Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to:

Heni M, Wagner R, Willmann C et al. Insulin action in the hypothalamus increases second phase insulin secretion in humans.

Table of Contents

Supplementary Table 1.

Clinical characteristics of brain insulin resistant vs brain insulin sensitive subjects. Parameters shown were measured at baseline and are given as means ± SD. NEFA – non-esterified fatty acids; TG – triglycerides.

	Brain insulin resistant	Brain insulin sensitive	p
N	8	7	
Age	27.5 ± 2.6	26.3 ± 4.2	0.5
BMI	25.1 ± 2.9	24.0 ± 1.7	0.4
Body fat content (%)	19.6 ± 6.3	18.0 ± 3.6	0.6
HbA1c (%)	5.2 ± 0.2	5.0 ± 0.2	0.3
Glucose (mmol/l)	5.0 ± 0.42	4.94 ± 0.23	0.8
Glucagon (pg/ml)	90.24 ± 31.91	103.85 ± 10.47	0.6
insulin (pmol/l)	50.75 ± 34.36	61.86 ± 25.84	0.5
C-peptide (pmol/l)	363.9 ± 193.4	404.6 ± 146.5	0.7
NEFA (µmol/l)	479.9 ± 126.3	464.7 ± 127.5	0.8
TG (mg/dl)	80.6 ± 35.6	105.3 ± 54.0	0.3
IGF-1 (ng/ml)	152.9 ± 64.9	175.0 ± 35.7	0.4
Cortisol (nmol/l)	354.0 ± 87.0	446.6 ± 143.1	0.1

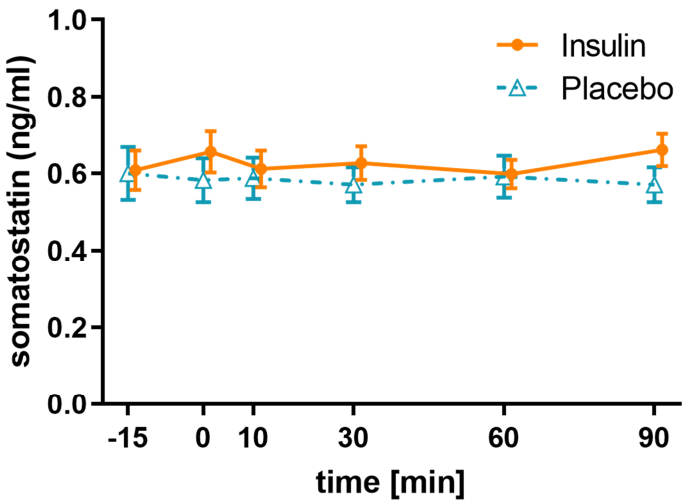
Supplementary Table 2.

Mean and median values of CBF (cerebral blood flow) in brain insulin resistant and brain insulin sensitive subjects

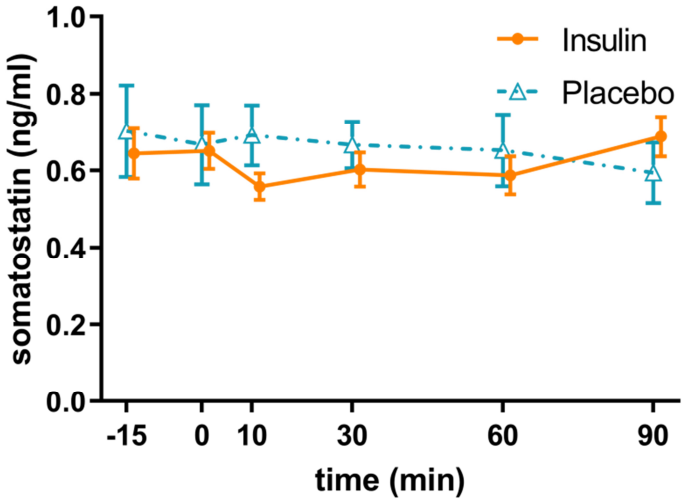
	CBF baseline Mean+/- SD	CBF 30 min post insulin spray Mean+/- SD	CBF baseline Median (Q1/Q3)	CBF 30 min Median (Q1/Q3)
Brain insulin resistant (N=8)	33.7 +/-4.4	43 +/-5.3	32.9 (32.5/33.6)	41.1 (38.6/45.4)
Brain insulin sensitive (N=7)	45.1 +/-6.9	40.4 +/-8.3	43.6 (42.7/47.1)	40.9 (34/46.1)

Supplementary Figure 1

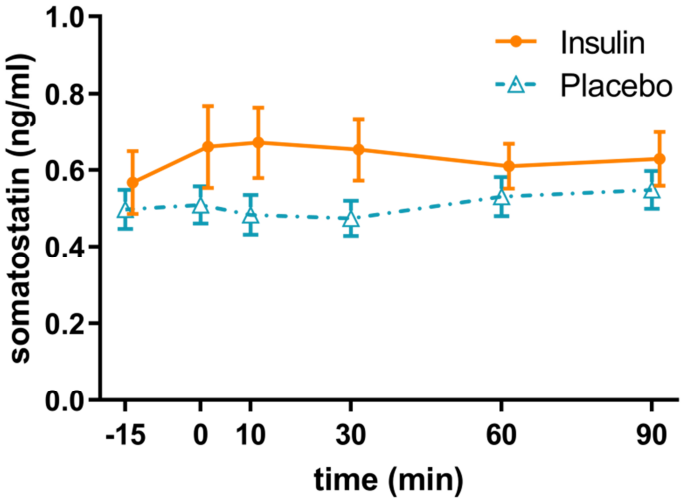
A



B



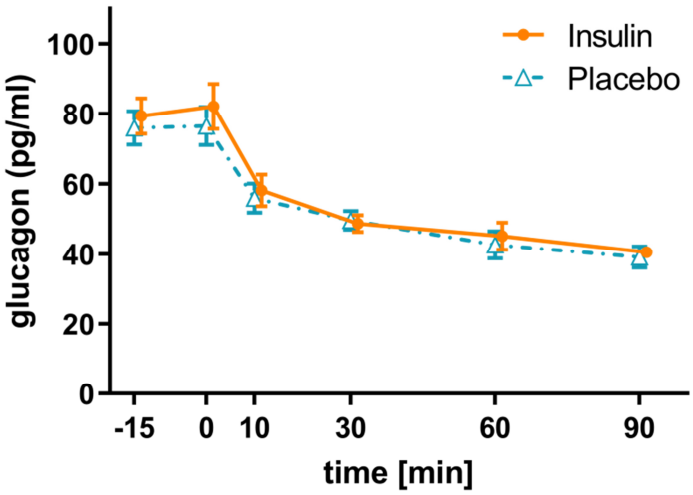
C



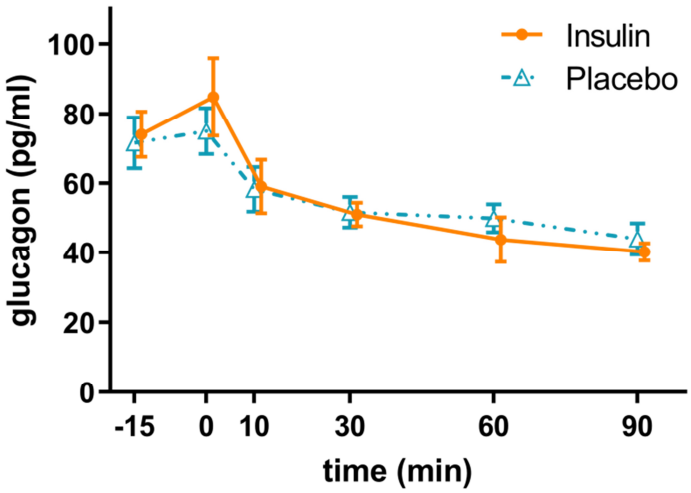
Plasma somatostatin levels. Plasma somatostatin levels during clamp from whole cohort (A; n=15) and in the subgroups with low (B; n=8) and high (C; n=7) hypothalamic insulin sensitivity. Values are shown as mean ± SE.

Supplementary Figure 2

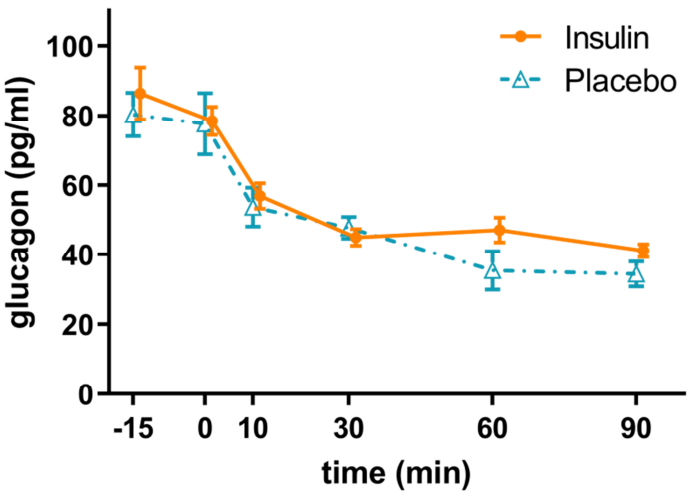
A



B

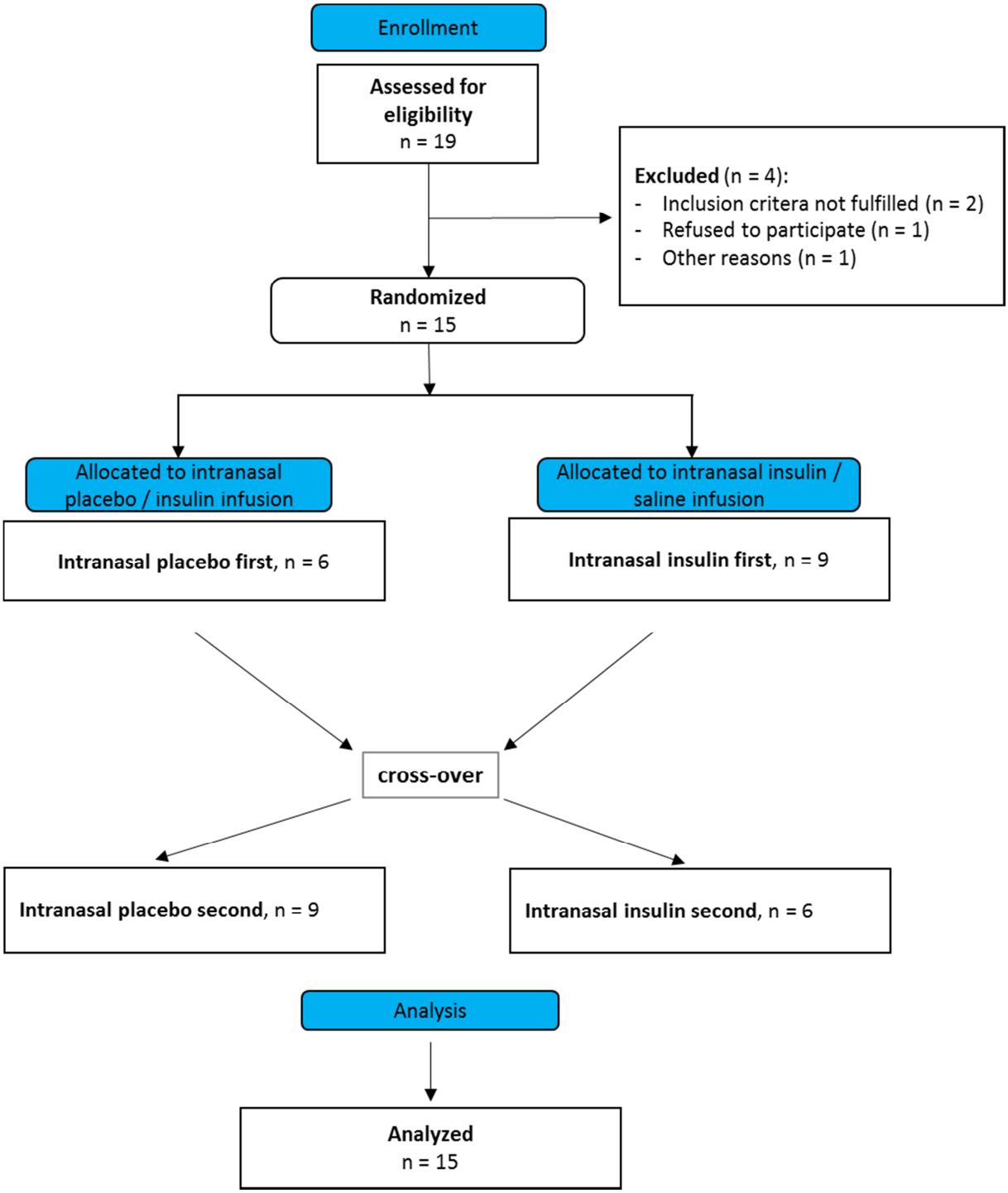


C



Plasma glucagon levels. Plasma glucagon levels during clamp from whole cohort (A; n=15) and in the subgroups with low (B; n=8) and high (C; n=7) hypothalamic insulin sensitivity. Values are shown as mean ± SE.

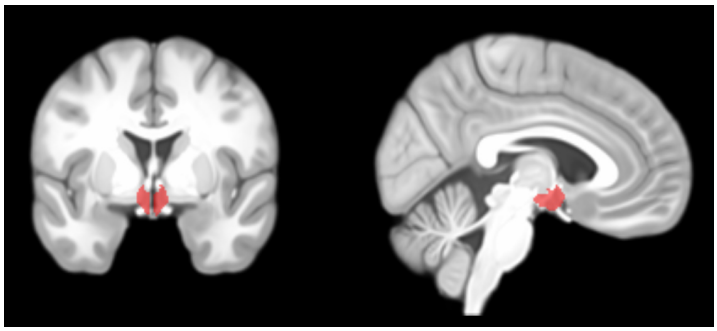
Supplementary Figure 3



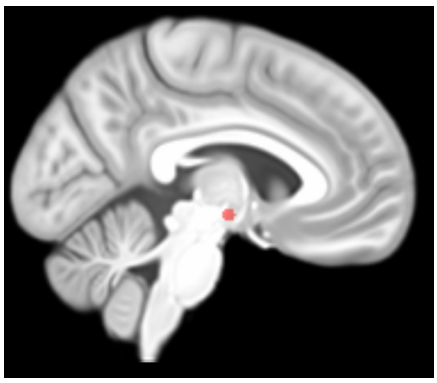
CONSORT diagram. CONSORT (Consolidated Standards Of Reporting Trials) diagram showing the flow of participants through this double-blind randomized crossover trial.

Supplementary Figure 4

A



B



Hypothalamus displayed on standard anatomical template. Picture A shows the whole hypothalamus on a coronal and sagittal section. Picture B shows the hypothalamic region revealing a significant change after application of intranasal insulin, as previously reported (Kullmann et al. 2015, Diabetes Care).