SIMPOSIO 10
SINERGIE TRA RICERCA E TERRITORIO PER UN'EFFICACE
IDENTIFICAZIONE PRECOCE DEL RISCHIO PER PSICOSI

KING'S College LONDON

UniBa UNIVERSITÀ DEGLI STUDI DI BARI ALDO MORO

TRAIETTORIE DI METABOLISMO CEREBRALE NELLE FASI PRECOCI DELLA PSICOSI ED IL RUOLO DEL TRATTAMENTO CON ANTIPSICOTICI

Pierluigi Selvaggi, MD, PhD
Ricercatore (RTdA) – Università degli Studi di Bari Aldo Moro
Clinical Research Fellow - King's College London

BRAIN METABOLISM IN PSYCHOSIS

- The brain absorbs the highest metabolic demand of any organ at rest (20 % of O_2 basal consumption and 50-65% of total metabolic requirement) with minimal reserve capacity (Kuzawa et al. PNAS 2014).
- SCZ patients show reduced glucose utilization (18F-FDG PET) in several cortical regions (meta-analytical evidence, with methodological caveats) (Hill et al. Acta Psych Scan 2004)
- Meta-analytical evidence of reduced cortical perfusion in SCZ from 15O-H2O PET studies (Goozée et al. Neurosci. Biobehav. Rev. 2014)
- Meta-analytical evidence of increased lactate and decreased ph in post-mortem SCZ brains (controlled for post-mortem intervals and agonal state) (Hagihara et al. Neuropsychopharm. 2018)
- The same pattern has been observed *in vivo* using Magnetic Resonance Spectroscopy (MRS) (Dogan et al. Neuropsychopharm. 2018) and CSF biochemistry (Regenold Biol. Psych. 2009)
- Converging evidence from transcriptomics, proteomics, metabolomics indicates deficits in mitochondrial activity in SCZ (Prabakaran et a. Mol Psych. 2004; Rajasekaran et al. Neurosc. Biobehav. Rev. (2015)

BRAIN METABOLISM IN PSYCHOSIS

Psychological Medicine

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Brain glucose metabolism in schizophrenia: a systematic review and meta-analysis of ^{18}FDG-PET studies in schizophrenia

Leigh Townsend[1], Toby Pillinger[2], Pierluigi Selvaggi[3,4], Mattia Veronese[3,5], Federico Turkheimer[3] and Oliver Howes[1,2]

Original Article

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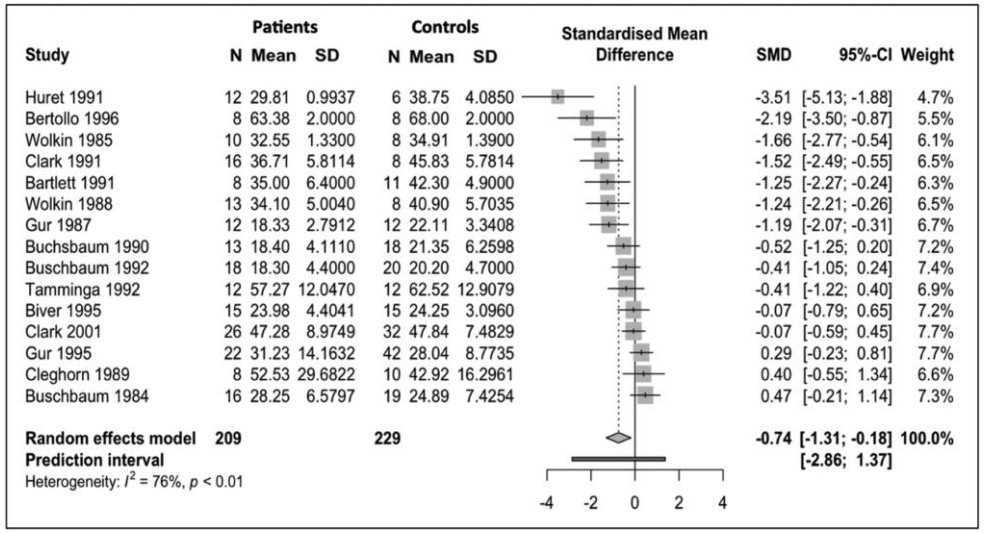


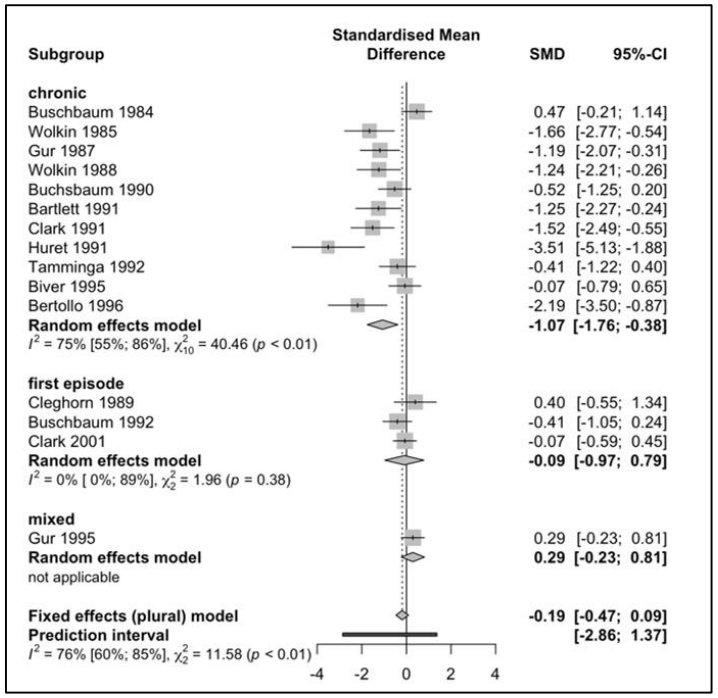
Study	Patients N	Mean	SD	Controls N	Mean	SD	SMD	95%-CI	Weight
Huret 1991	12	29.81	0.9937	6	38.75	4.0850	-3.51	[-5.13; -1.88]	4.7%
Bertollo 1996	8	63.38	2.0000	8	68.00	2.0000	-2.19	[-3.50; -0.87]	5.5%
Wolkin 1985	10	32.55	1.3300	8	34.91	1.3900	-1.66	[-2.77; -0.54]	6.1%
Clark 1991	16	36.71	5.8114	8	45.83	5.7814	-1.52	[-2.49; -0.55]	6.5%
Bartlett 1991	8	35.00	6.4000	11	42.30	4.9000	-1.25	[-2.27; -0.24]	6.3%
Wolkin 1988	13	34.10	5.0040	8	40.90	5.7035	-1.24	[-2.21; -0.26]	6.5%
Gur 1987	12	18.33	2.7912	12	22.11	3.3408	-1.19	[-2.07; -0.31]	6.7%
Buchsbaum 1990	13	18.40	4.1110	18	21.35	6.2598	-0.52	[-1.25; 0.20]	7.2%
Buschbaum 1992	18	18.30	4.4000	20	20.20	4.7000	-0.41	[-1.05; 0.24]	7.4%
Tamminga 1992	12	57.27	12.0470	12	62.52	12.9079	-0.41	[-1.22; 0.40]	6.9%
Biver 1995	15	23.98	4.4041	15	24.25	3.0960	-0.07	[-0.79; 0.65]	7.2%
Clark 2001	26	47.28	8.9749	32	47.84	7.4829	-0.07	[-0.59; 0.45]	7.7%
Gur 1995	22	31.23	14.1632	42	28.04	8.7735	0.29	[-0.23; 0.81]	7.7%
Cleghorn 1989	8	52.53	29.6822	10	42.92	16.2961	0.40	[-0.55; 1.34]	6.6%
Buschbaum 1984	16	28.25	6.5797	19	24.89	7.4254	0.47	[-0.21; 1.14]	7.3%
Random effects model	**209**			**229**			**-0.74**	**[-1.31; -0.18]**	**100.0%**
Prediction interval								**[-2.86; 1.37]**	

Heterogeneity: I^2 = 76%, p < 0.01

Standardised Mean Difference: -4, -2, 0, 2, 4

Lower 18F-FDG uptake in SCZ in the frontal cortex
(Hedge's g = -0.66 (moderate to large effect size)

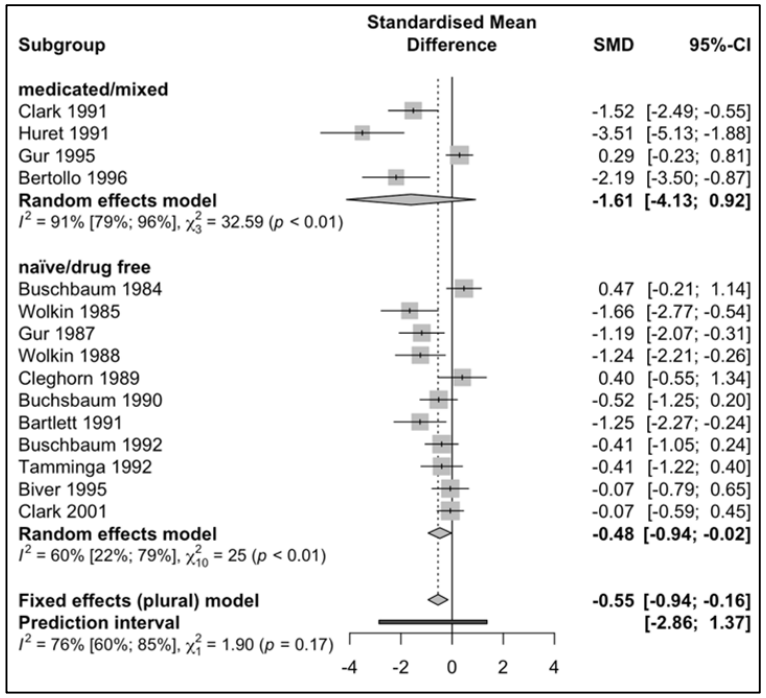
Chronic patients show lower frontal metabolism as compared with FEP



Subgroup	SMD	95%-CI
chronic		
Buschbaum 1984	0.47	[-0.21; 1.14]
Wolkin 1985	-1.66	[-2.77; -0.54]
Gur 1987	-1.19	[-2.07; -0.31]
Wolkin 1988	-1.24	[-2.21; -0.26]
Buchsbaum 1990	-0.52	[-1.25; 0.20]
Bartlett 1991	-1.25	[-2.27; -0.24]
Clark 1991	-1.52	[-2.49; -0.55]
Huret 1991	-3.51	[-5.13; -1.88]
Tamminga 1992	-0.41	[-1.22; 0.40]
Biver 1995	-0.07	[-0.79; 0.65]
Bertollo 1996	-2.19	[-3.50; -0.87]
Random effects model	**-1.07**	**[-1.76; -0.38]**
I^2 = 75% [55%; 86%], χ^2_{10} = 40.46 (p < 0.01)		
first episode		
Cleghorn 1989	0.40	[-0.55; 1.34]
Buschbaum 1992	-0.41	[-1.05; 0.24]
Clark 2001	-0.07	[-0.59; 0.45]
Random effects model	**-0.09**	**[-0.97; 0.79]**
I^2 = 0% [0%; 89%], χ^2_2 = 1.96 (p = 0.38)		
mixed		
Gur 1995	0.29	[-0.23; 0.81]
Random effects model	**0.29**	**[-0.23; 0.81]**
not applicable		
Fixed effects (plural) model	**-0.19**	**[-0.47; 0.09]**
Prediction interval		**[-2.86; 1.37]**
I^2 = 76% [60%; 85%], χ^2_2 = 11.58 (p < 0.01)		

Standardised Mean Difference: -4, -2, 0, 2, 4

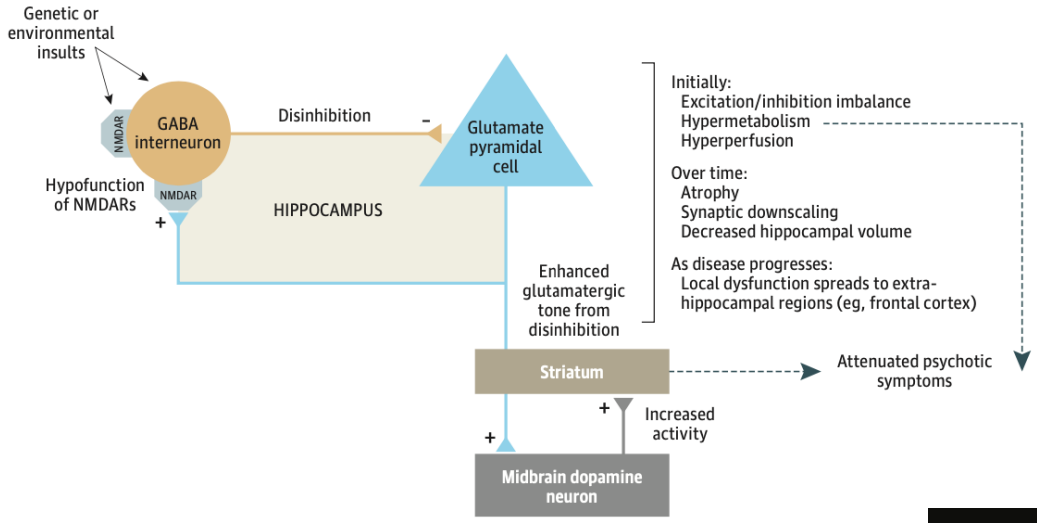
Medicated patients show lower frontal metabolism as compared with free/naive



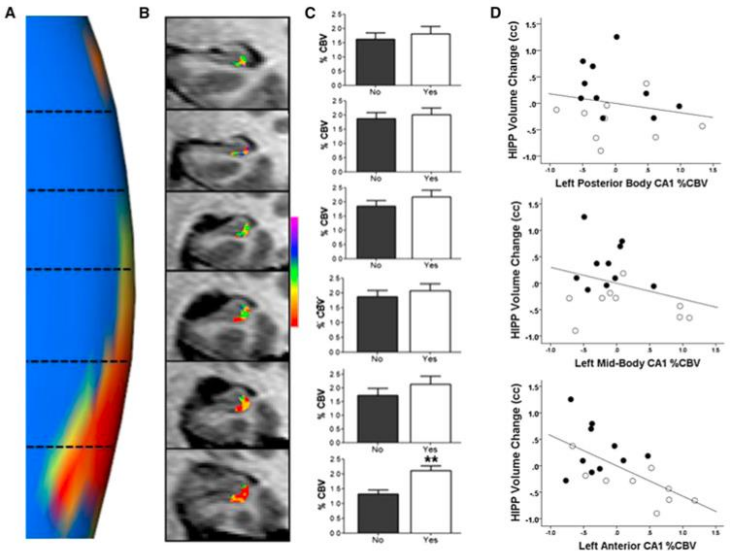
Subgroup	SMD	95%-CI
medicated/mixed		
Clark 1991	-1.52	[-2.49; -0.55]
Huret 1991	-3.51	[-5.13; -1.88]
Gur 1995	0.29	[-0.23; 0.81]
Bertollo 1996	-2.19	[-3.50; -0.87]
Random effects model	**-1.61**	**[-4.13; 0.92]**
I^2 = 91% [79%; 96%], χ^2_3 = 32.59 (p < 0.01)		
naïve/drug free		
Buschbaum 1984	0.47	[-0.21; 1.14]
Wolkin 1985	-1.66	[-2.77; -0.54]
Gur 1987	-1.19	[-2.07; -0.31]
Wolkin 1988	-1.24	[-2.21; -0.26]
Cleghorn 1989	0.40	[-0.55; 1.34]
Buchsbaum 1990	-0.52	[-1.25; 0.20]
Bartlett 1991	-1.25	[-2.27; -0.24]
Buschbaum 1992	-0.41	[-1.05; 0.24]
Tamminga 1992	-0.41	[-1.22; 0.40]
Biver 1995	-0.07	[-0.79; 0.65]
Clark 2001	-0.07	[-0.59; 0.45]
Random effects model	**-0.48**	**[-0.94; -0.02]**
I^2 = 60% [22%; 79%], χ^2_{10} = 25 (p < 0.01)		
Fixed effects (plural) model	**-0.55**	**[-0.94; -0.16]**
Prediction interval		**[-2.86; 1.37]**
I^2 = 76% [60%; 85%], χ^2_1 = 1.90 (p = 0.17)		

Standardised Mean Difference: -4, -2, 0, 2, 4

BRAIN METABOLISM IN THE EARLY STAGE

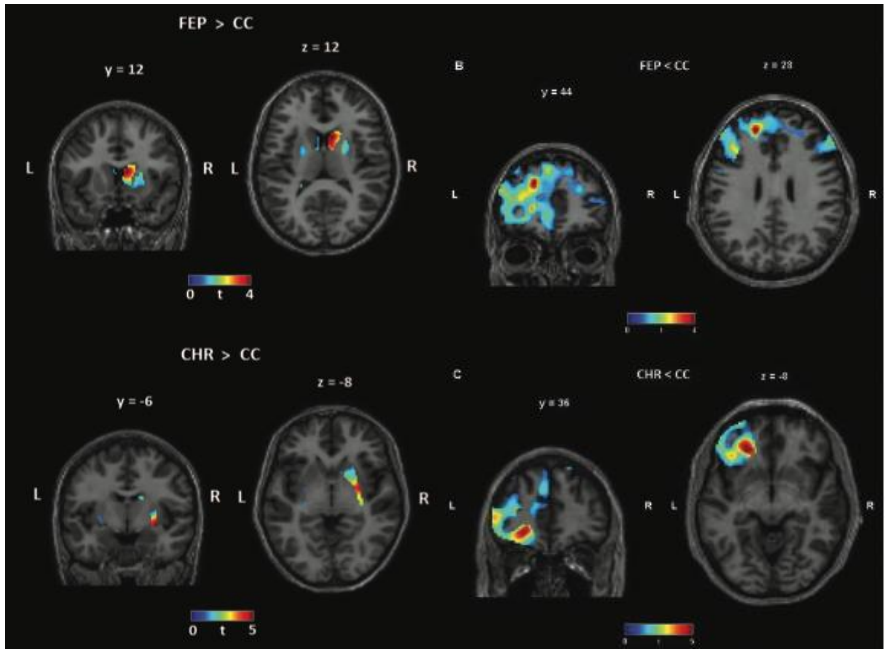


Fusar-Poli et al. JAMA Psychiatry (2020)



Shobel et al. Neuron (2013)

Hippocampal hyper-perfusion in CHR-P has been replicated in different cohorts (Allen et al. 2016; Allen et al. 2018, Modinos et al. 2018).



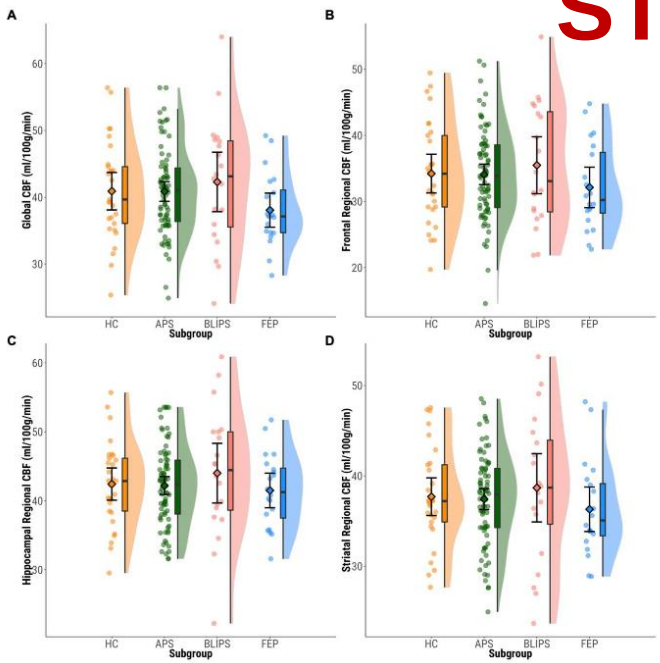
Kindler et al. Schiz Bull (2018)

BRAIN PERFUSION IN THE EARLY STAGE

frontiers | Frontiers in Psychiatry

Parsing neurobiological heterogeneity of the clinical high-risk state for psychosis: A pseudo-continuous arterial spin labelling study

Dominic Oliver[1,2,3], Cathy Davies[4,5], Fernando Zelaya[5], Pierluigi Selvaggi[5,6], Andrea De Micheli[1,7], Ana Catalan[1,8], Helen Baldwin[1,9], Maite Arribas[1], Gemma Modinos[4,5], Nicolas A. Crossley[2,10], Paul Allen[4,11], Alice Egerton[4], Sameer Jauhar[12], Oliver D. Howes[4], Philip McGuire[2,3,4,7,13] and Paolo Fusar-Poli[1,7,13,14]*



Psychological Medicine

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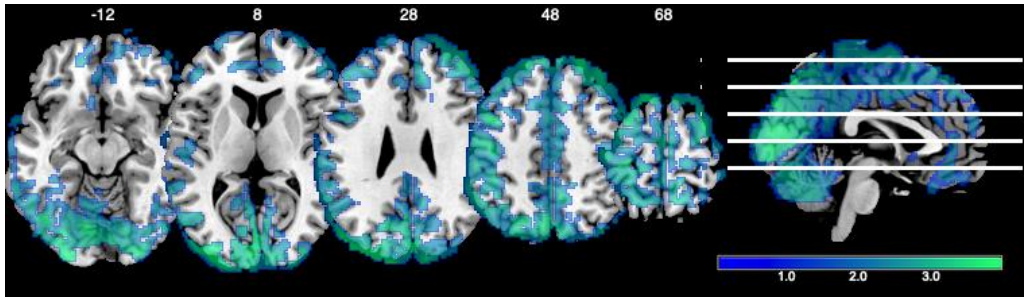
Original Article

*Designates equal contribution as first author.

Cite this article: Selvaggi P *et al* (2023).

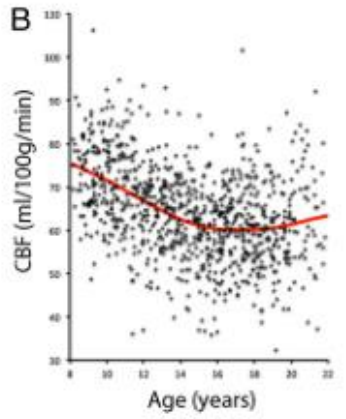
Reduced cortical cerebral blood flow in antipsychotic-free first-episode psychosis and relationship to treatment response

Pierluigi Selvaggi[1,2,*], Sameer Jauhar[3,4,*], Vasileia Kotoula[1], Fiona Pepper[3], Mattia Veronese[1], Barbara Santangelo[1], Fernando Zelaya[1], Federico E. Turkheimer[1], Mitul A. Mehta[1] and Oliver D. Howes[3,5,6]

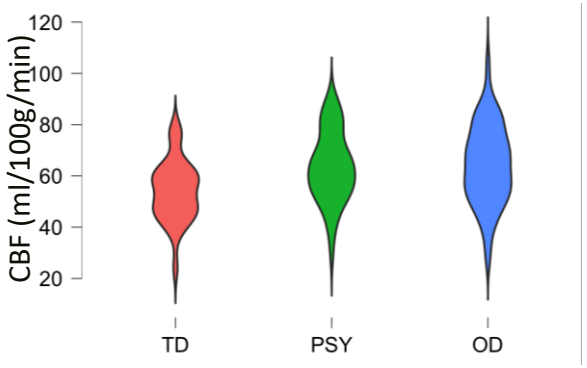


FEP < HC TFCE corrected, 5000 permutations

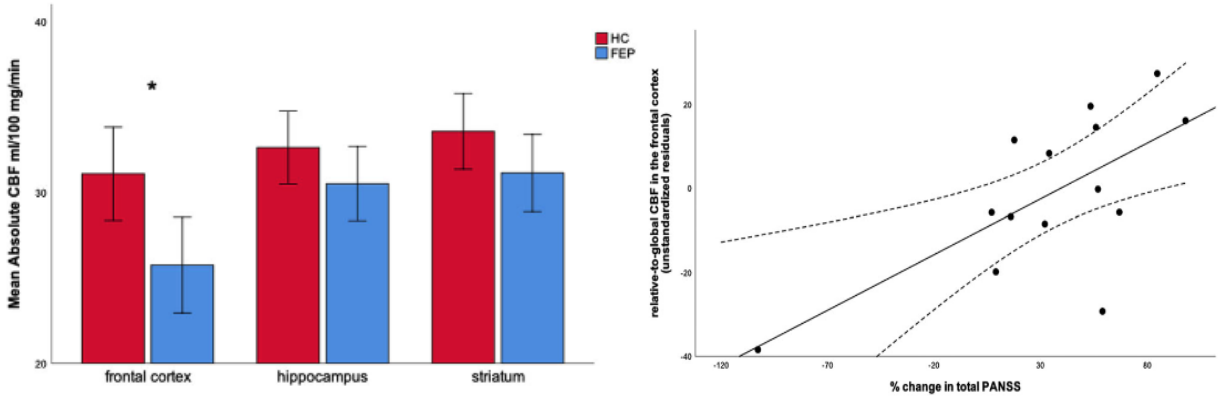
Brain Perfusion during brain development



Satterthwaite et al. PNAS (2014)



Selvaggi et al. (unpublished data)



ANTIPSYCHOTIC EFFECTS ON BRAIN PERFUSION

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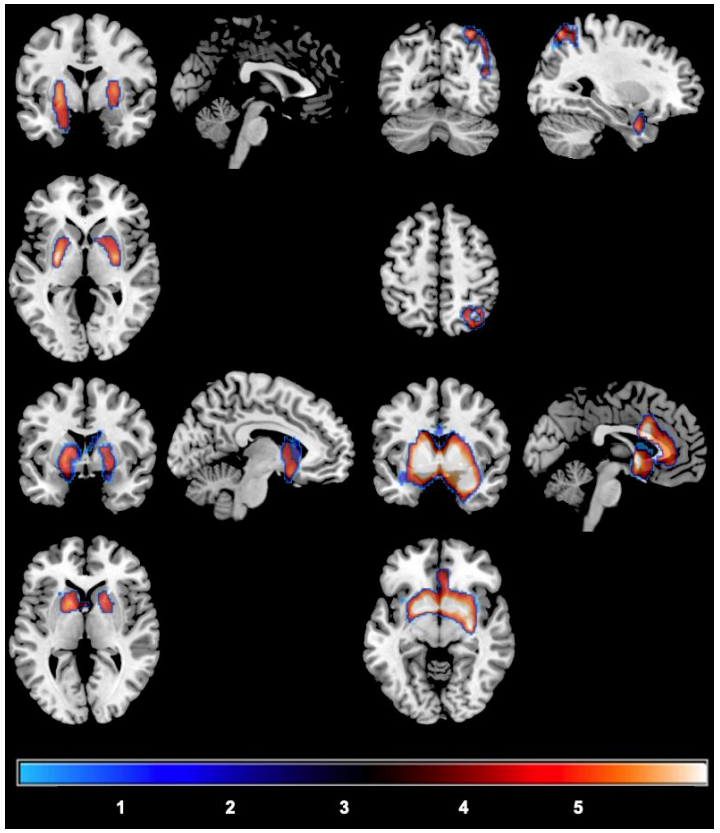
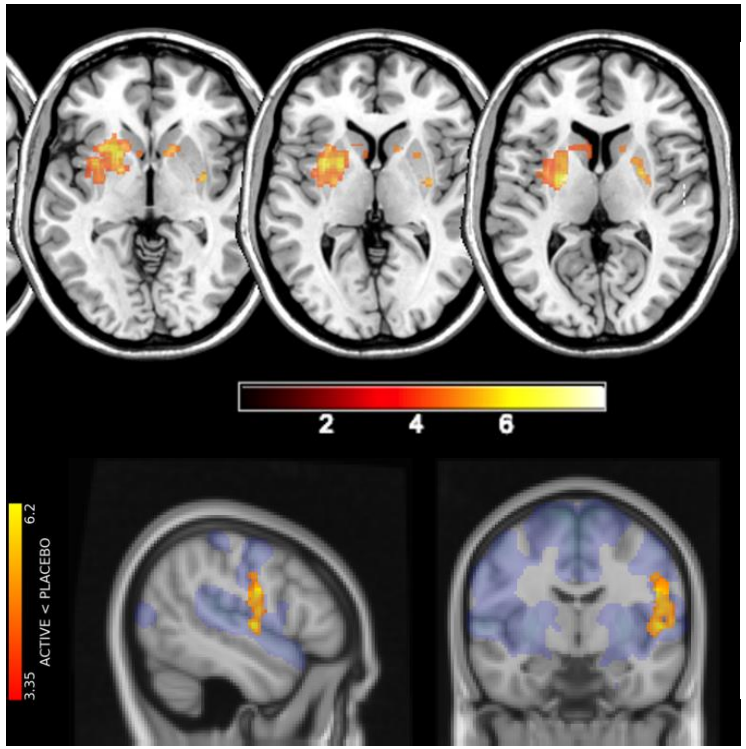
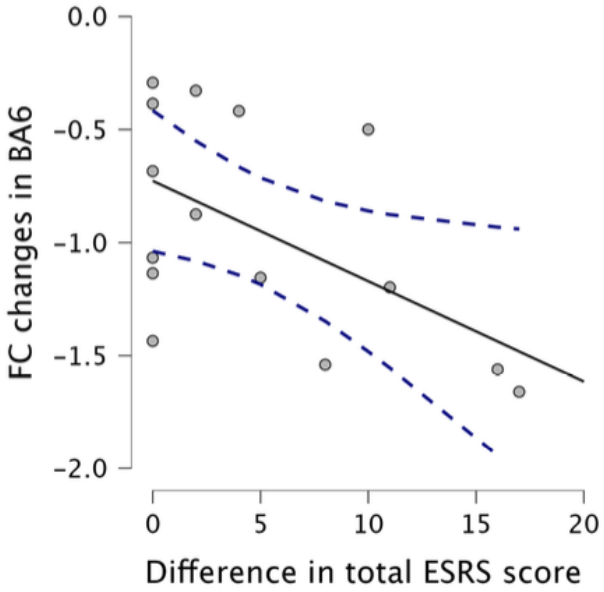
Increased cerebral blood flow after single dose of antipsychotics in healthy volunteers depends on dopamine D2 receptor density profiles

Pierluigi Selvaggi [a,*], Peter C.T. Hawkins [a], Ottavia Dipasquale [a], Gaia Rizzo [b,c], Alessandro Bertolino [d], Juergen Dukart [e], Fabio Sambataro [f], Giulio Pergola [d], Steven C.R. Williams [a], Federico Turkheimer [a], Fernando Zelaya [a], Mattia Veronese [a,1], Mitul A. Mehta [a,1]



The effect persists also after one week exposure to amisupride in healthy volunteers and it is linked with EPS





Selvaggi et al. (in preparation)

CONCLUSION

- Brain metabolism is altered in psychosis
- Alterations in brain metabolism are present at the early stage of the disease, possibly reflecting abnormal neurodevelopment
- Antipsychotic treatment alters brain metabolism. What is the interaction with baseline anomalies? Are all AP equivalent?
- The investigation of brain metabolism in longitudinal cohorts might reveal pathophysiological mechanisms underlying altered brain function and behaviour, biomarkers for stratification and maybe new treatment targets.

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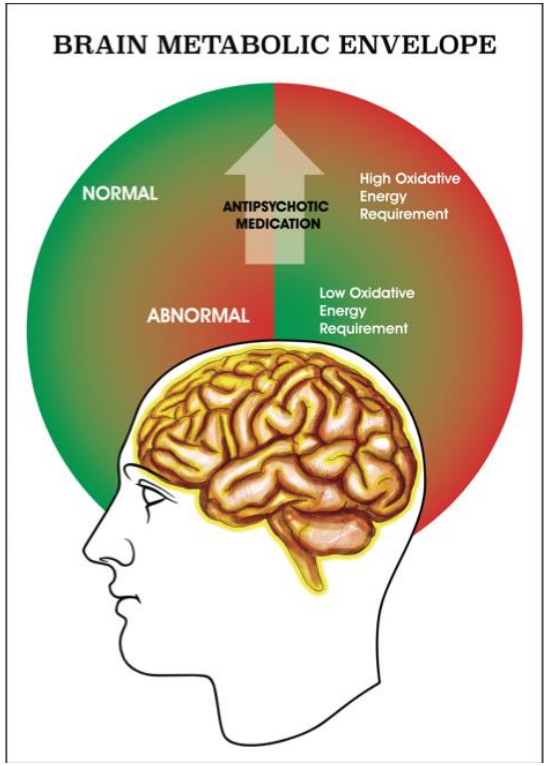
Advance Access publication 22 November 2019

Normalizing the Abnormal: Do Antipsychotic Drugs Push the Cortex Into an Unsustainable Metabolic Envelope?

Federico E. Turkheimer*[,1,2,•], Pierluigi Selvaggi[1,•], Mitul A. Mehta[1], Mattia Veronese[1], Fernando Zelaya[1], Paola Dazzan[3], and Anthony C. Vernon[2,4]



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