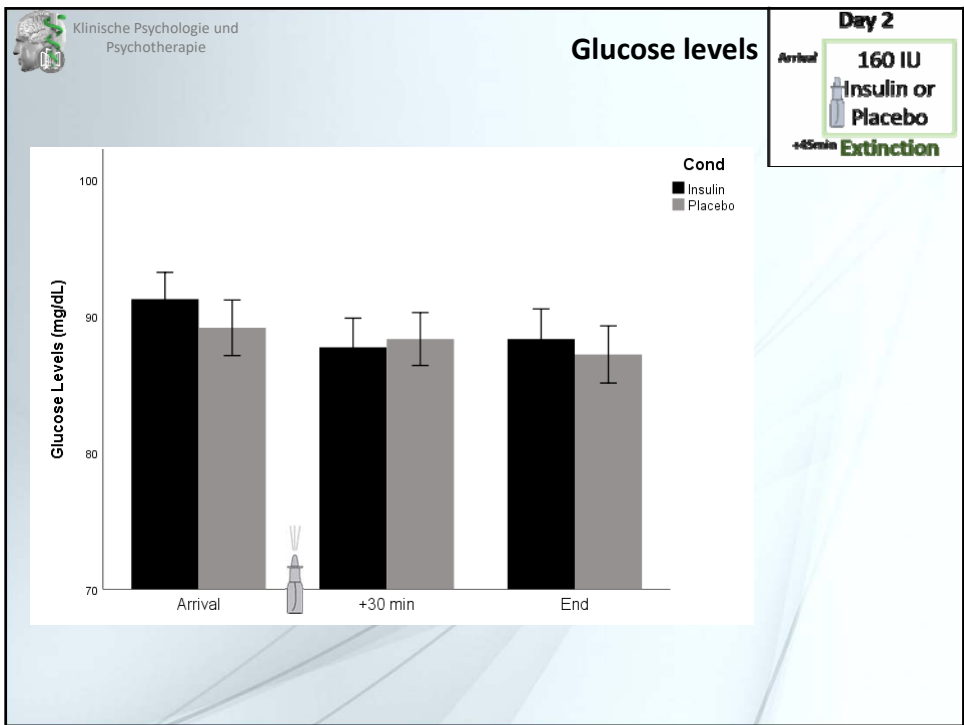
Does intranasal insulin facilitate fear extinction?



Pre-Registered Trial: DRKS-ID DRKS00010551

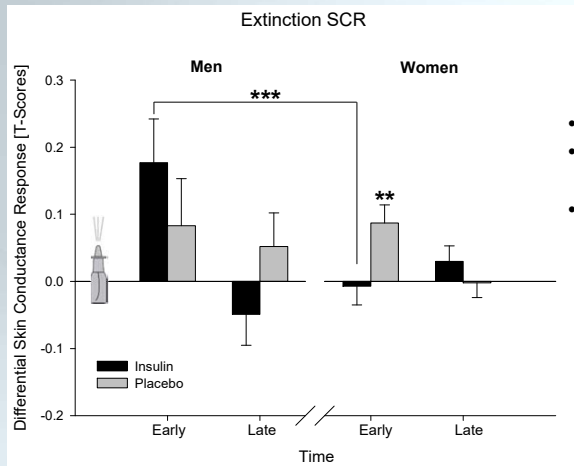
- Double-blind, placebo controlled study
- 123 healthy participants
 - Intranasal insulin - 160 I.U.
 - 62 participants (31 ♀)
 - Placebo - vehicle solution
 - 61 participants (32 ♀)
- Similar insulin-glucose levels:
 - Food restriction for at least 10 h
 - Controlled for time of day (8h-13h)





Differential SCR CS+ - CS-

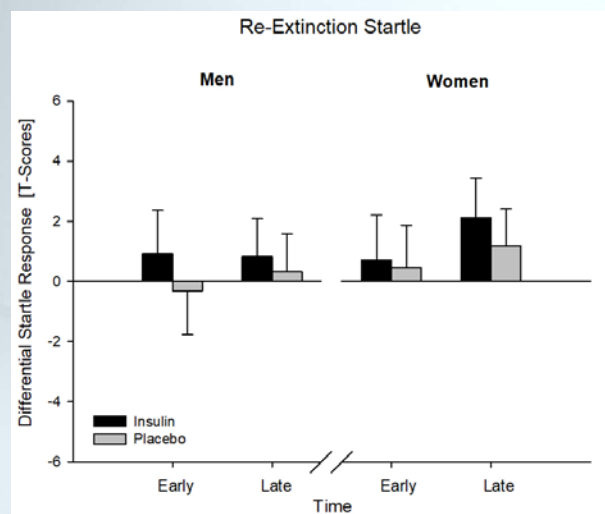
Day 2
 Arrival 160 IU
 Insulin or Placebo
 +45min Extinction



- Condition, $p > .05$
- Time*Condition, $p > .05$
- **Time*Condition*Sex, $p = .006$**

Re-Extinction Learning Differential Startle

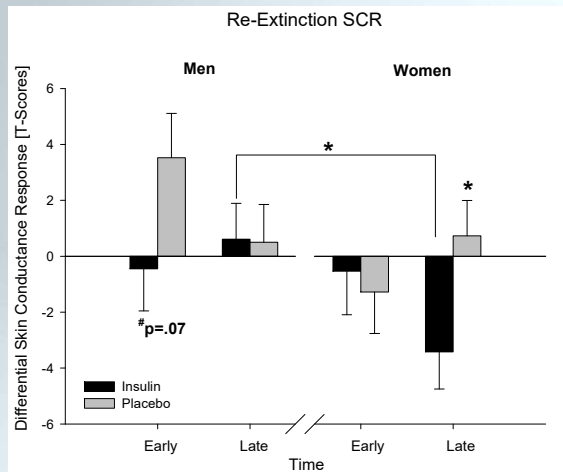
Day 3
 Reinstatement
 3 UCS
 Re-Extinction





Re-Extinction Learning Differential SCR

Day 3
Reinstatement
3 UCS
Re-Extinction



- **Time*Condition*Sex**, $p < .05$
- **Time**, $p < .001$



Summary of results and discussion

- **Extinction**
 - Men and women receiving insulin show enhanced extinction on FPS.
 - Only women receiving insulin show enhanced extinction on SCR (effect only present in early extinction)
- **Re-Extinction**
 - No insulin effect on FPS
 - Only women in the insulin group show enhanced re-extinction on SCR (effect only present in late re-extinction)
- Intra-nasal insulin is a promising enhancer of exposure therapy, but sex effects need to be taken into consideration.



Thank you!

Tanja Michael

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Questions?