Brain Insulin Signaling: Implications for Disease Modelling and Treatment of Mood Disorders

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Presenter Disclosure

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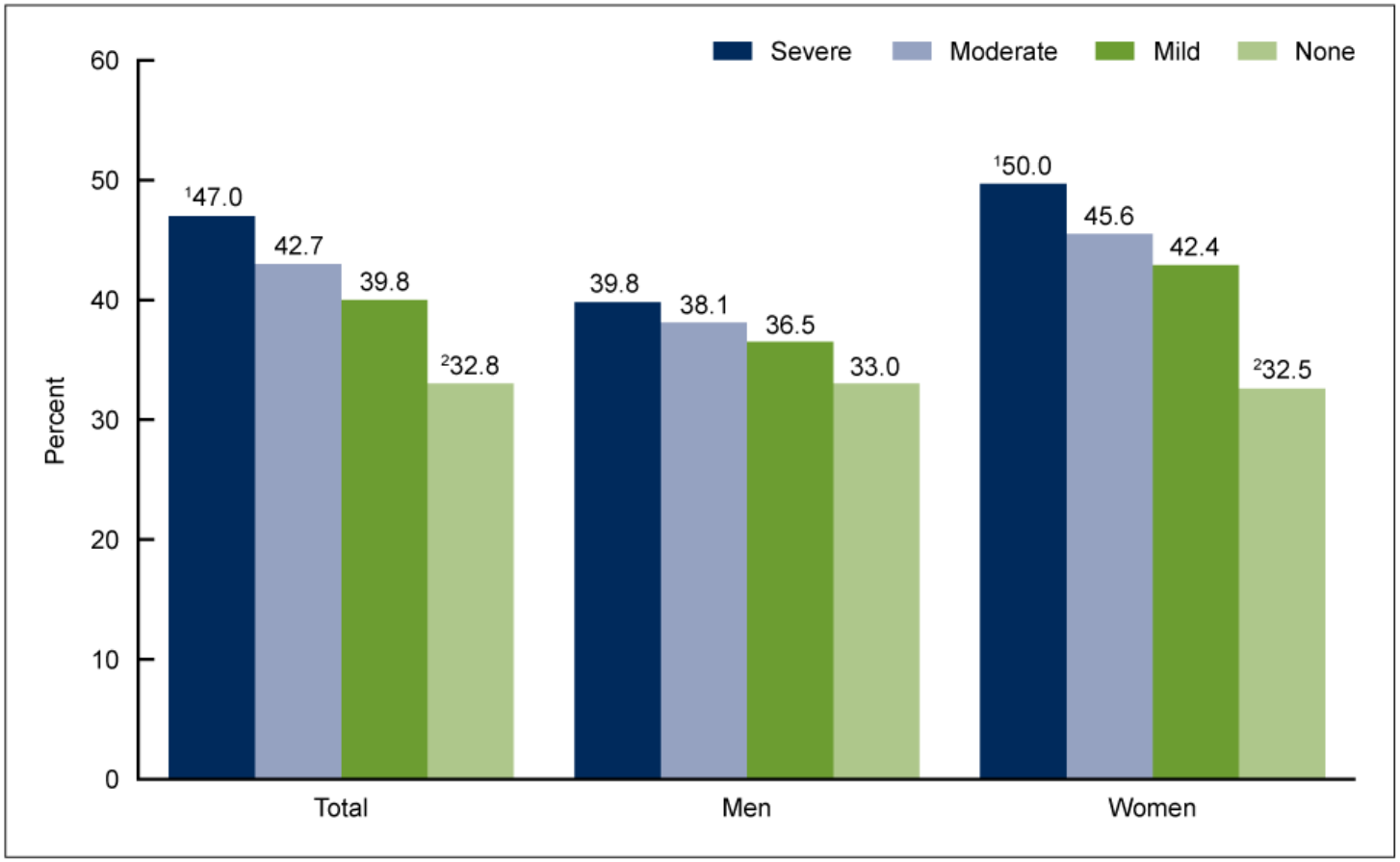
  - Other: None

Summary

- **Introduction**
  - **Metabolic dysregulation in mood disorders**
  - **The role of insulin signaling in the brain**
- Insulin signaling and Domains of Psychopathology
  - Cognition
  - Reward
- Implications
  - Disease Modelling
  - Therapeutic

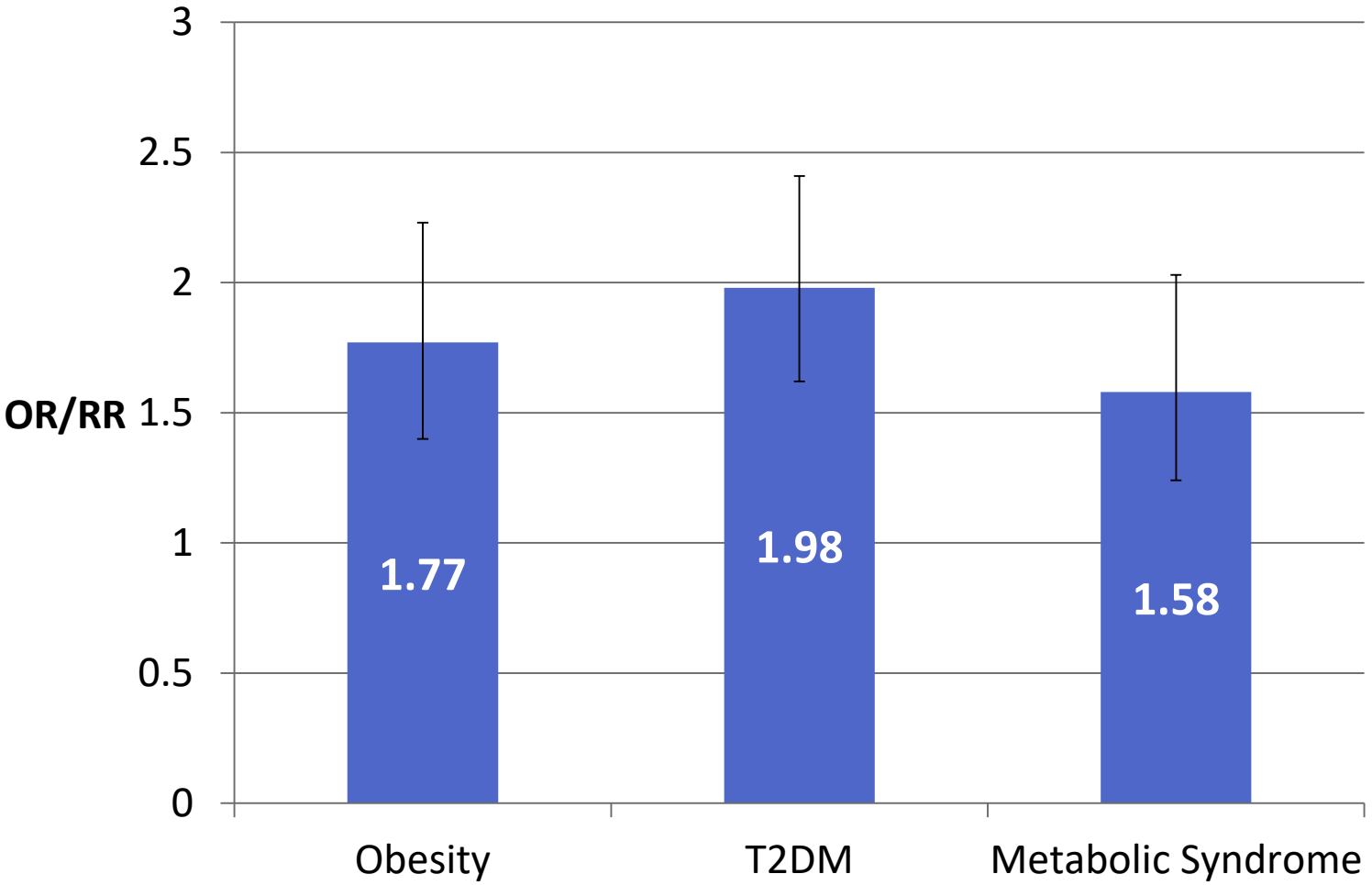
Obesity and Major Depressive Disorder

Figure 4. Age-adjusted percentage of adults aged 20 and over who were obese, by sex and depression severity: United States, 2005–2010



[1]Statistically significant trend.
[2]Significantly different than other severity categories.
NOTES: Estimates were age-adjusted by the direct method to the 2000 U.S. census population using the age groups 20–39, 40–59, and 60 and over. Moderate and severe indicate depression, while mild indicates mild depressive symptoms, which are not included in the definition of depression. Access data table for Figure 4 at: http://www.cdc.gov/nchs/data/databriefs/db167_table.pdf#4.
SOURCE: CDC/NCHS, National Health and Nutrition Examination Survey, 2005–2010.

Metabolic Comorbidities and Bipolar Disorder



Jackson et a. Bipolar Disord. 2015; Zhao et al. J Affect Disord. 2016
Vancampfort et al. J Clin Psychiatry. 2015; Vancampfort et al. World Psychiatry. 2015; Grant et al. Arch Gen Psychiatry 2004.

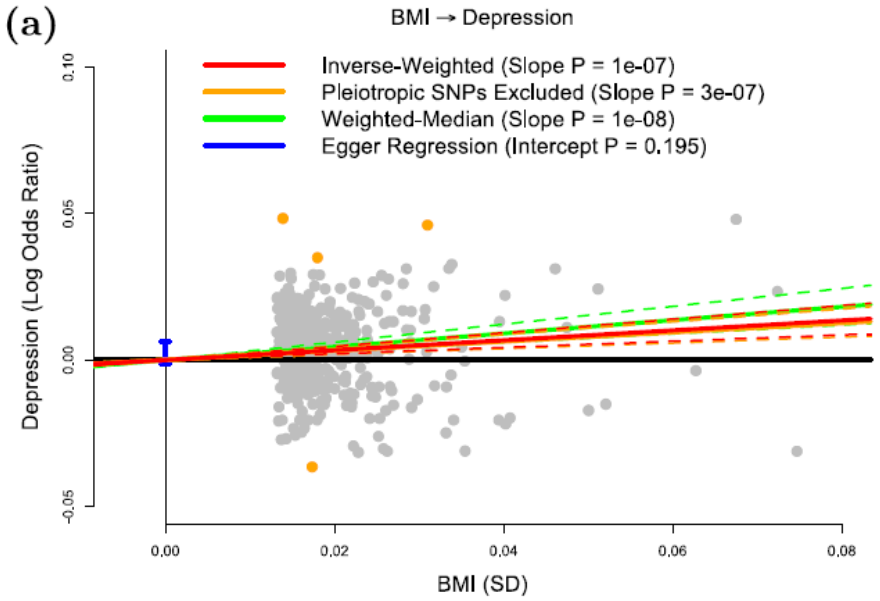
Insulin Resistance in MDD

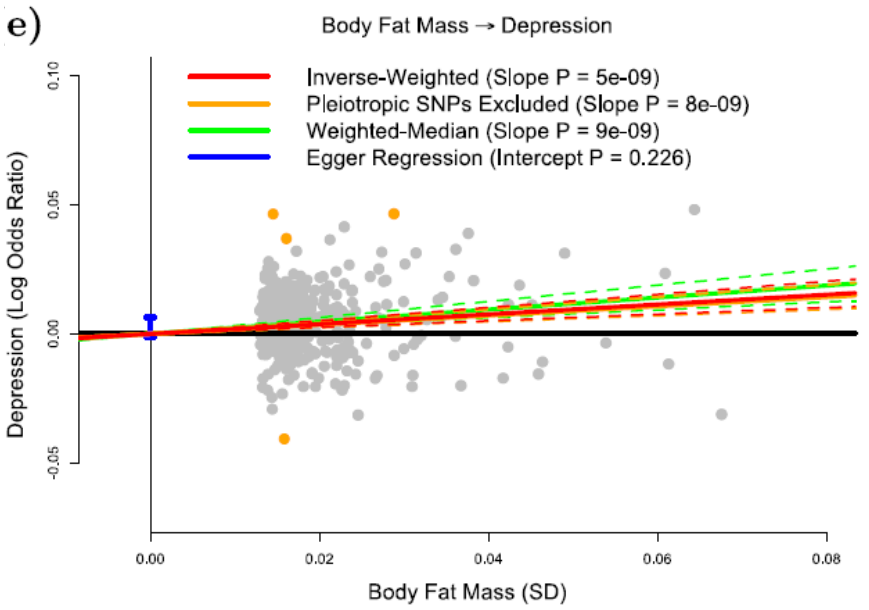
Table 1
Statistics summary of between-group meta-analyses of peripheral insulin resistance in depression.

Group-wise	No. of Pairwise	No. of Subjects		Meta-analysis		
Between-Group Meta-analyses		**Dep**	**HC**	**Hedges' *g***	**95 % CI**	***P***
Depression Acute - ALL						
Insulin						
*All**	49	26,197	195,314	0.29	0.21–0.37	< 0.001
*Age paired**	26	2,288	14,003	0.33	0.19–0.48	< 0.001
*Sex paired**	26	2,025	14,622	0.34	0.20–0.48	< 0.001
*BMI paired**	25	20,084	162,584	0.30	0.17–0.44	< 0.001
HOMA Index						
*All**	34	21,695	183,163	0.30	0.18–0.41	< 0.001
*Age paired**	17	2,077	11,961	0.31	0.15–0.48	< 0.001
*Sex paired**	18	2,217	12,714	0.20	0.04–0.36	0.01
*BMI paired**	18	19,801	159,585	0.32	0.14–0.50	< 0.001

B.S. Fernandes et al. Neuroscience and Biobehavioral Reviews 139 (2022) 104758

Bidirectional Risk?





Speed et al. Transl Psychiatry. 2019 Aug 5;9(1):184.

Metabolic Abnormalities Precede the Onset of Mental Illnesses

TABLE 2. Cox regression models of the association between triglyceride-HDL ratio, waist circumference, and fasting plasma glucose level at study enrollment and incident major depressive disorder in adults (N=601)[a]

Model	Adjusted Hazard Ratio	95% CI
Model 1: triglyceride-HDL ratio (insulin resistance; 1 ratio unit)	1.89	1.15, 3.11
Model 2: waist circumference (5 cm)	1.11	1.01, 1.21
Model 3: fasting plasma glucose[b] (1 mmol/L)	1.37	1.05, 1.77

[a] Data are for participants in the Netherlands Study of Depression and Anxiety. Each model was adjusted for age, sex, education, physical activity, harmful alcohol use, and smoking status. Follow-up time was 4,579 person-years for all models. HDL=high-density lipoprotein.

[b] Adjusted for medication use as described by Révész et al. (35).

Watson et al. Am J Psychiatry. 2021 Oct 1;178(10):914-920.

Expression of Insulin Receptors in the Brain

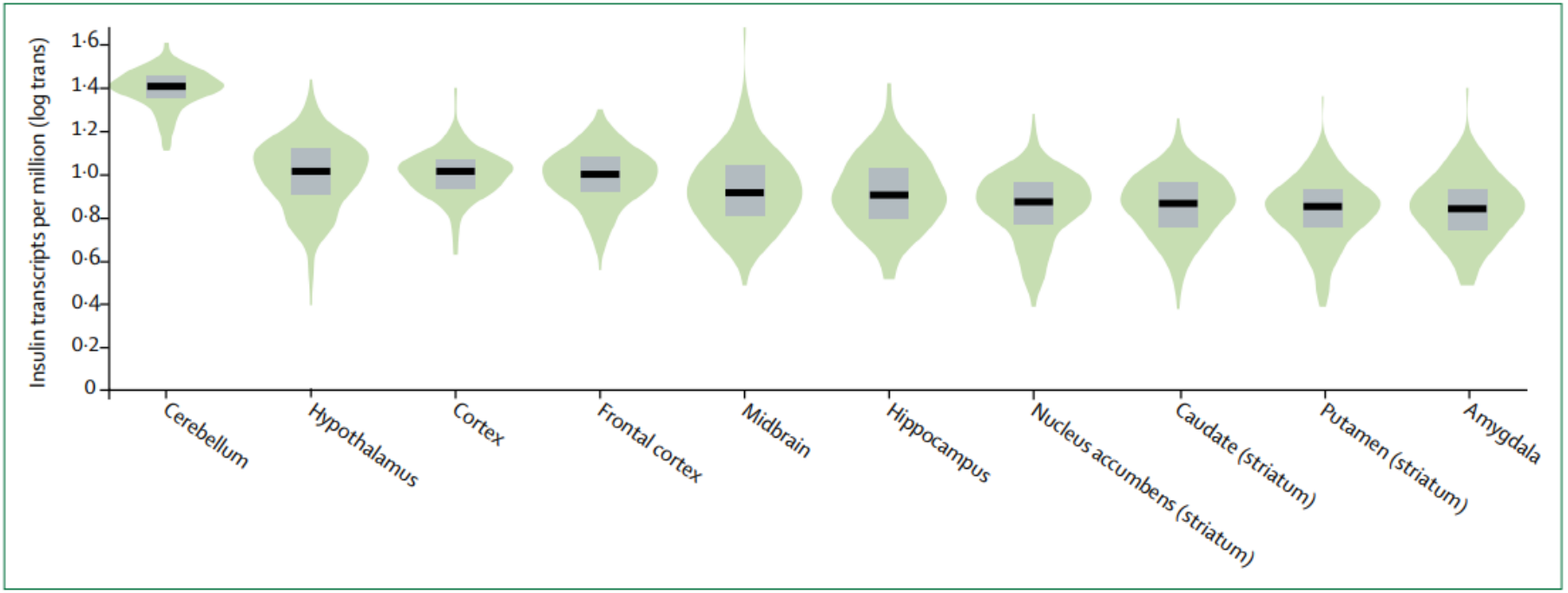


Figure 1: **Expression of the insulin receptor in the human brain**

Kullmann et al. Lancet Diabetes Endocrinol 2020; 8 524–34.

Brain Insulin Signaling

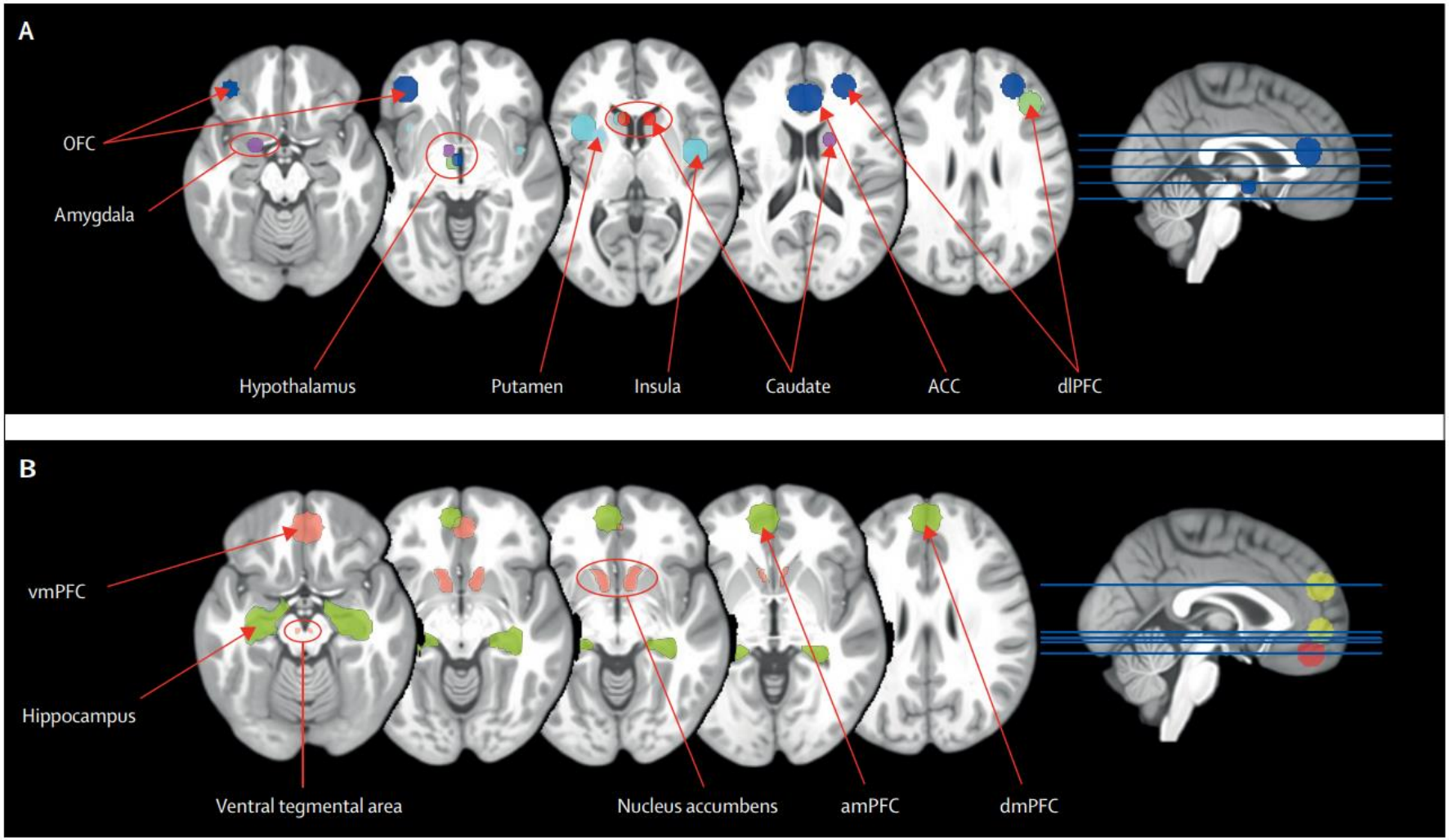


Figure 3: Central insulin action in humans

Kullmann et al. Lancet Diabetes Endocrinol 2020; 8 524–34.

Insulin and Functional Connectivity

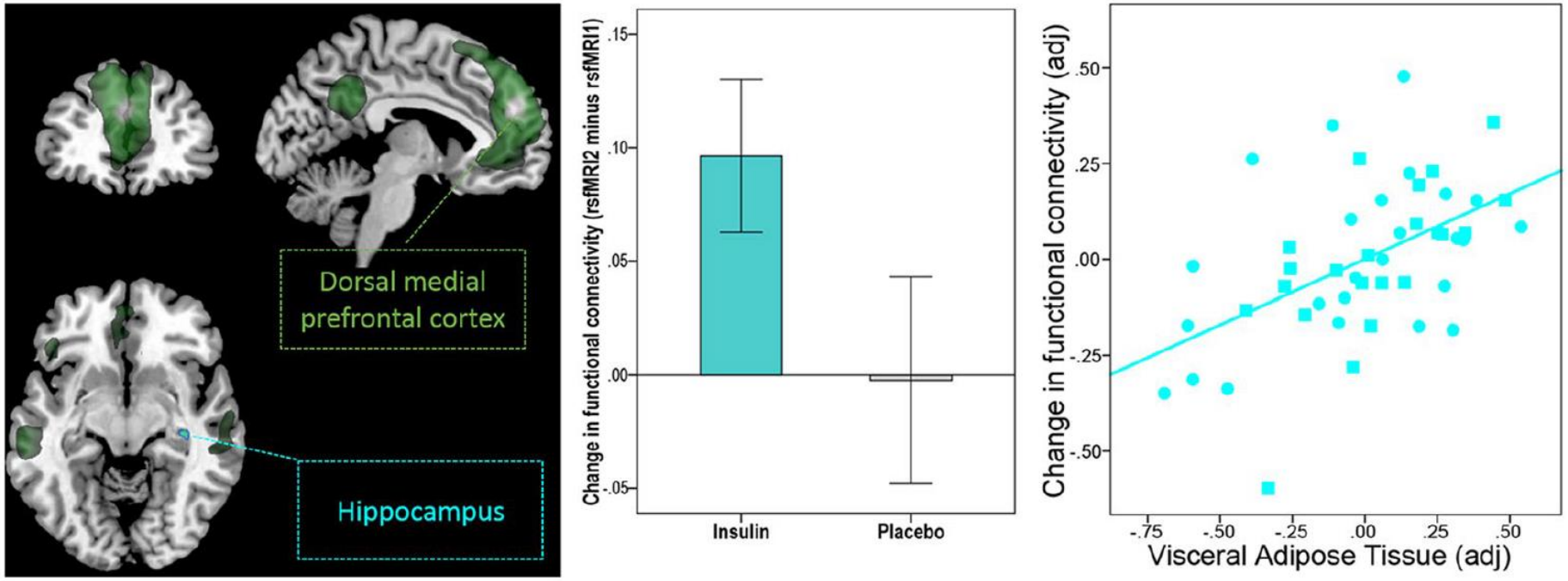
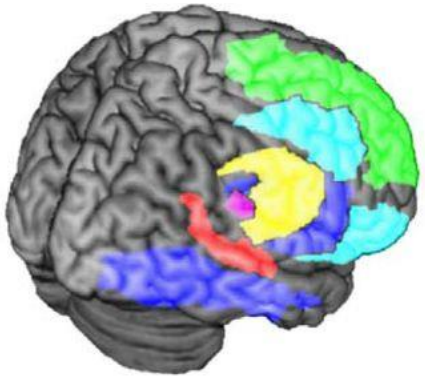


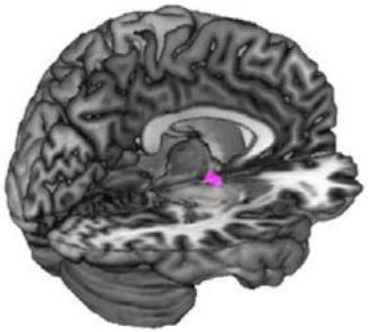
Figure 3. Intranasal insulin increases functional connectivity between the dorsal medial prefrontal cortex (PFC) of the default-mode network (DMN) and the hippocampus in lean, overweight and obese participants.

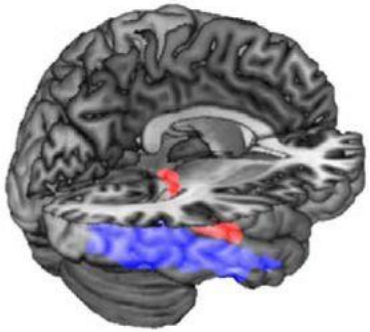
Kullmann et al. Sci Rep. 2017 May 9;7(1):1627.

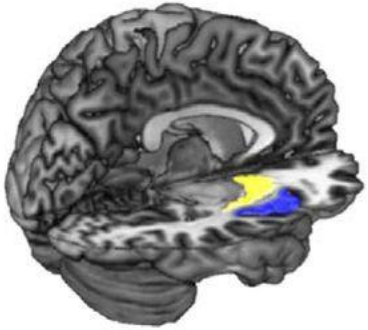
Brain Insulin Signaling

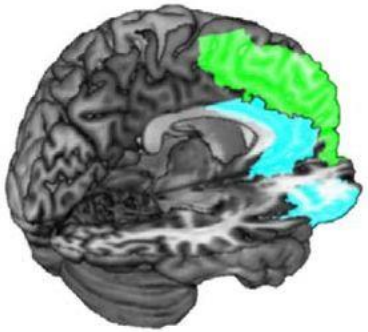


Insulin sensitive brain regions









Homeostasis
Hypothalamus

Memory
Hippocampus

Reward
Striatum

Inhibition
Lateral prefrontal cortex

Attention
Fusiform gyrus

Sensory perception
Insular cortex

Motivation
Orbitofrontal cortex
Anterior cingulate cortex

Kullmann et al. Physiol Rev. 2016 Oct;96(4):1169-209.

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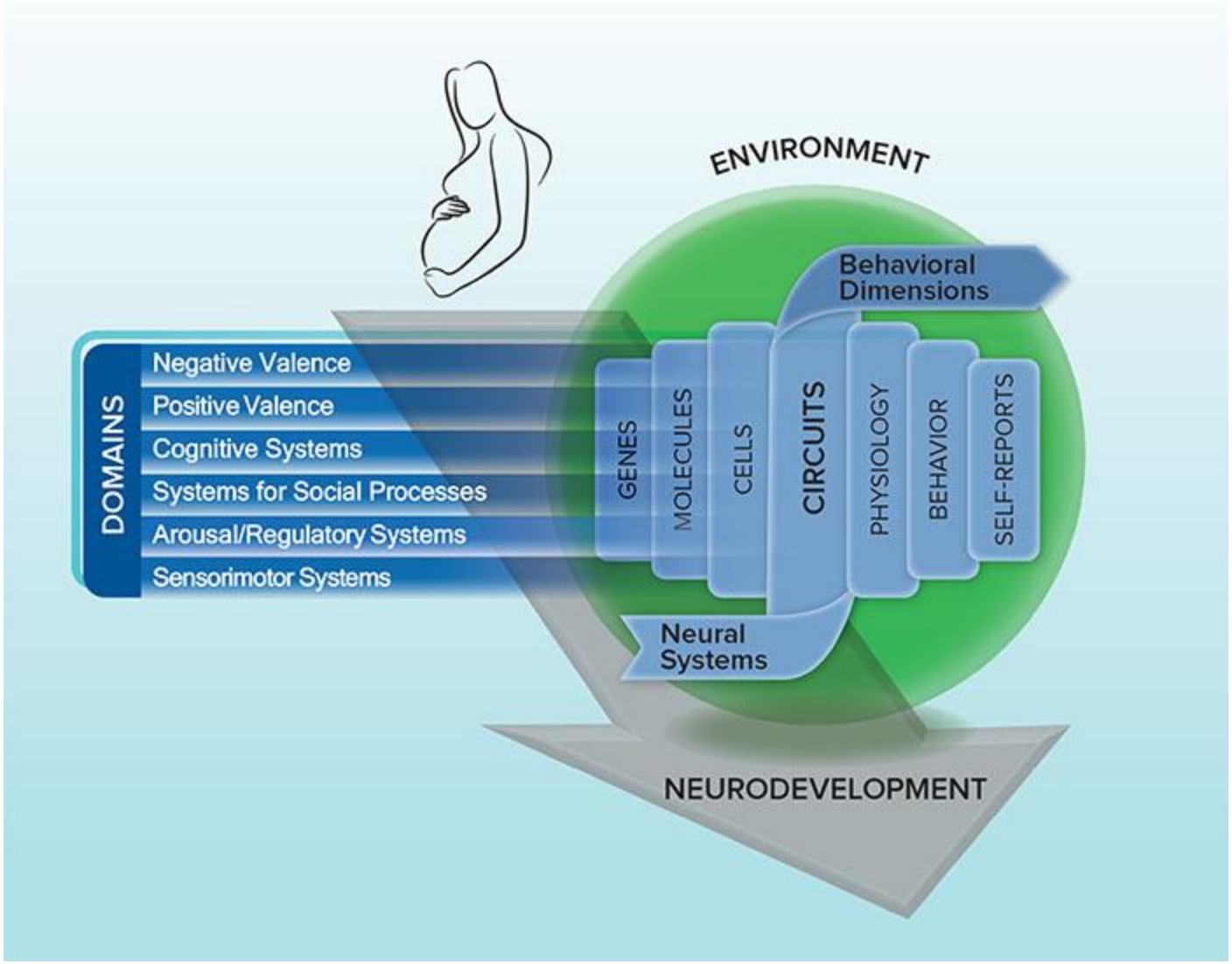
Research Domain Criteria (RDoC) Framework



https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/about-rdoc.shtml

Cognitive Function and Mood Disorders

Meta-analysis of first episode bipolar disorder

Table 3
Number of studies (k), pooled sample size (N), pooled ES (Hedges' g), homogeneity (Q, I, tau^2), publication bias, and sensitivity analyses (pooled ES range; each study removed), by cognitive domain.

Cognitive domain	k	BD N	CTL N	Hedges' g	95% CI	Q	I	tau^2	Egger's test (t)	Fail-safe N	Trim & Fill	Sensitivity analyses
Psychomotor speed	6	170	349	0.56**	0.19–0.92	15.67*	68%	0.14	3.27*	35	0.56*	0.42–0.67
Attention/working memory	8	259	891	0.37***	0.22–0.51	6.28	0%	0.00	1.77	–	–	0.34–0.44
Learning and Memory												
Verbal	6	194	486	0.30***	0.13–0.48	4.38	0%	0.00	1.46	–	–	0.25–0.36
Visual	5	172	445	0.17	–0.02–0.35	3.61	0%	0.00	–	–	–	–
Executive Functioning												
Attentional switching	6	170	349	0.52***	0.28–0.78	6.70	25%	0.02	6.30**	37	0.34*	0.44–0.61
Verbal fluency	10	296	939	0.32***	0.18–0.47	9.43	5%	0.00	2.42*	51	0.32*	0.28–0.37
Cognitive flexibility	7	198	356	0.41**	0.12–0.70	14.69*	59%	0.09	0.38	–	–	0.33–0.49
Response inhibition	5	161	288	0.44***	0.24–0.65	3.82	0%	0.00	0.25	–	–	0.36–0.51
Total k/N	12	341	1009									

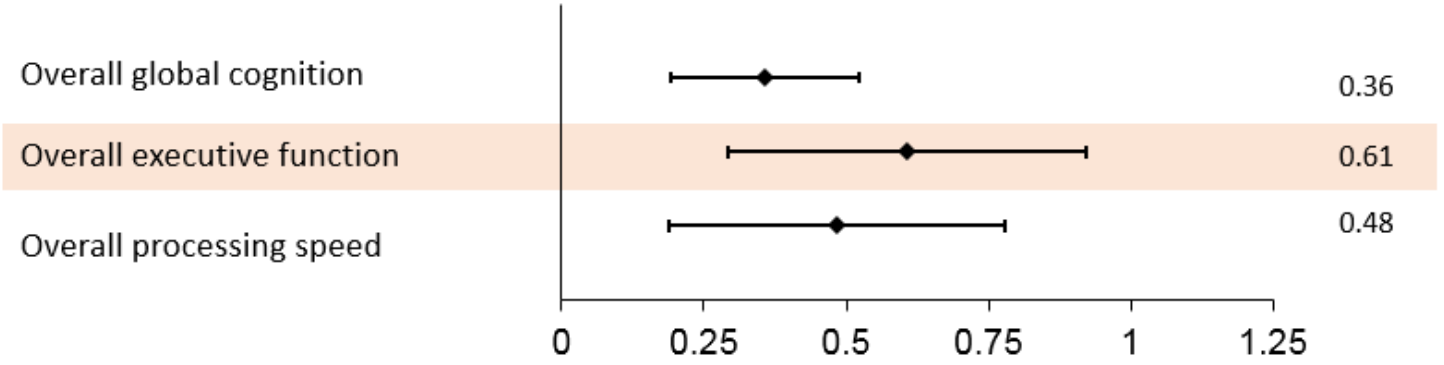
BD = Bipolar Disorder. CTL = Control. ES = effect size.
*$p \leq 0.05$. **$p \leq 0.01$. ***$p \leq 0.001$.

Lee et al. J Psychiatr Res. 2014 Oct;57:1-11.

Obesity and Metabolic Syndrome Are Associated With Cognitive Deficits in Patients With BD

Patients with BD who were overweight/obese had significantly impaired global cognition and performed significantly worse in executive functions and processing speed than patients with BD whose weight was normal*

Overall differences (95% CI) between obese/overweight and normal-weight patients with BD



Bora E1, McIntyre RS2, Ozerdem A1.Psychol Med. 2019;49:738-749.

Cognition and Energy Metabolism

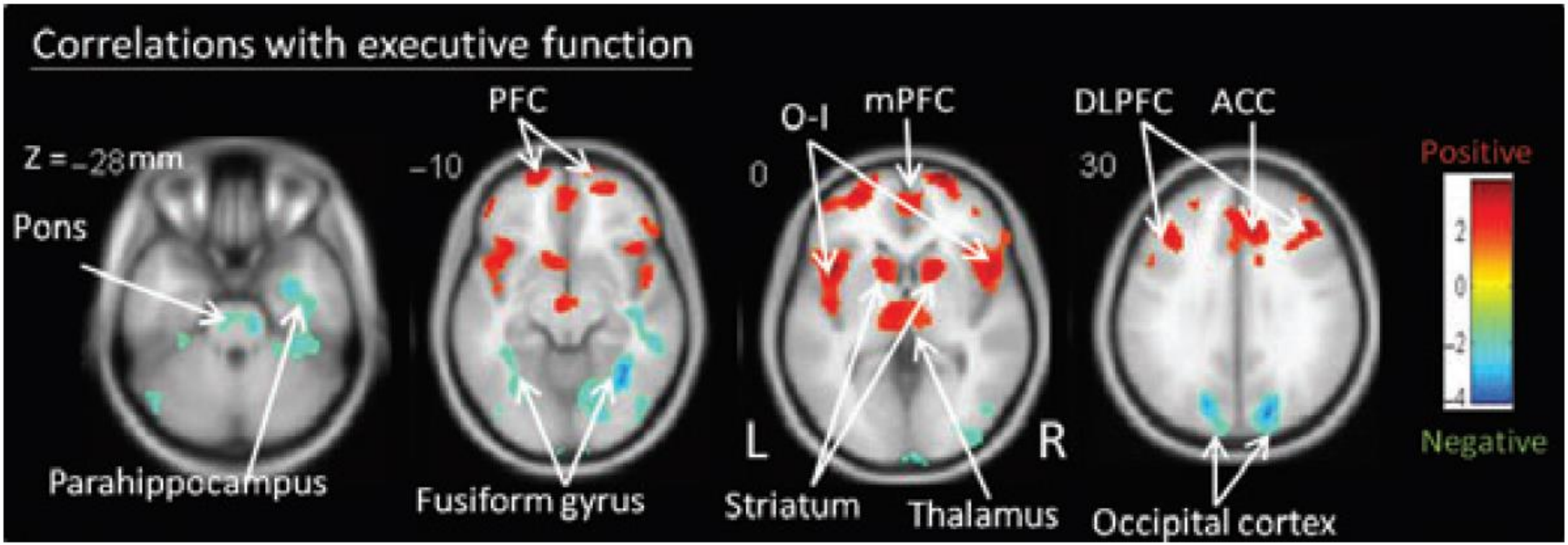
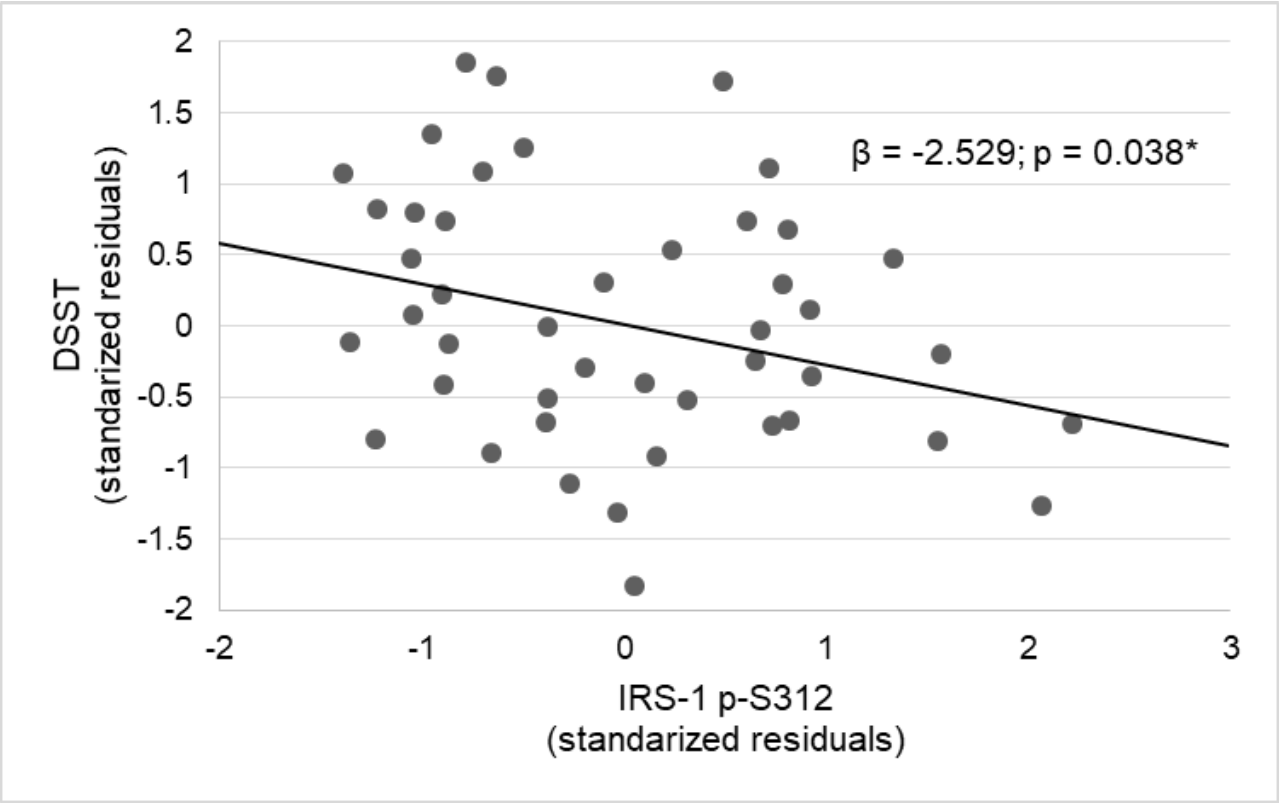


Fig. 1. Correlations between cerebral glucose metabolism and executive function in patients with remitted bipolar disorder and healthy subjects. ACC = anterior cingulate cortex; DLPFC = dorsolateral PFC; L = left; mPFC = medial PFC; O-I = operculum-insula; PFC = prefrontal cortex; R = right.

Li et al. Bipolar Disord. 2012 Dec;14(8):831-42.

Brain Insulin Resistance and Cognitive Function in Individuals with BD

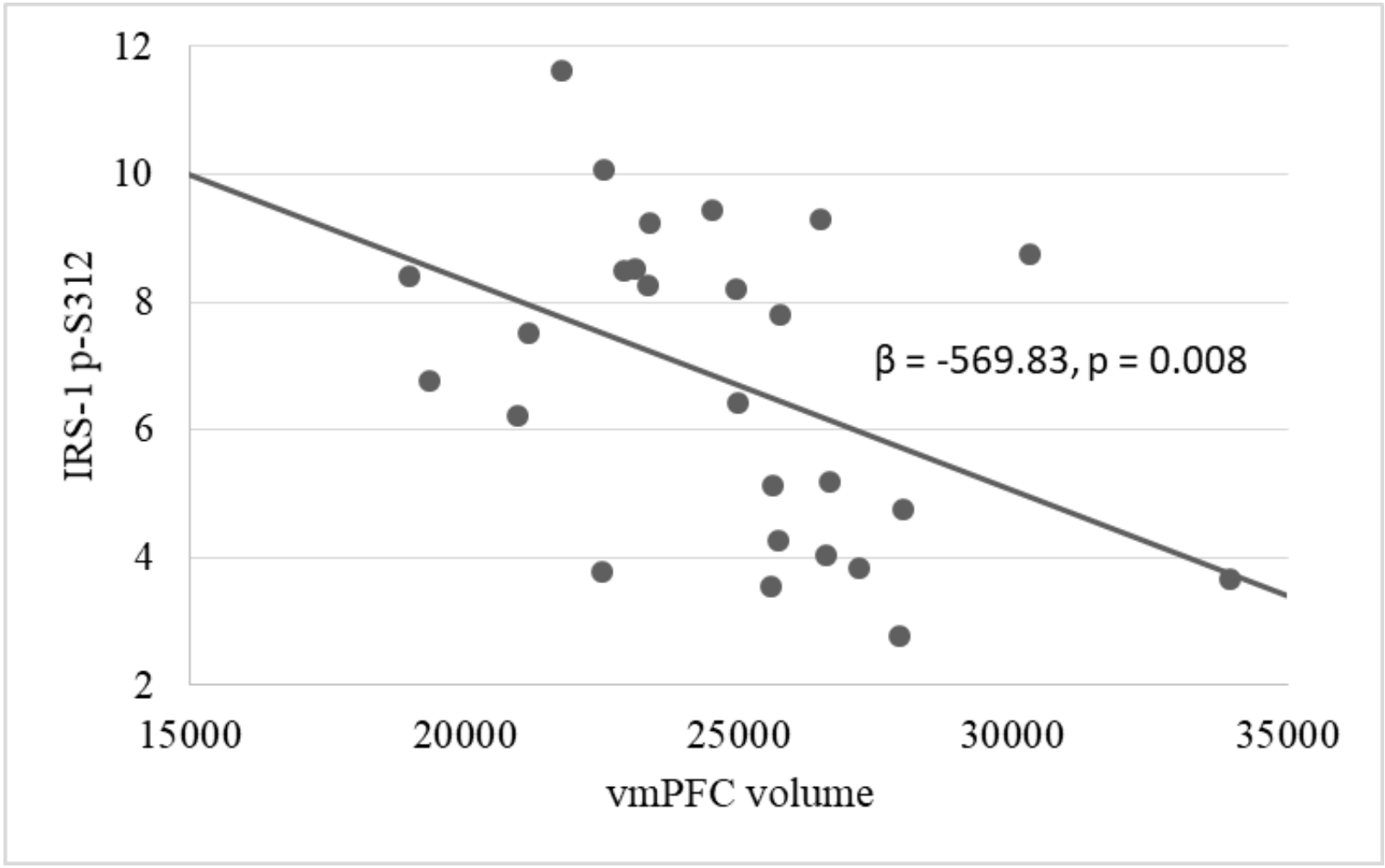


* Adjusted for age, gender, education, depressive symptoms severity and EV concentration

Insulin receptor substrate-1 phosphorylation at serine site 312 (IRS-1 p-S312), measured in neuronal origin-enriched extracellular vesicles, which has been associated with attenuated insulin signaling

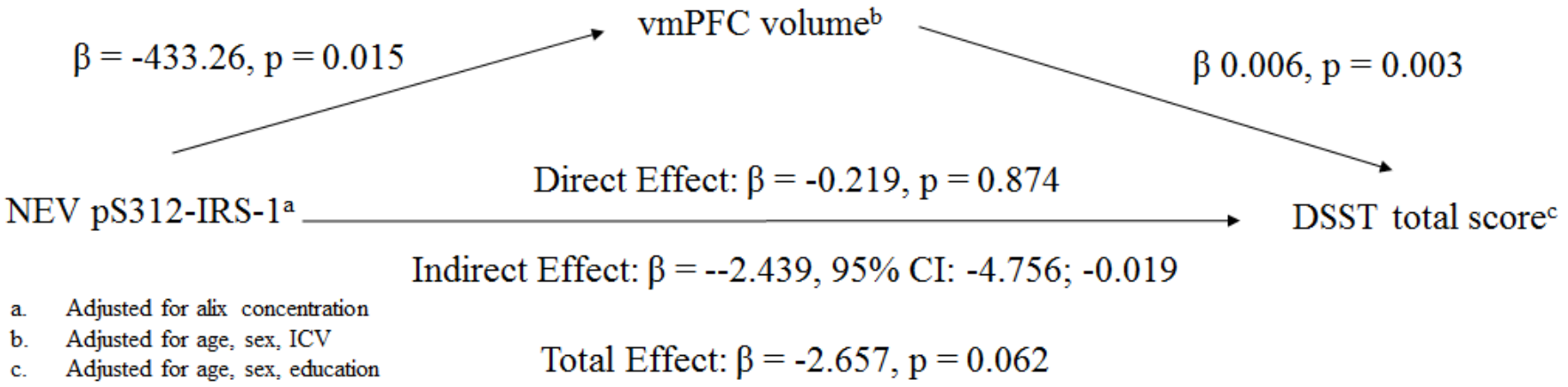
Mansur, Lee, Delgado-Peraza, Nogueras-Ortiz, Chawla, Kapogiannis, McIntyre. Unpublished data

Brain Insulin Resistance and Atrophy in BD



Mansur, Lee, Delgado-Peraza, Nogueras-Ortiz, Chawla, Kapogiannis, McIntyre. Unpublished data

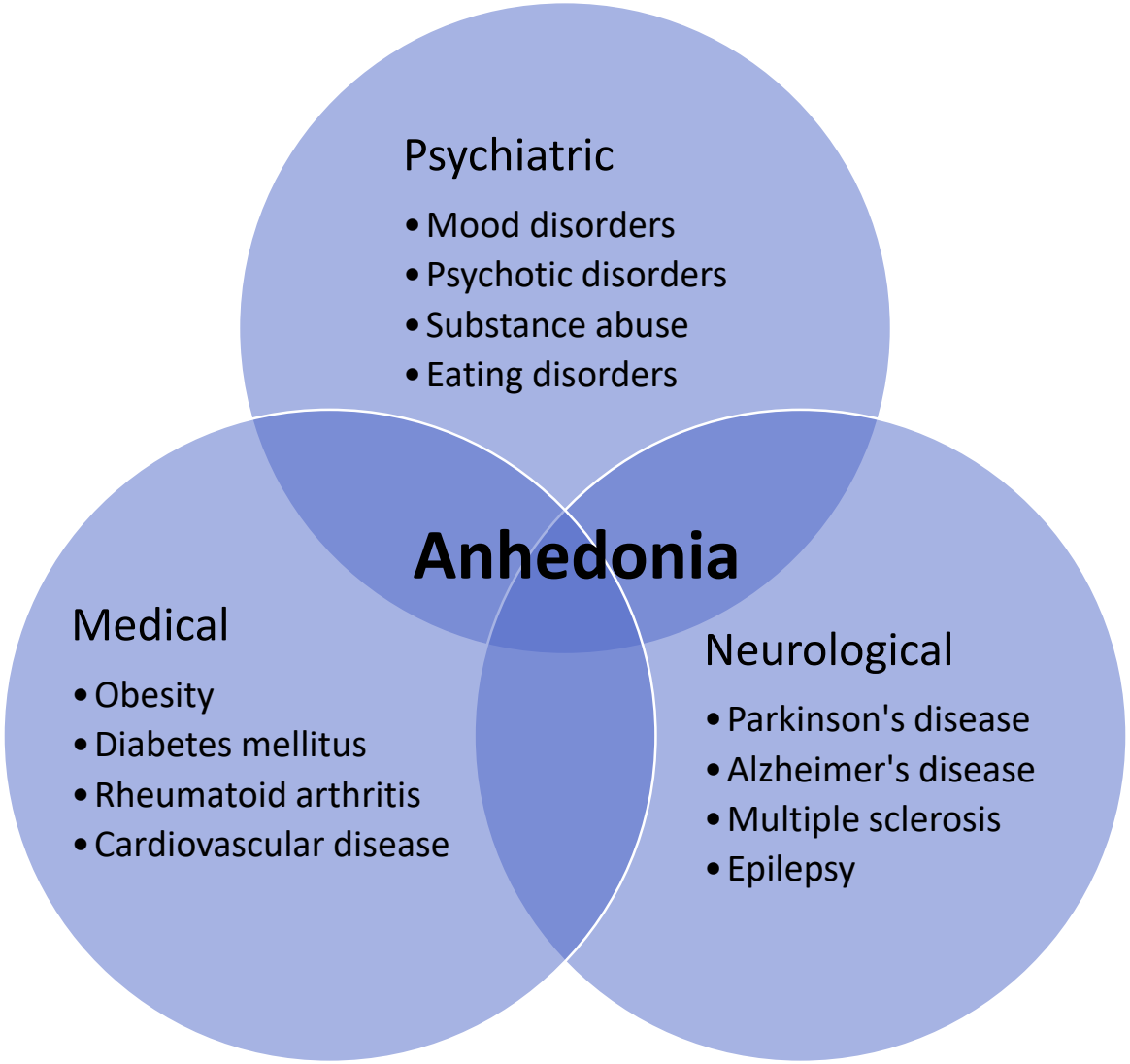
Brain Insulin Resistance and Atrophy in BD



a. Adjusted for alix concentration
b. Adjusted for age, sex, ICV
c. Adjusted for age, sex, education

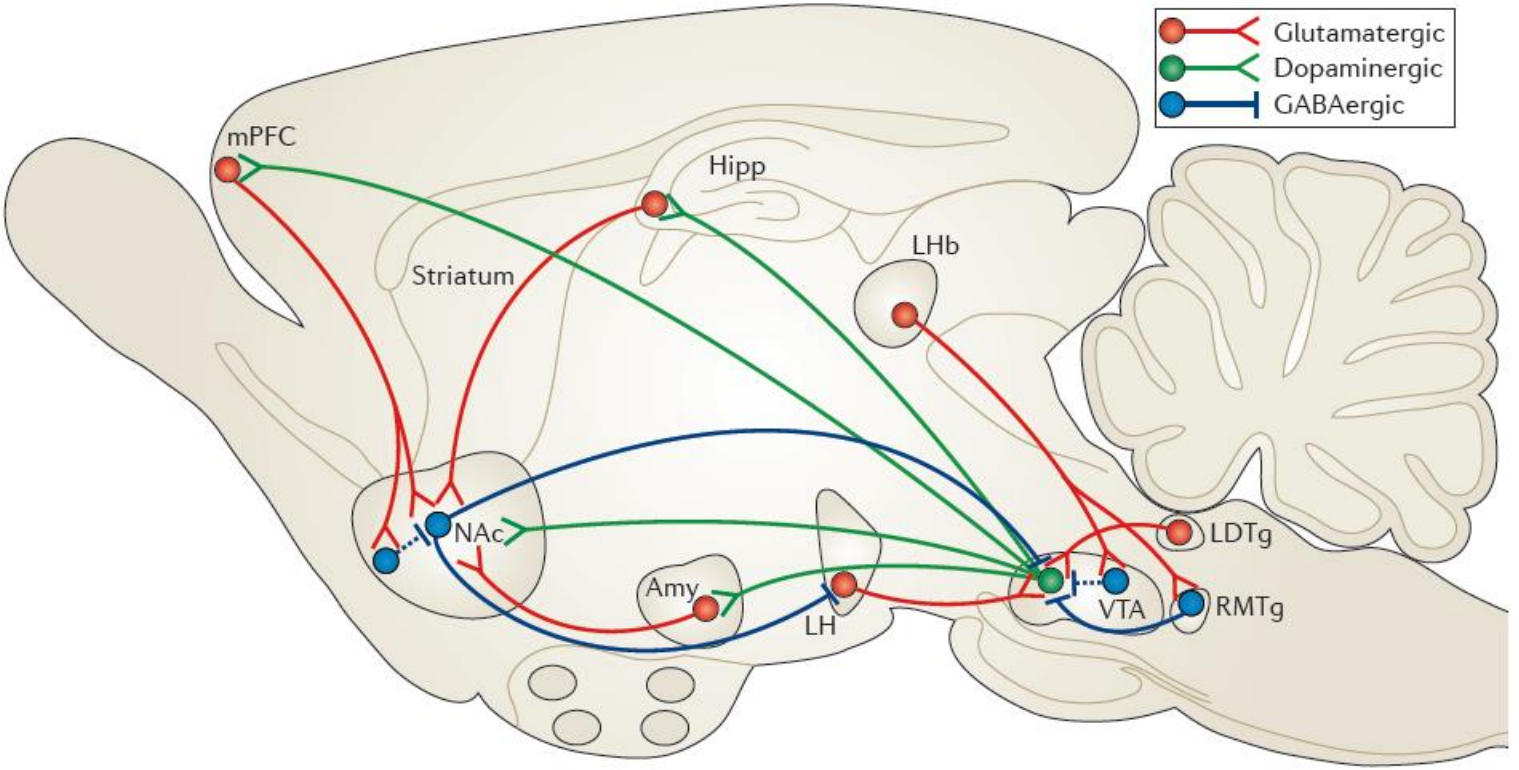
Mansur, Lee, Delgado-Peraza, Nogueras-Ortiz, Chawla, Kapogiannis, McIntyre. Unpublished data

Anhedonia is a Transdiagnostic Construct



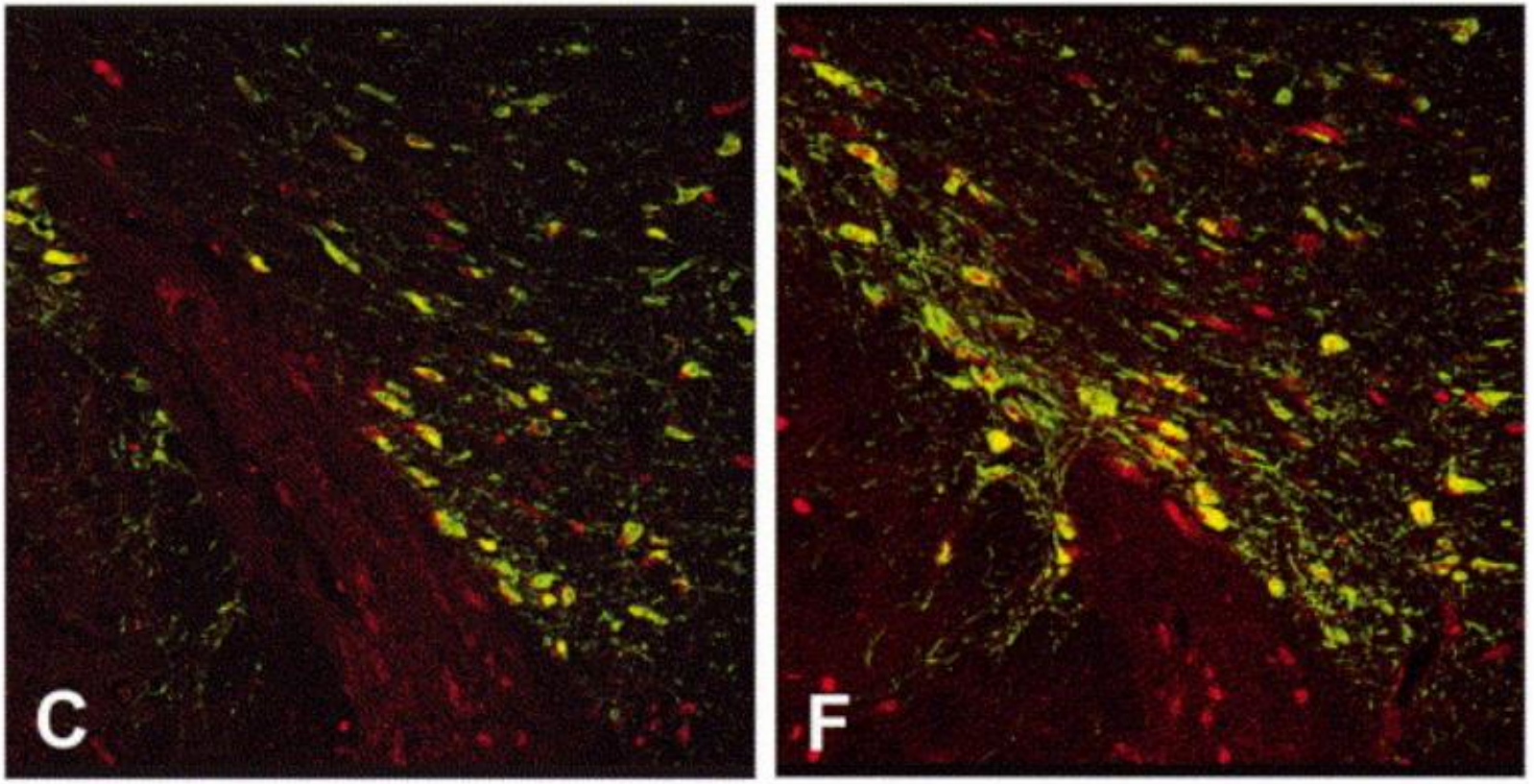
Pizzagalli DA. Annu Rev Clin Psychol. 2014;10:393-423.

Reward Circuits



Russo and Nestler. Nat Rev Neurosci. 2013 Sep;14(9):609-25.

Insulin, Leptin and Dopamine Neurons

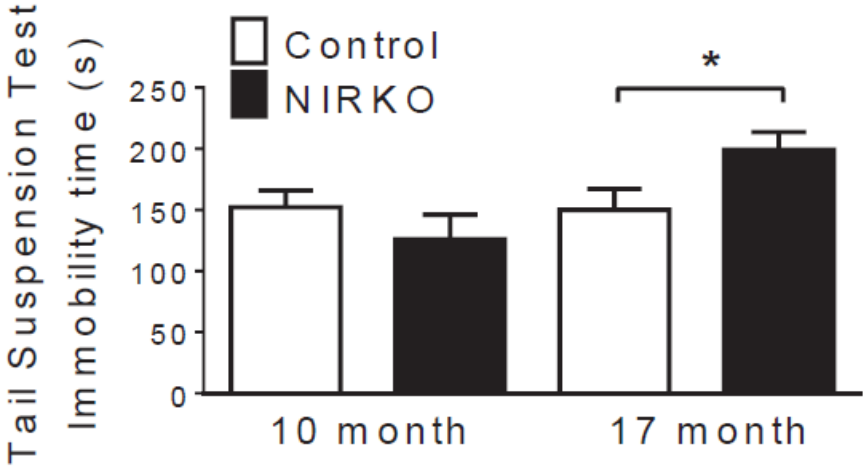


Expression of leptin receptors and insulin receptors in DA neurons of the VTA.

Co-localization is shown by yellow neurons in the merged images of tyrosine hydroxylase/leptin receptor (C) and tyrosine hydroxylase/insulin receptor (F).

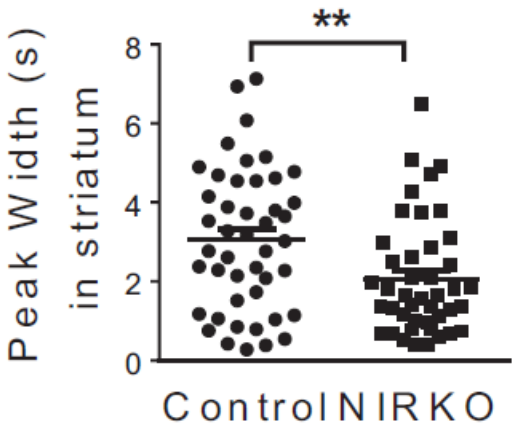
Figlewicz et al. Brain Res. 2003 Feb 21;964(1):107-15.

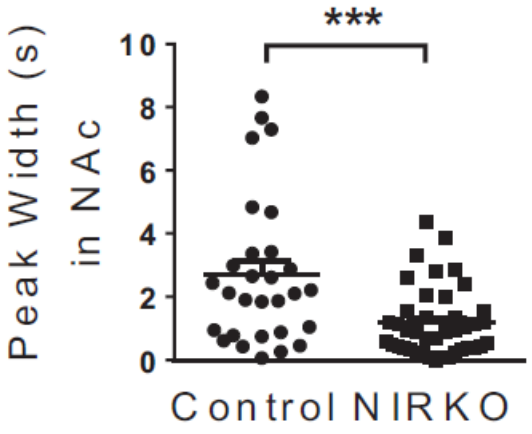
Brain Insulin Resistance

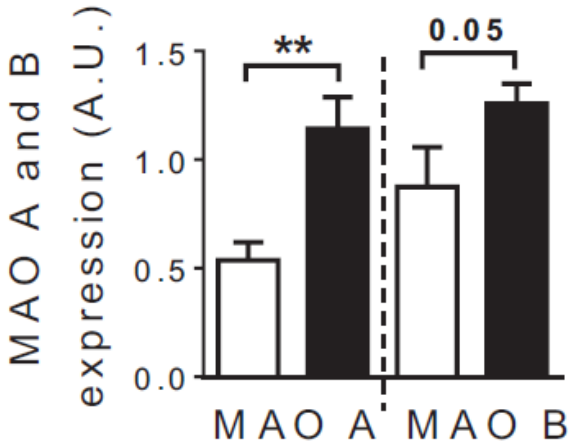


NIRKO mice:

Mice with a neuron-specific disruption of the insulin receptor gene

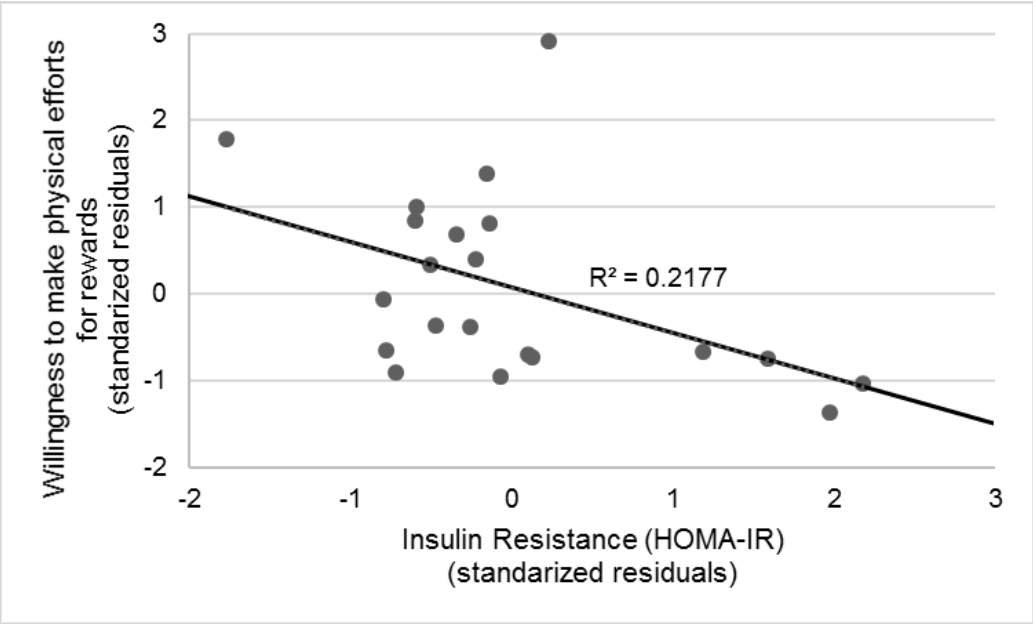






Kleinridders et al. Proc Natl Acad Sci U S A. 2015 Mar 17;112(11):3463-8.

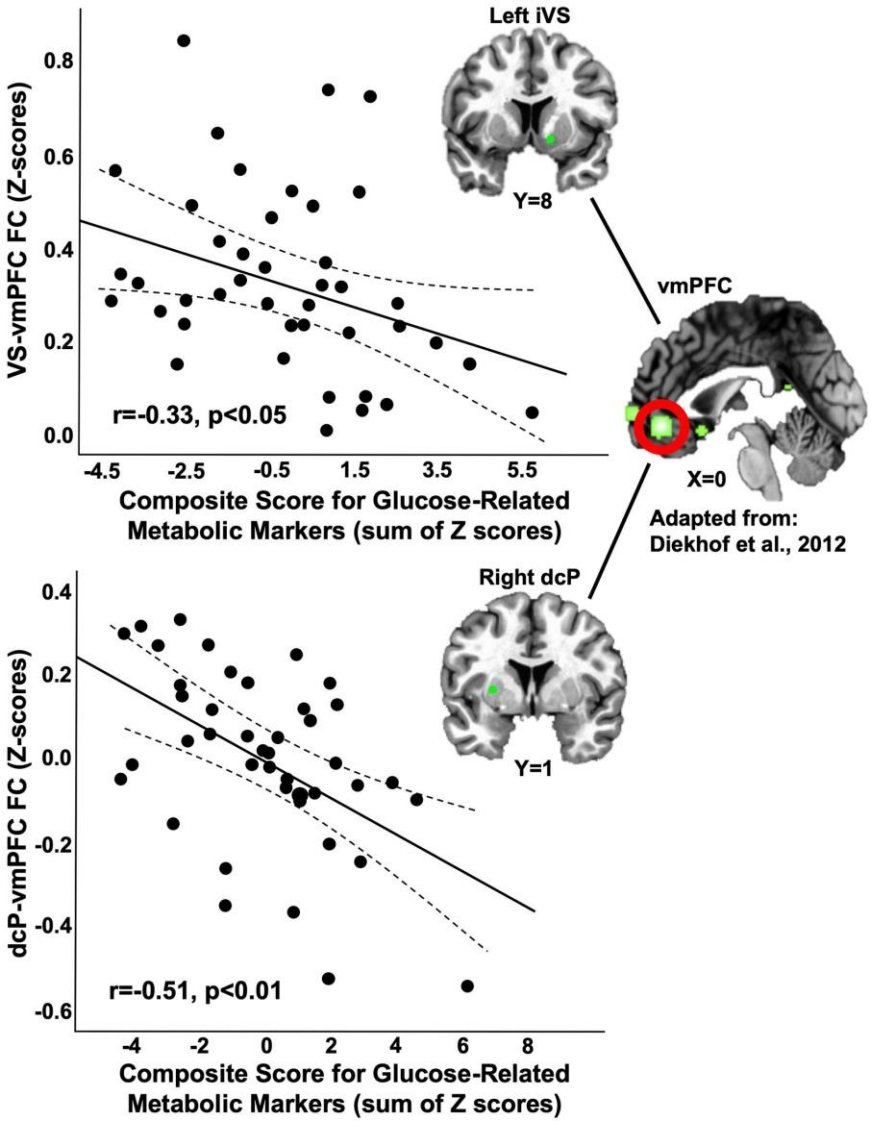
Insulin and Reward Behavior in MDD



Willingness to make physical efforts for rewards is associated with peripheral insulin resistance, after adjustment for relevant confounders, in individuals with major depressive disorder.

Mansur et al. J Affect Disord. 2019

Insulin Resistance and Reward Neurocircuitry



A composite score for glucose-related markers was negatively associated with ventral striatum (VS)-ventromedial prefrontal cortex (vmPFC) and dorsal caudal putamen (dcP)-vmPFC functional connectivity (FC) in unmedicated MDD patients

Goldsmith et al. .Brain Behav Immun. 2020.

Central Insulin and Dopamine Signaling

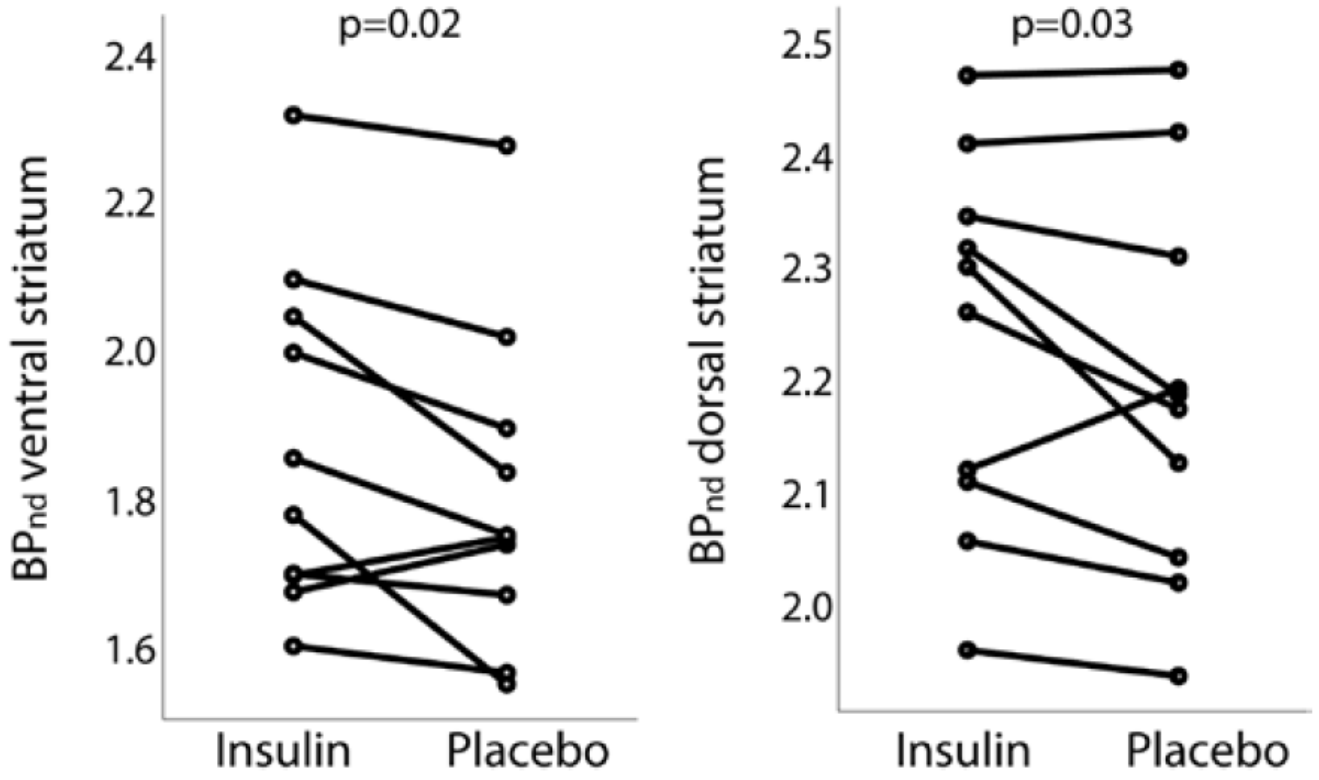


Figure 3. [^{11}C]-raclopride binding potential (BP_{nd}) in ventral and dorsal striatum on insulin and placebo day. Line diagrams show significant higher BP_{nd} in ventral and dorsal striatum after insulin compared with placebo spray application.

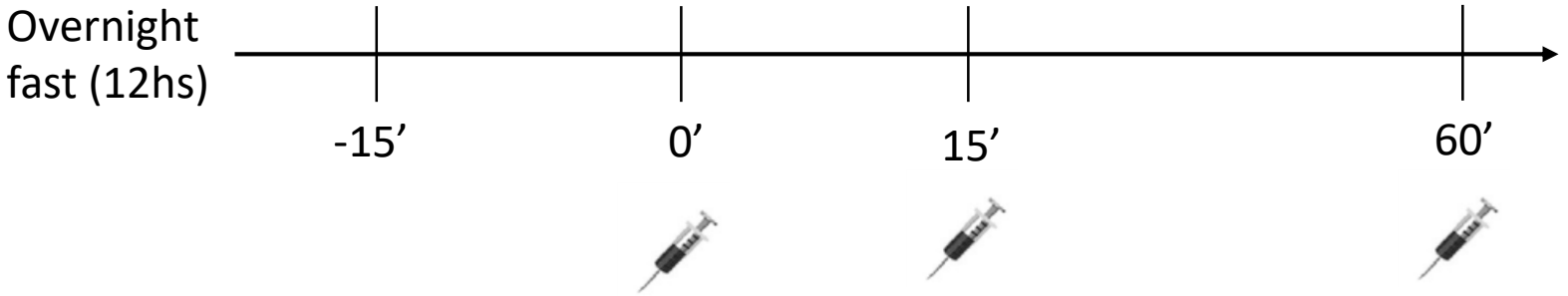
Kullmann et al. J Clin Endocrinol Metab. 2021 Sep 27;106(10):2949-2961.

Brain Insulin Sensitivity and Reward in MDD

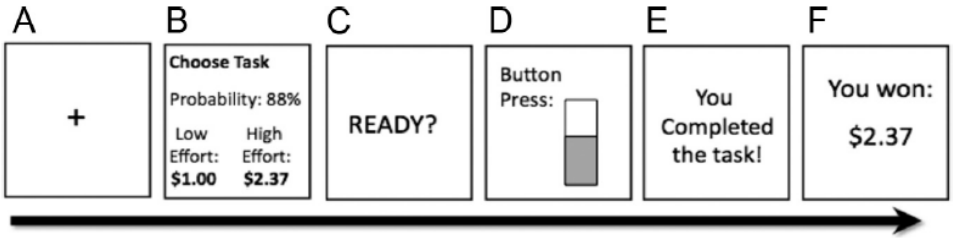
fMRI session

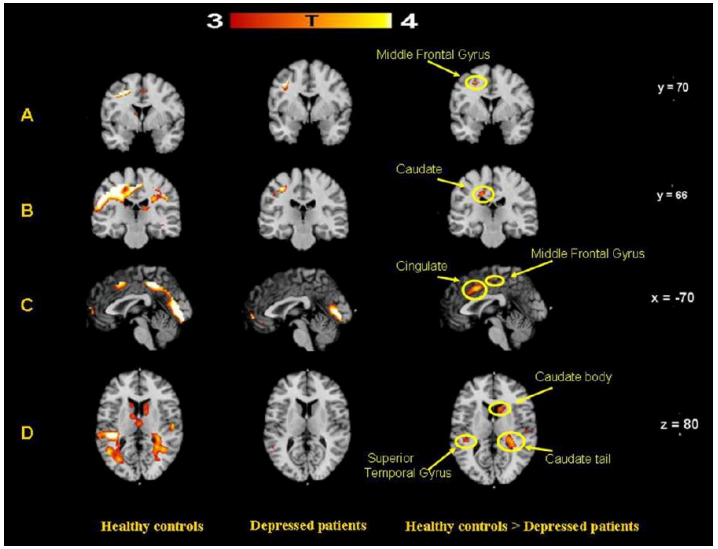
Mood Rating Scales and Cognitive Tests

160 IU of Intranasal Insulin or Placebo



Effort Expenditure for Rewards Task





BASZUCKI BRAIN RESEARCH FUND

CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

UHN Toronto General Toronto Western Princess Margaret Toronto Rehab

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  - Metabolic dysregulation in mood disorders
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  - Cognition
  - Reward
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  - **Disease Modelling**
  - Therapeutic

What are Psychiatric Diagnosis?

- Four ways of thinking
  - Essentialist categories
    - Classes whose members share an essence from which their defining features arise.
  - Social constructions
    - Classes whose members are defined by the cultural context in which they arise.
  - Practical kinds
    - Defer metaphysical questions about ‘ reality ’ and focus on defining classes that are useful.
  - Mechanistic property cluster model of kinds
    - Defined not in terms of essences but in terms of complex, mutually reinforcing networks of causal mechanisms.

Kendler et al. Psychological Medicine (2011)

What are Psychiatric Diagnosis?

Essentialist categories

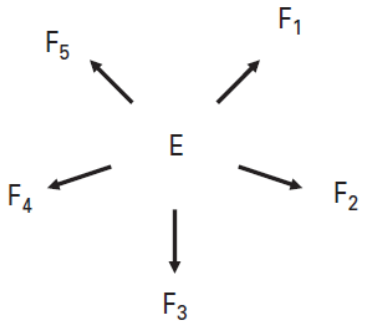


Fig. 1. An essentialist model for a psychiatric disorder in which an essence (E) is directly and causally responsible for all of the key defining features of the disorder (labeled F_1 to F_5).

Mechanistic property cluster

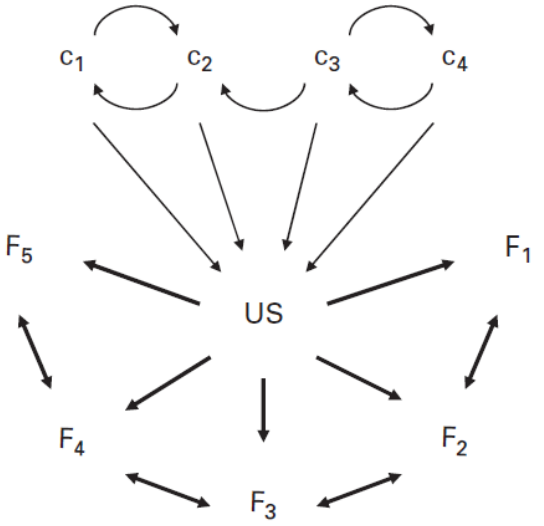
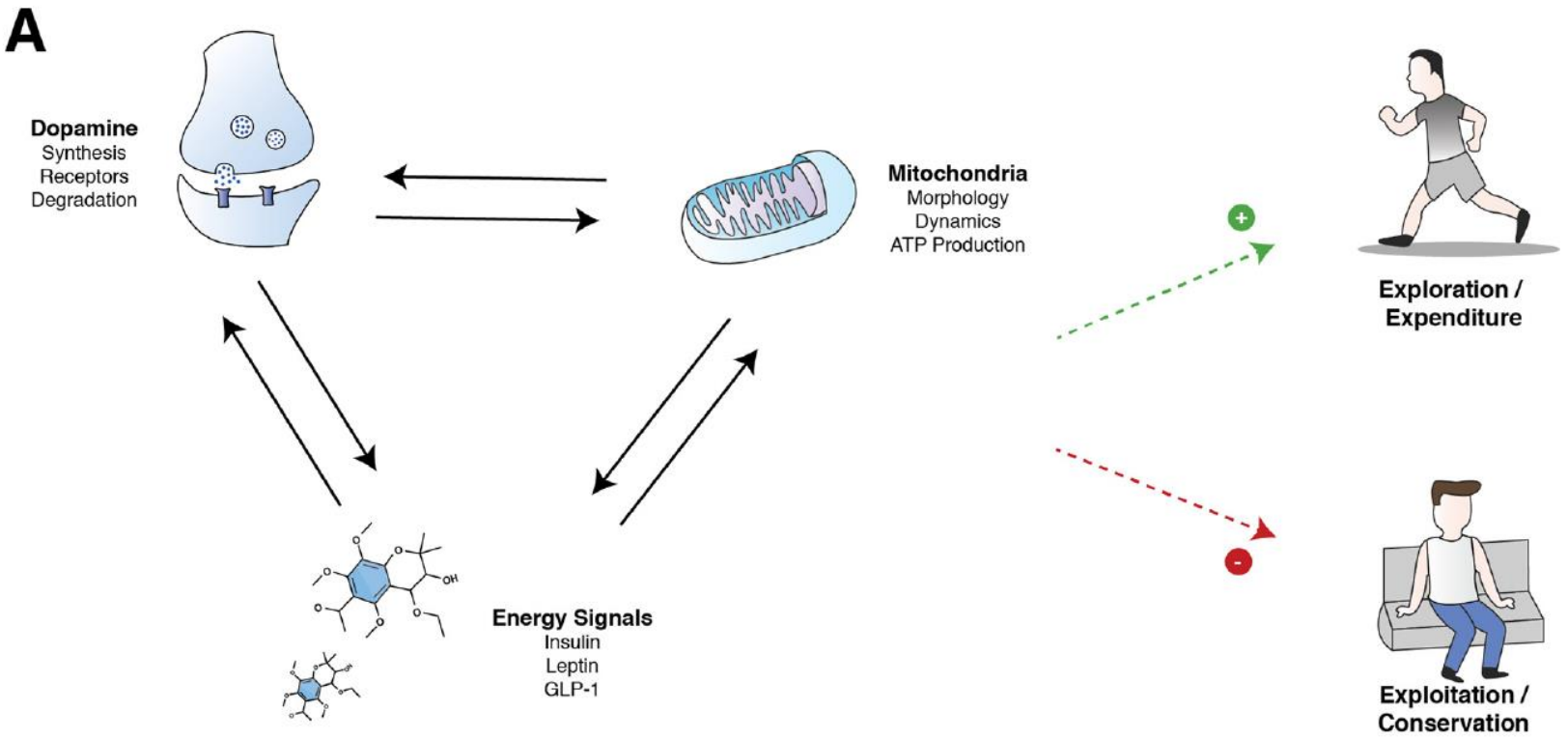


Fig. 3. Another possibility for a property cluster kind in which we have a series of causes (C_1 to C_4) that interact with each other to produce an underlying state (US) that in turn leads to the individual clinical features (F_1 to F_5). These causal processes could be psychological or biological. These clinical features in turn could causally interact with each other.

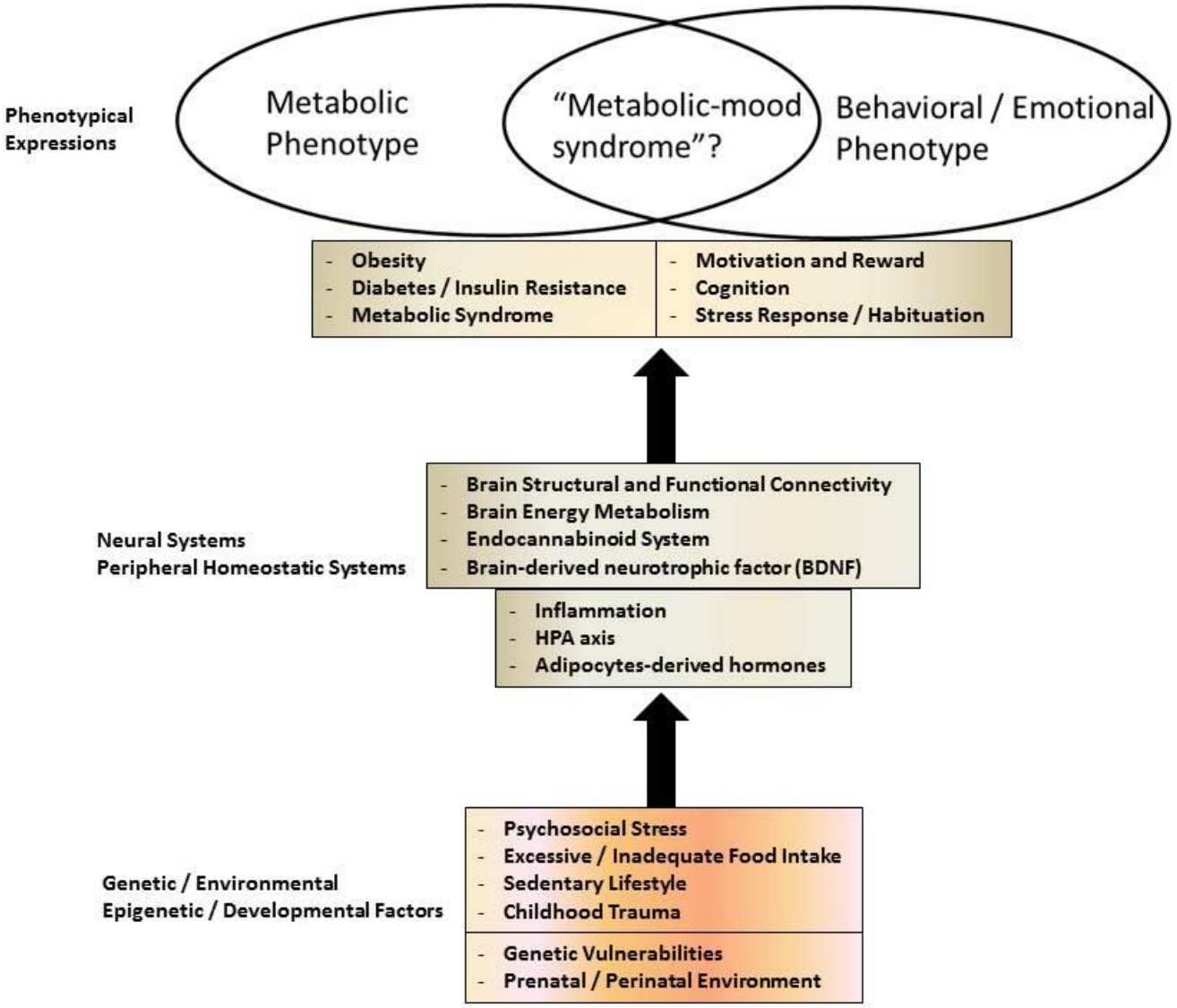
Kendler et al. Psychological Medicine (2011)

Neural Control of Energy Expenditure



Mansur et al., 2020.

Heuristic Implications



Mansur et al. Neurosci Biobehav Rev. 2015 May;52:89-104.

Identifying Subgroups

Insulin Resistance, T2DM and BD course

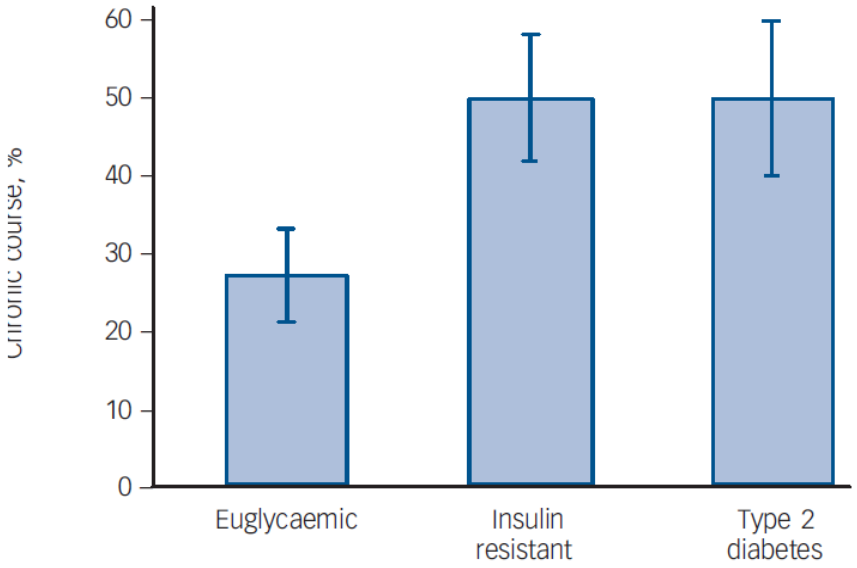


Fig. 1 Chronic course of bipolar disorder in individuals with euglycaemia, insulin resistance and type 2 diabetes.

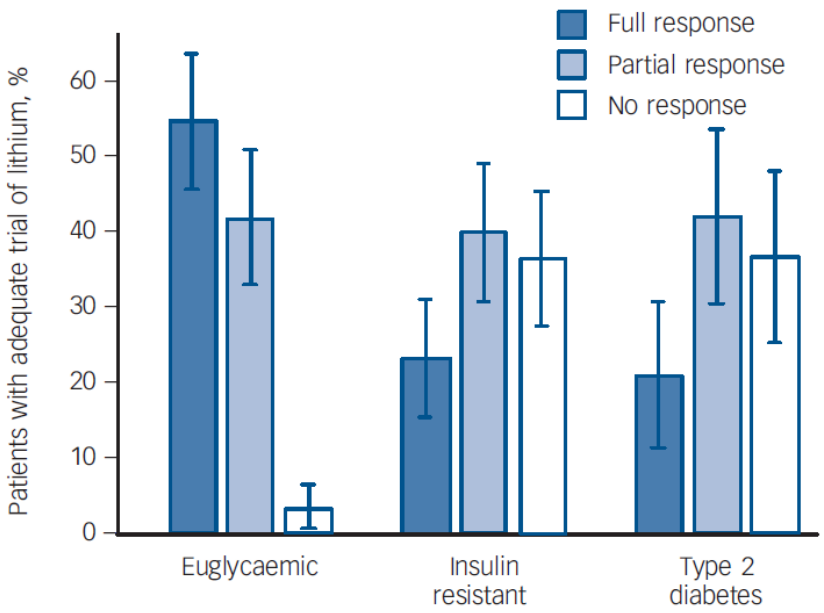
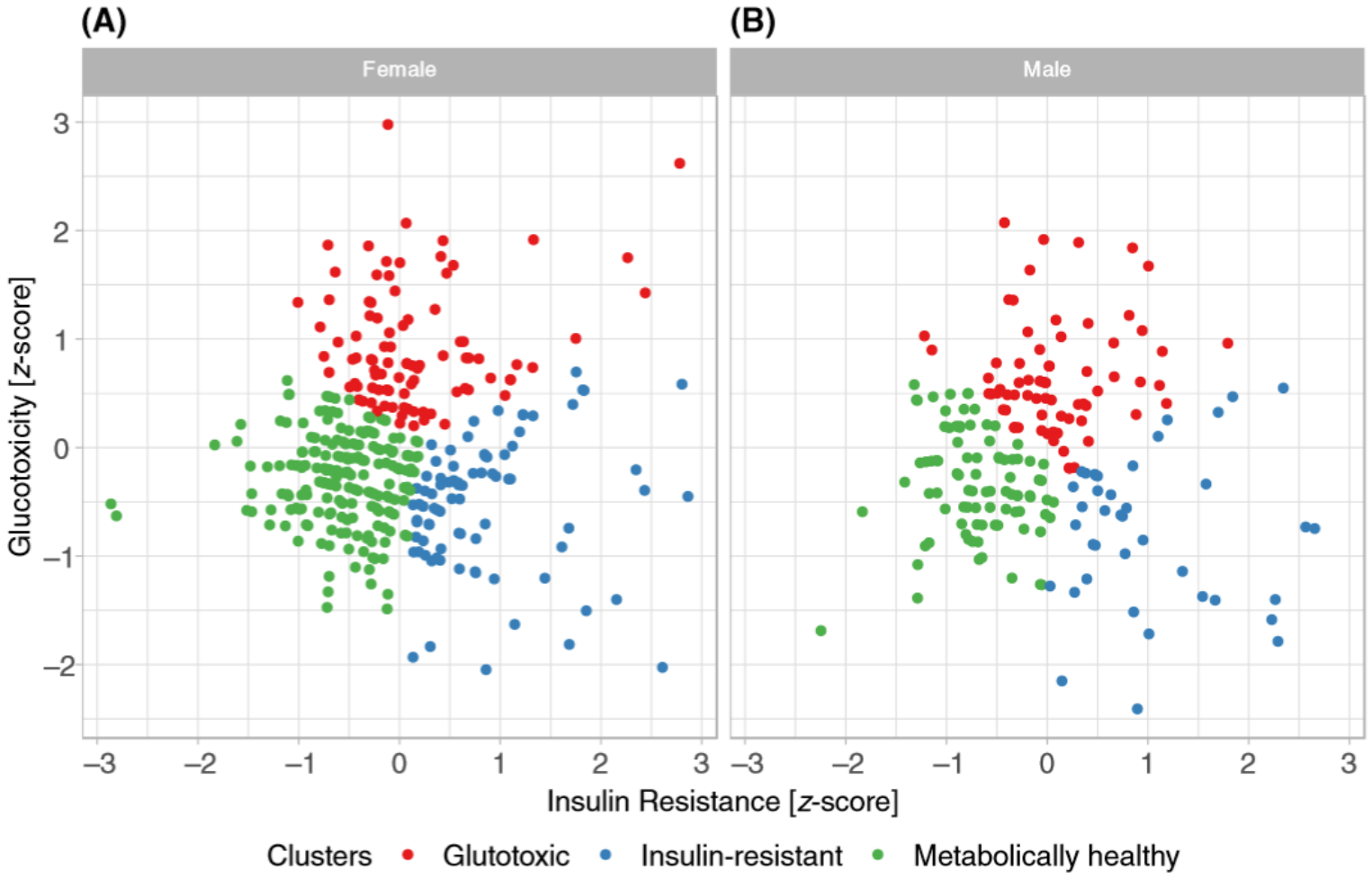


Fig. 2 Response to prophylactic lithium in individuals with euglycaemia, insulin resistance and type 2 diabetes.

Calkin et al. Br J Psychiatry. 2015 Jan;206(1):52-7.

Identifying Subgroups



Mansur et al. Bipolar Disord. 2020 Feb;22(1):79-88.

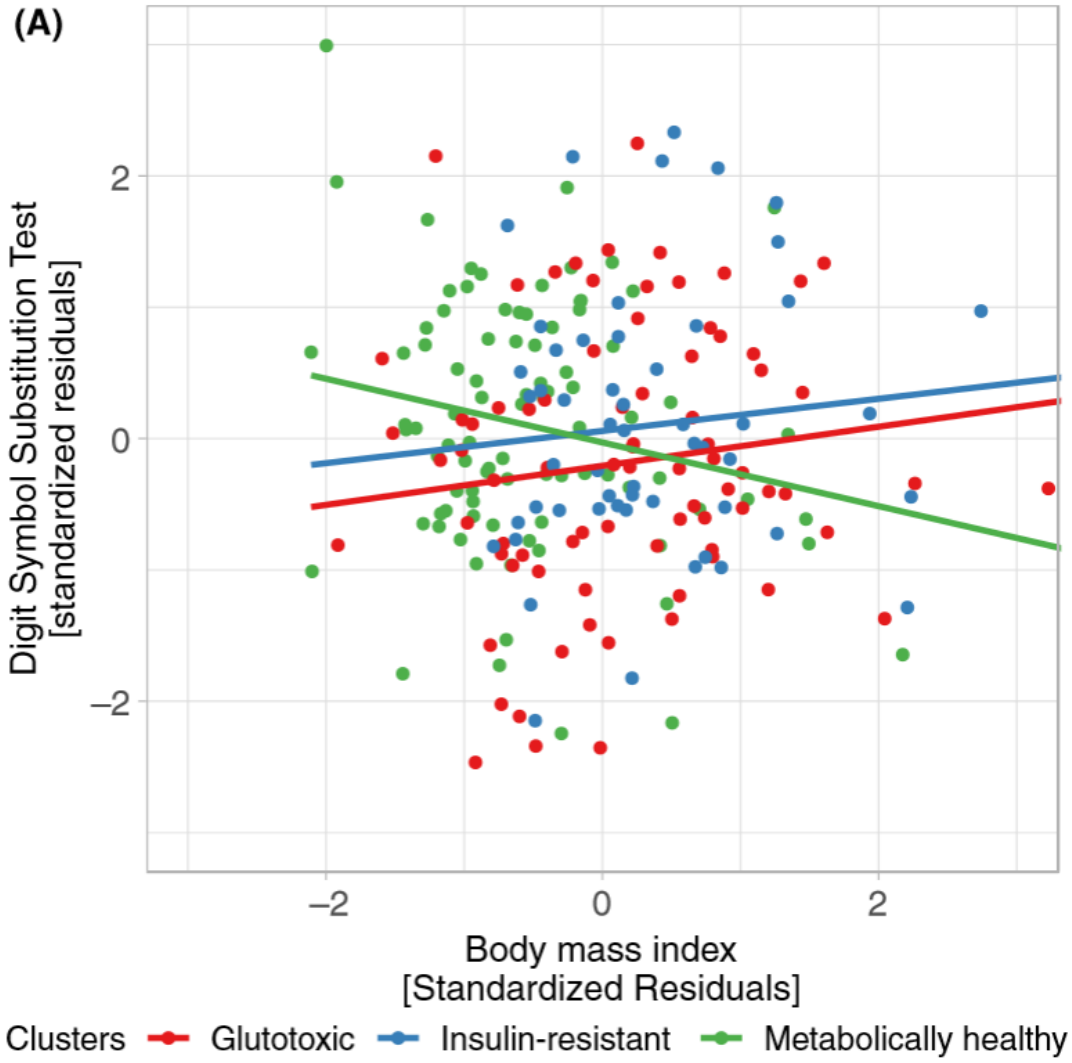
Identifying Subgroups

TABLE 3 Differences between clusters

	MH n = 137	GT n = 131	IR n = 84	n	Overall *P*-value
Adjusted for age, gender, cohort, diagnosis, and use of antipsychotics					
Body mass index (kg/m^2), mean (SE)	26.60 (0.50)	30.96 (0.60)	32.77 (0.78)	296	<.001[c]
Metabolic syndrome (z-score), mean (SE)	−0.19 (0.29)	0.77 (0.31)	0.50 (0.35)	191	<.001[d]
MAP, mean (SE)	92.90 (1.51)	96.01 (1.70)	101.59 (1.97)	194	<.001[c]
CRP, mean (SE)	3.38 (0.34)	4.92 (0.53)	4.40 (0.51)	155	.015[c]
MET-hs (total), mean (SE)	30.00 (5.19)	22.36 (3.26)	22.48 (4.67)	117	.290
Depressive symptoms, mean (SE)	16.62 (0.89)	15.39 (0.85)	15.32 (1.03)	277	.435[c]
SHPS, mean (SE)	5.67 (0.40)	5.44 (0.37)	5.58 (0.51)	138	.869[e]
DSST, mean (SE)	54.45 (1.78)	49.91 (1.87)	55.99 (2.05)	186	.038[d,f]
SDS, mean (SE)	20.04 (1.04)	23.29 (1.27)	19.77 (1.23)	169	.038[c,f]
Age at onset (years), mean (SE)	20.80 (0.97)	21.41 (1.06)	19.10 (1.16)	285	.292[c,f]
Illness duration, mean (SE)	17.46 (1.16)	15.91 (1.10)	19.57 (1.65)	283	.145[c,f]
Number of mood episodes, mean (SE)	18.16 (2.81)	15.30 (2.21)	21.09 (3.77)	229	.320[c,f]

Mansur et al. Bipolar Disord. 2020 Feb;22(1):79-88.

Identifying Subgroups

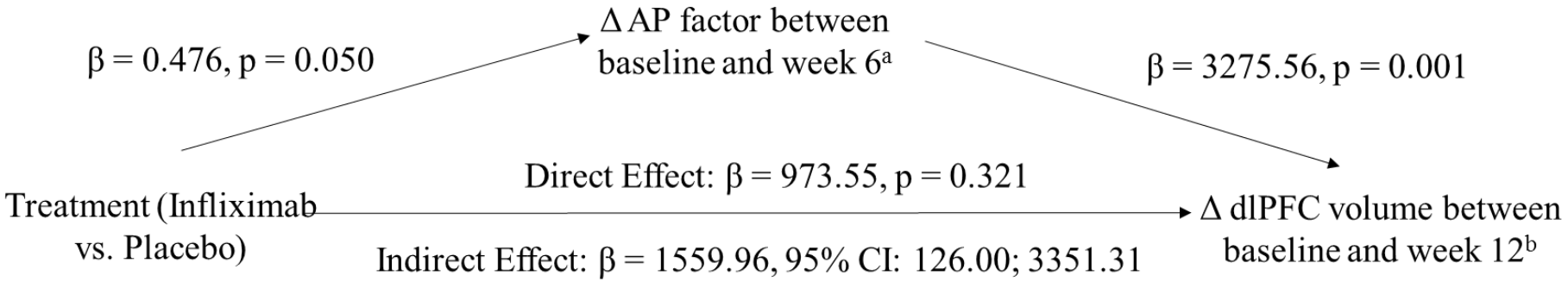


Mansur et al. Bipolar Disord. 2020 Feb;22(1):79-88.

Summary

- Introduction
  - Metabolic dysregulation in mood disorders
  - The role of insulin signaling in the brain
- Insulin signaling and Domains of Psychopathology
  - Cognition
  - Reward
- **Implications**
  - Disease Modelling
  - **Therapeutic**

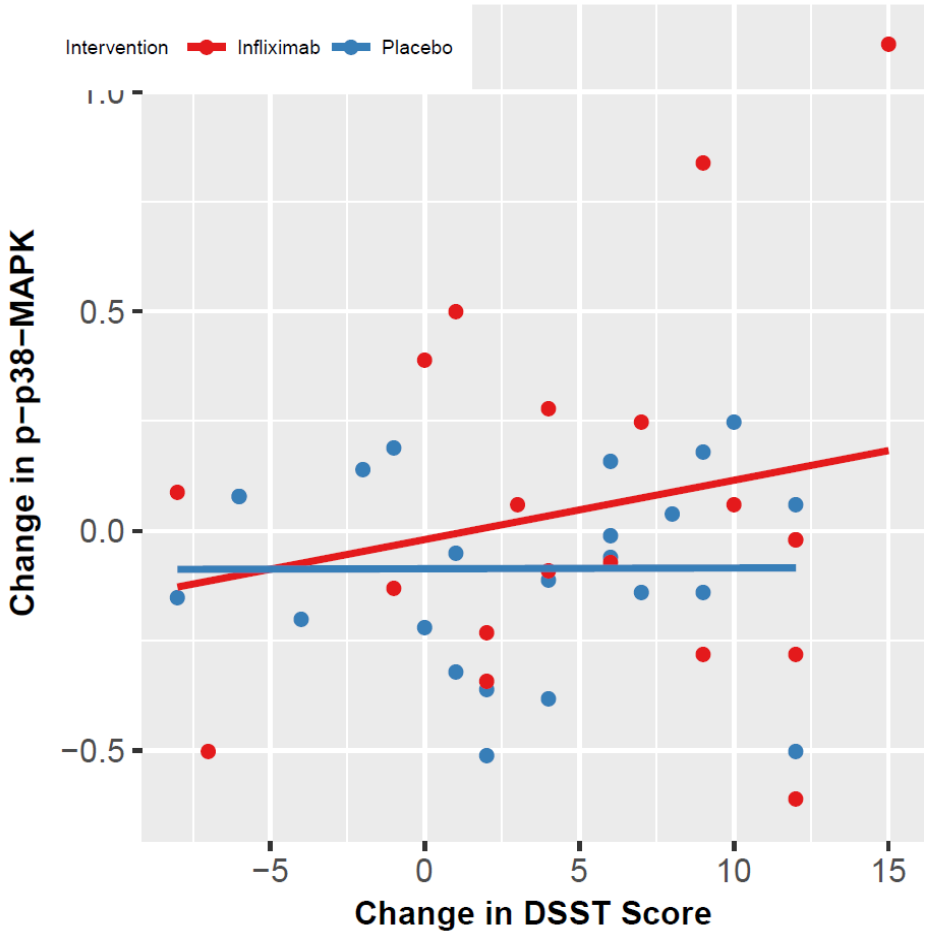
Changes in Insulin Biomarkers and Brain Structure



a. Adjusted for age, sex, alix concentration
b. Adjusted for age, sex, ICV

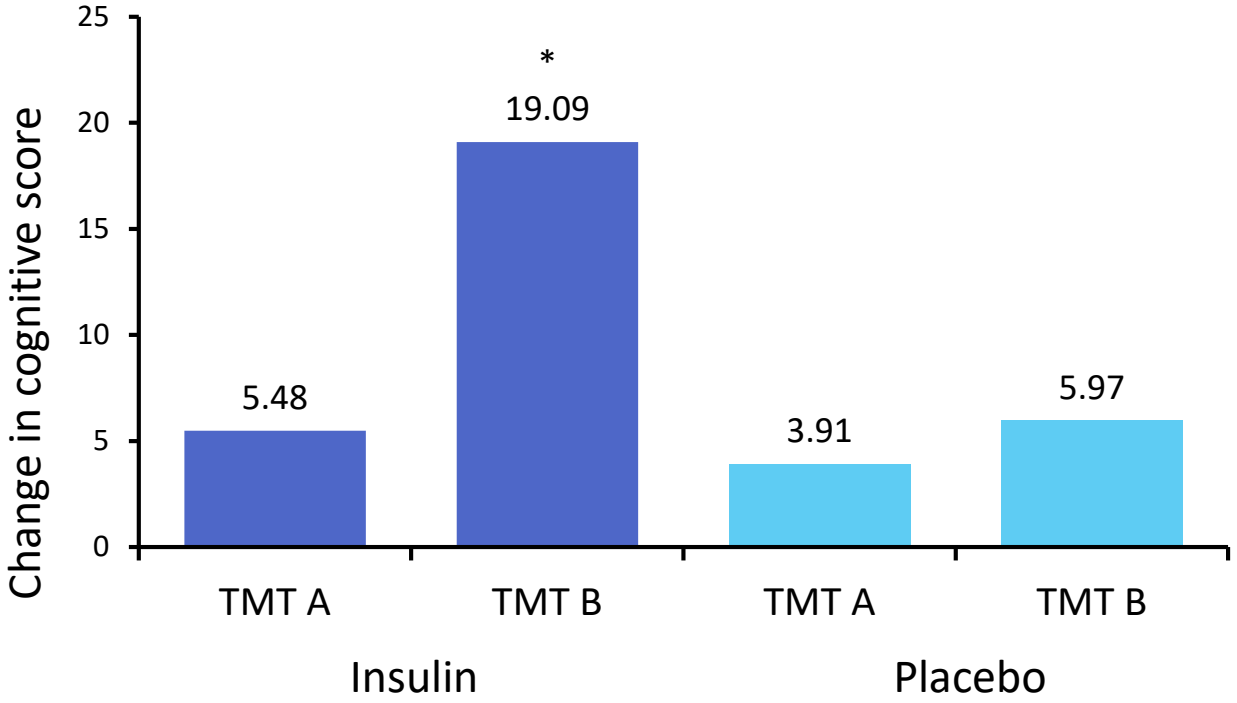
Mansur et al. J Psychiatr Res. 2021 Jan;133:82-92.

Changes in Insulin Biomarkers and Cognitive Improvement



Mansur et al. J Psychiatr Res. 2021 Jan;133:82-92.

Therapeutic Implications – Intranasal Insulin



62 adults with bipolar disorder I / II received intranasal insulin (40 IU QID, n=34) or placebo (n=28) for 8 weeks

TMT A: time × treatment interaction, p=0.70

TMT B: time × treatment interaction, *p<0.05

McIntyre RS et al. Bipolar Disord 2012;14:697-706

Intranasal Insulin and MDD

Table 5
Treatment effects analyses and statistics (F- and p-values) following subchronic intranasal insulin administration.

	Time			Treatment			Time x Treatment		
	F-value	p-value	Effect Size d	F-value	p-value	Effect Size d	F-value	p-value	Effect Size d
Mood Scales									
MADRS	F(1,34) = 3.066	p = 0.090	0.584	F(1,34) = 0.641	p = 0.429	0.267	F(1,33) = 0.487	p = 0.490	0.233
PANAS Positive Subscale	F(1,34) = 31.582	p = 0.112	1.873	F(1,34) = 0.547	p = 0.595	0.247	F(1,33) = 0.093	p = 0.811	0.102
PANAS Negative Subscale	F(1,34) = 0.076	p = 0.829	0.092	F(1,34) = 4.836	p = 0.272	0.733	F(1,33) = 0.114	p = 0.792	0.113
Neurocognitive Measures									
*Global Index of Neurocognition	F(1,34) = 8.465	p = 0.006	0.970	F(1,34) = 0.008	p = 0.929	0.030	F(1,33) = 0.069	p = 0.795	0.088
AGN (Correct Response)	F(1,33) = 0.170	p = 0.683	0.137	F(1,33) = 0.203	p = 0.655	0.150	F(1,33) = 0.498	p = 0.533	0.235
*ERT (Correct Response)	F(1,34) = 1076.00	p = 0.019	10.934	F(1,34) = 0.082	p – 0.822	0.095	F(1,33) = 28.24	p = 0.118	1.771
*ERT (Response Time)	F(1,34) = 137.69	p = 0.054	3.911	F(1,34) = 0.270	p = 0.695	0.173	F(1,33) = 0.014	p = 0.924	0.039

35 adults with MDD were randomized to 4 weeks of either intranasal insulin (40 IU QID, n=19) or placebo (n=16) in a double blind, placebo-controlled, crossover design.

Cha et al. J Affect Disord. 2016 Dec 18;210:57-65.

GLP-1R Agonists and Neuronal Insulin Signaling

Figure 3. Association of Exenatide With Phosphorylation of Insulin Receptor Signaling Substrate 1 (IRS-1) Proteins

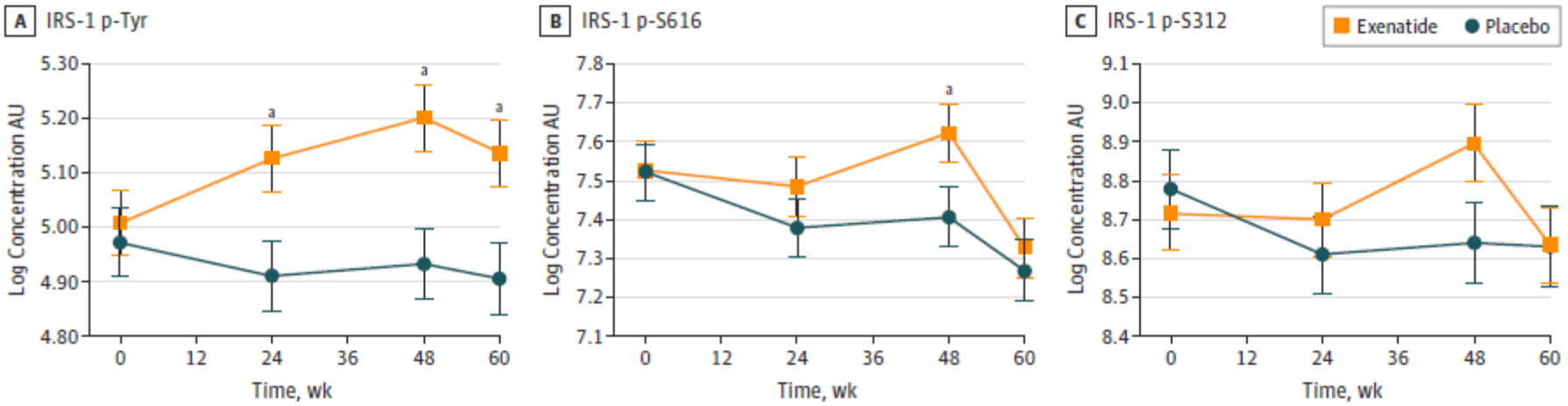
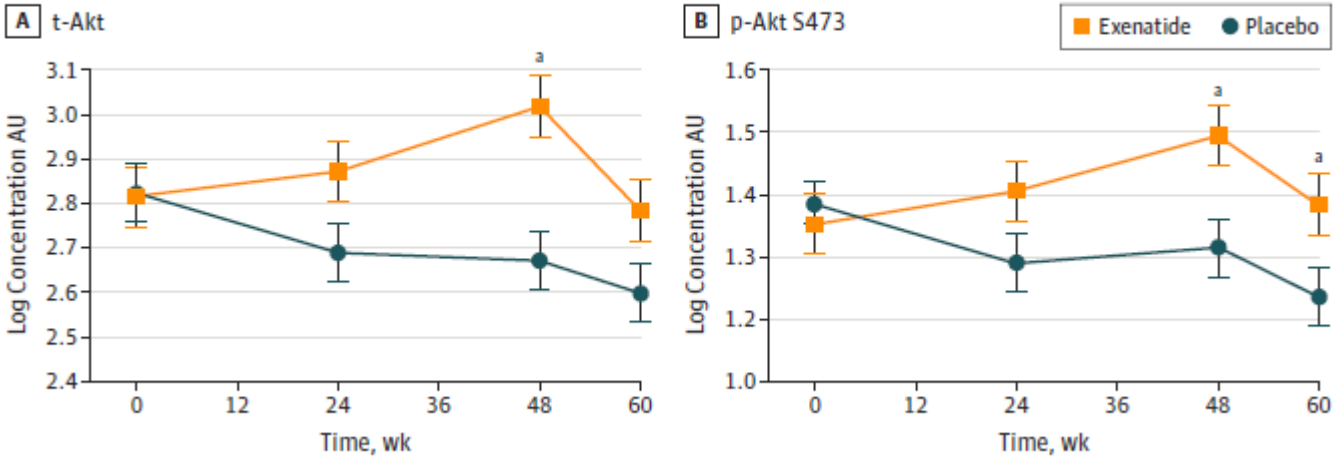
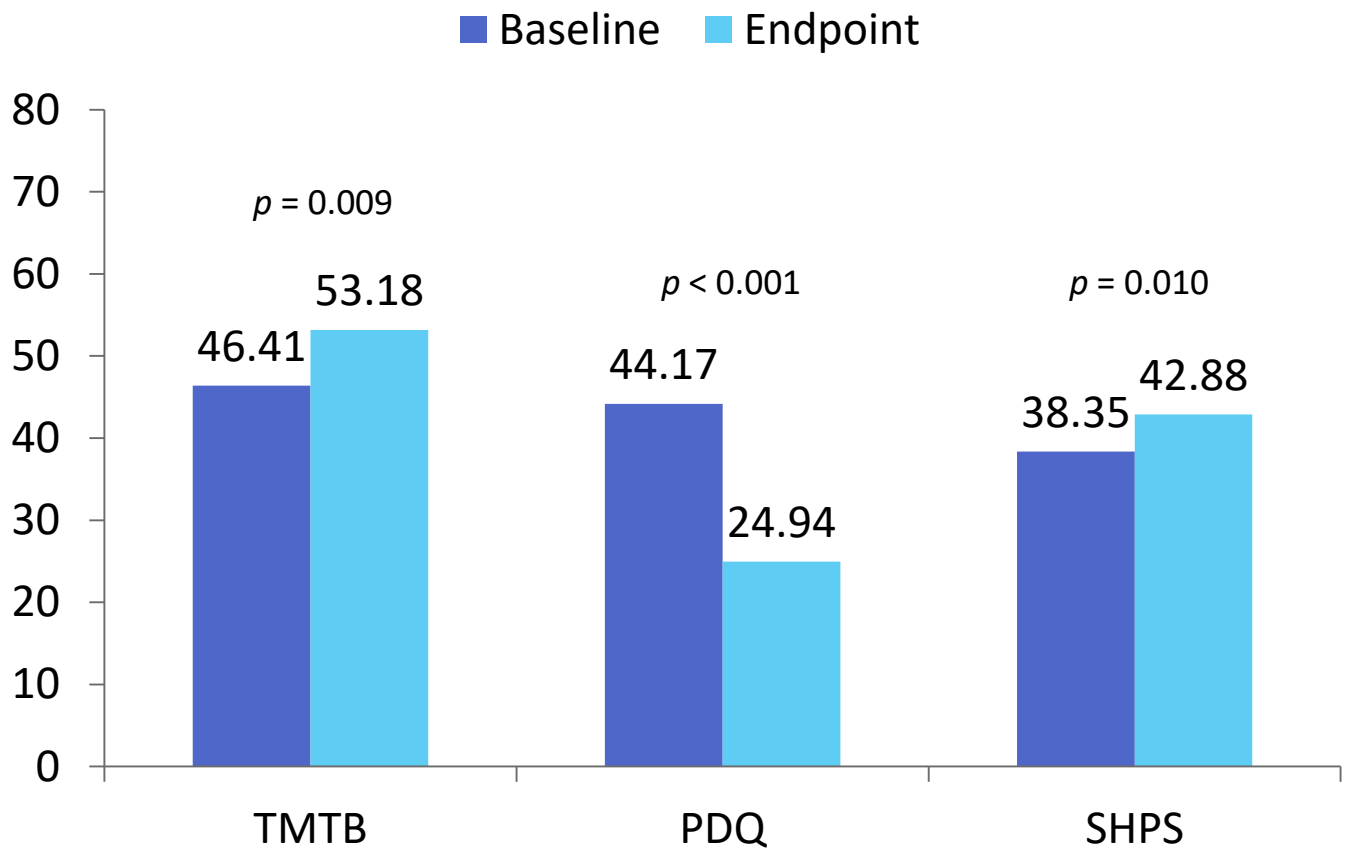


Figure 4. Association of Exenatide With Downstream Targets of Insulin Receptor Signaling Substrate 1 (IRS-1)



Athauda et al. JAMA Neurol. 2019 Apr 1;76(4):420-429.

GLP1 Receptor Agonists

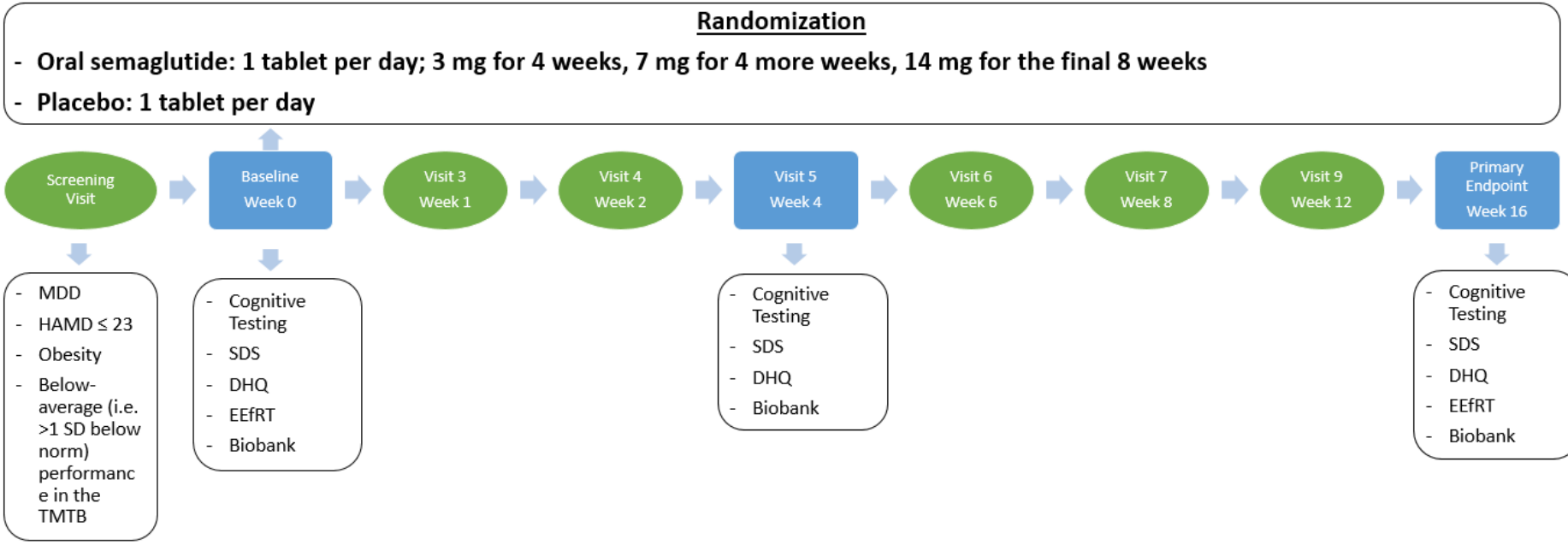


19 individuals with MDD or bipolar disorder BD and an impairment in executive function received liraglutide 1.8mg/day for 4 weeks in an open-label, proof-of-concept design

Mansur et al. J Affect Disord. 2017 Jan 1;207:114-120.

GLP-1R Agonists in Mood Disorders

Adjunctive Semaglutide for the Treatment of Cognitive Dysfunction in Major Depressive Disorder: a Randomized, Double-Blind, Placebo-Controlled Study (NCT04466345)



PSI FOUNDATION

UHN Toronto General Toronto Western Princess Margaret Toronto Rehab

Collaborative Care

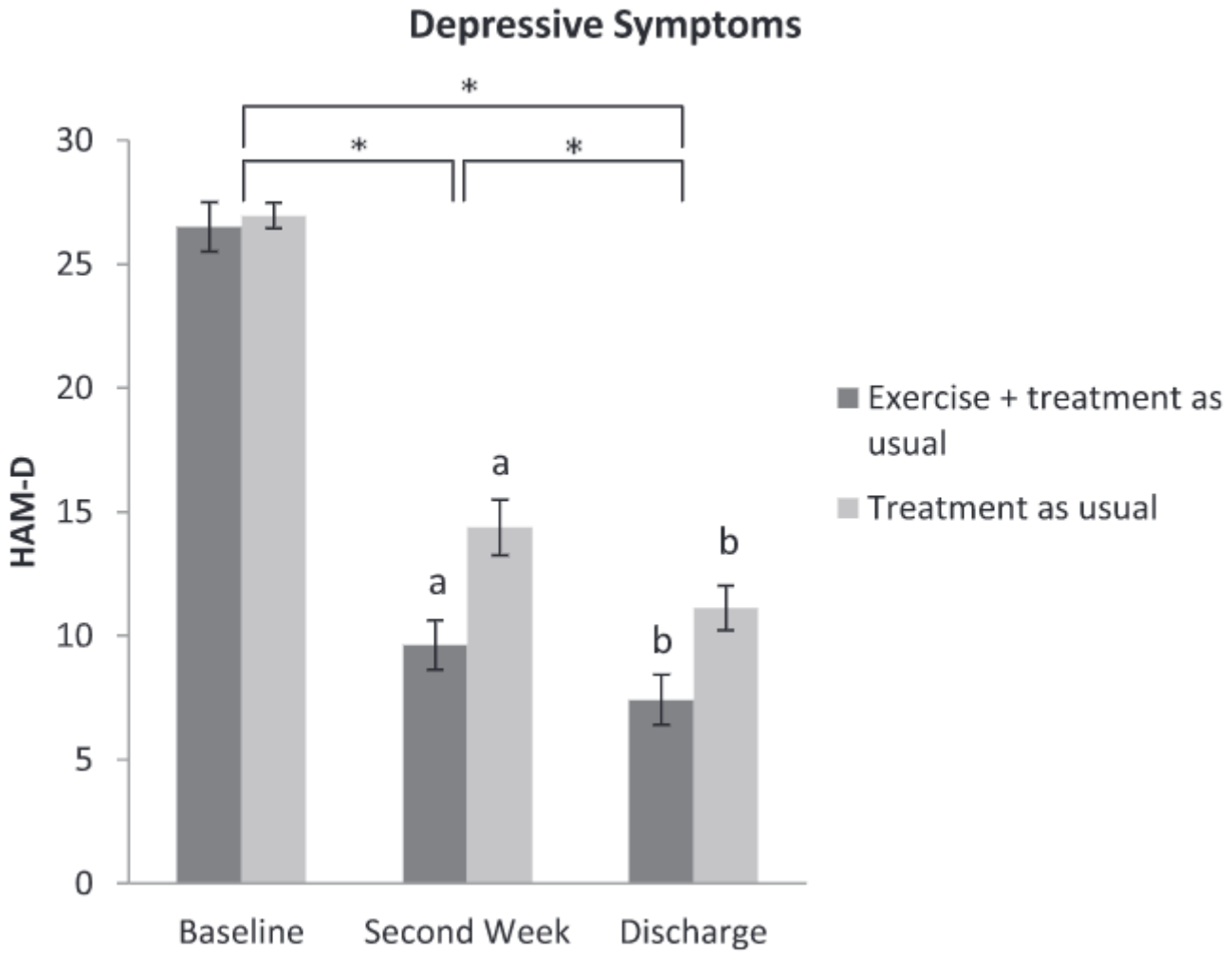
- 12-month intervention that integrated a Diabetes Prevention Program–based behavioral weight loss treatment with problem-solving therapy for depression and, if indicated, antidepressant medications

Table 2. Weight Loss, Depression, and Anxiety Outcomes

	Unadjusted Estimates		Treatment Difference	
	Intervention	Usual Care	Adjusted Between-Group Difference (95% CI)[a]	*P* Value
Primary Outcomes				
Body mass index				
No. of participants	202	198		
At 6 mo, mean (SD)	36.0 (6.9)	36.6 (6.2)	Mean, −0.6 (−0.9 to −0.3)	<.001
At 12 mo, mean (SD)	35.9 (7.1)	36.6 (6.0)	Mean, −0.7 (−1.1 to −0.2)	.01
20-Item Depression Symptom Checklist (SCL-20) score[b]				
No. of participants	184	187		
At 6 mo, mean (SD)	1.1 (0.7)	1.4 (0.8)	Mean, −0.3 (−0.4 to −0.1)	<.001
At 12 mo, mean (SD)	1.1 (1.0)	1.4 (1.3)	Mean, −0.2 (−0.4 to 0)	.01

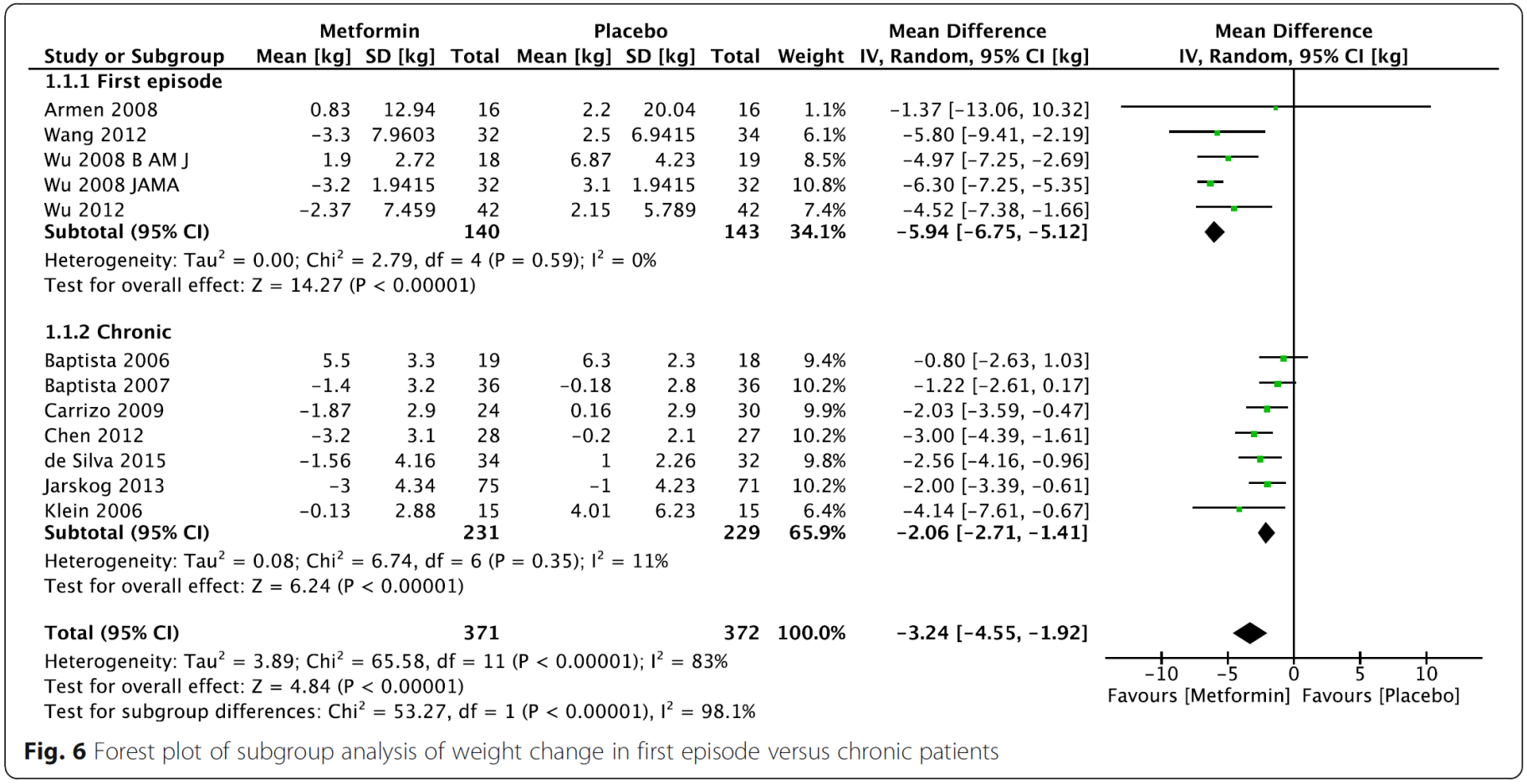
Ma et al. JAMA. 2019 Mar 5;321(9):869-879.

Exercise as an Anti-Depressant



Schuch et al. J Psychiatr Res. 2015 Feb;61:25-32.

Metformin for Weight-Gain Prevention



Study or Subgroup	Metformin Mean [kg]	Metformin SD [kg]	Metformin Total	Placebo Mean [kg]	Placebo SD [kg]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [kg]
1.1.1 First episode								
Armen 2008	0.83	12.94	16	2.2	20.04	16	1.1%	−1.37 [−13.06, 10.32]
Wang 2012	−3.3	7.9603	32	2.5	6.9415	34	6.1%	−5.80 [−9.41, −2.19]
Wu 2008 B AM J	1.9	2.72	18	6.87	4.23	19	8.5%	−4.97 [−7.25, −2.69]
Wu 2008 JAMA	−3.2	1.9415	32	3.1	1.9415	32	10.8%	−6.30 [−7.25, −5.35]
Wu 2012	−2.37	7.459	42	2.15	5.789	42	7.4%	−4.52 [−7.38, −1.66]
Subtotal (95% CI)			**140**			**143**	**34.1%**	**−5.94 [−6.75, −5.12]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.79$, df = 4 (P = 0.59); $I^2 = 0\%$								
Test for overall effect: Z = 14.27 (P < 0.00001)								
1.1.2 Chronic								
Baptista 2006	5.5	3.3	19	6.3	2.3	18	9.4%	−0.80 [−2.63, 1.03]
Baptista 2007	−1.4	3.2	36	−0.18	2.8	36	10.2%	−1.22 [−2.61, 0.17]
Carrizo 2009	−1.87	2.9	24	0.16	2.9	30	9.9%	−2.03 [−3.59, −0.47]
Chen 2012	−3.2	3.1	28	−0.2	2.1	27	10.2%	−3.00 [−4.39, −1.61]
de Silva 2015	−1.56	4.16	34	1	2.26	32	9.8%	−2.56 [−4.16, −0.96]
Jarskog 2013	−3	4.34	75	−1	4.23	71	10.2%	−2.00 [−3.39, −0.61]
Klein 2006	−0.13	2.88	15	4.01	6.23	15	6.4%	−4.14 [−7.61, −0.67]
Subtotal (95% CI)			**231**			**229**	**65.9%**	**−2.06 [−2.71, −1.41]**
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 6.74$, df = 6 (P = 0.35); $I^2 = 11\%$								
Test for overall effect: Z = 6.24 (P < 0.00001)								
Total (95% CI)			**371**			**372**	**100.0%**	**−3.24 [−4.55, −1.92]**
Heterogeneity: $Tau^2 = 3.89$; $Chi^2 = 65.58$, df = 11 (P < 0.00001); $I^2 = 83\%$								
Test for overall effect: Z = 4.84 (P < 0.00001)								
Test for subgroup differences: $Chi^2 = 53.27$, df = 1 (P < 0.00001), $I^2 = 98.1\%$								

Fig. 6 Forest plot of subgroup analysis of weight change in first episode versus chronic patients

de Silva et al. BMC Psychiatry. 2016

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- Sebastian Badulescu

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CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

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