Neuroimaging Inflammation in Clinical Depression and Obsessive Compulsive Disorder

Dr. Jeffrey Meyer MD PhD FRCP(C)
Canada Research Chair in Neurochemistry of Major Depression
Head, Neurochemical Imaging Program in Mood Disorders
Research Imaging Centre, Centre for Addiction and Mental Health,
Professor, Department of Psychiatry, University of Toronto

Campbell Family Mental Health Research Institute

camh
Centre for Addiction and Mental Health

VELUT ARBOR ÆVO

Canada Research Chairs

camhric | Azrieli Centre for Neuro-Radiochemistry

Funding Sources/Technology Interests

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Ontario Ministry for Innovation
Campbell Research Institute
MARS Innovation
Neuroscience Catalyst Program
CAMH Foundation

Industry- Consultation/Operating Funds (last 5 years)
Lundbeck/Takeda
Janssen

Patents (Accepted or in Submission)/Technology Development
Central Markers as predictor of mood disorder, treatment or outcome
Peripheral Markers of MAO-A as predictor of mood disorder or outcome
Creating Dietary Supplement to Prevent Postpartum Depression
Peripheral Marker of Neuroinflammation

Overview

(i) Clinical Challenges of Treatment for Major Depressive Disorder and Obsessive Compulsive Disorder

(ii) Imaging Neuroinflammation With Positron Emission Tomography

(iii) Translocator Protein Imaging in Clinical Depression

(iv) Translocator Protein Imaging in Obsessive Compulsive Disorder

(v) Interpretations, Implications and Potential for Improving Clinical Care

(vi) Technologies and Advances Ahead

Problem of Treatment Resistance and Missing Targets

Major depressive disorder

4% of the general population is in the midst of a major depressive episode (Ustun et al. 2004)

At least 50% of major depressive episodes do not respond adequately to treatment (Trivedi et al. 2006)

Obsessive compulsive disorder

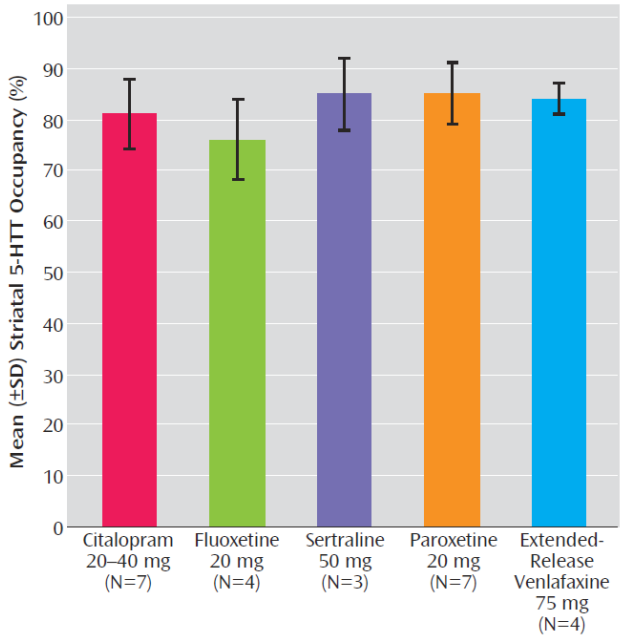
1 to 2% of population markedly affected by obsessive compulsive compulsive disorder

A third of OCD does not respond adequately to the best evidence based pharmacotherapies (serotonin reuptake inhibitors/clomipramine)

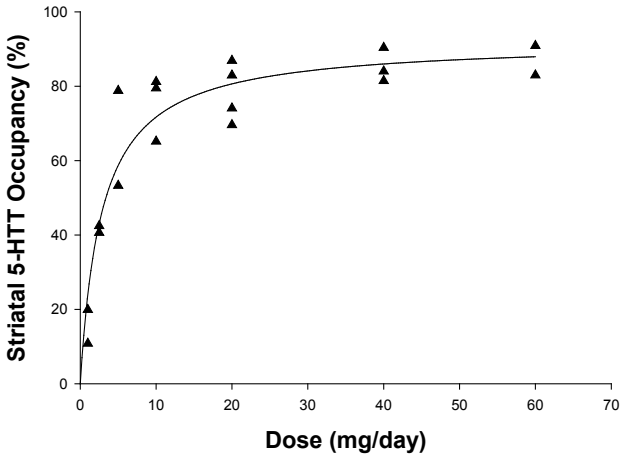
Do common antidepressant treatments miss targets during major depressive episodes?

80% Threshold for SSRI Doses that Distinguish from Placebo

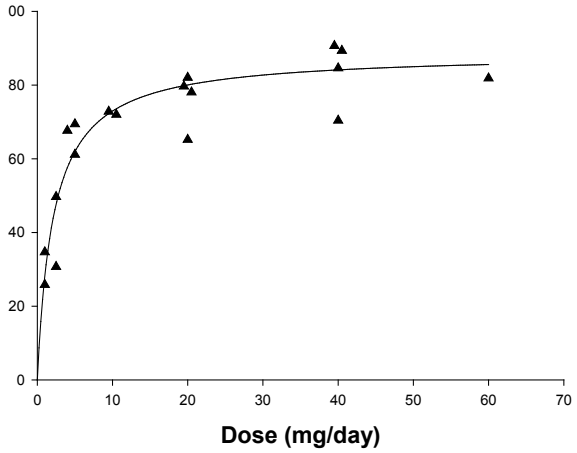
FIGURE 6. Striatal Serotonin Transporter (5-HTT) Occupancy in Depressed Subjects After 4 Weeks of Treatment at Minimum Therapeutic Doses of Five SSRIs



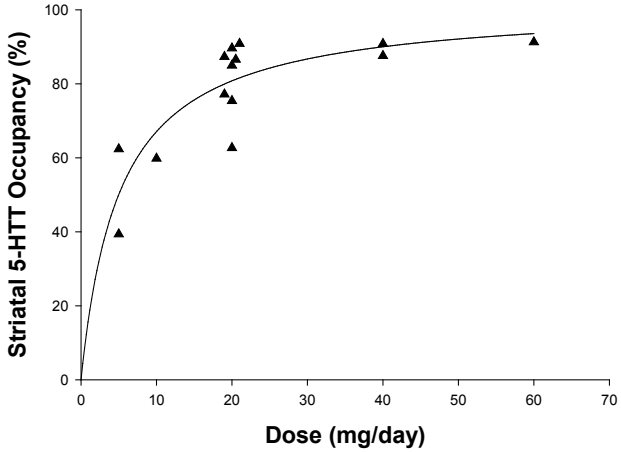
Citalopram



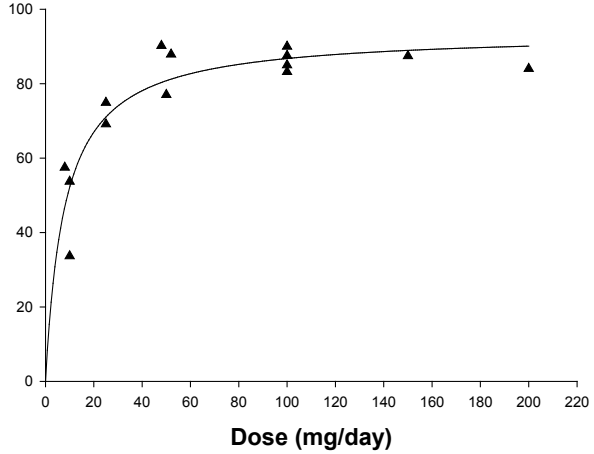
Fluoxetine



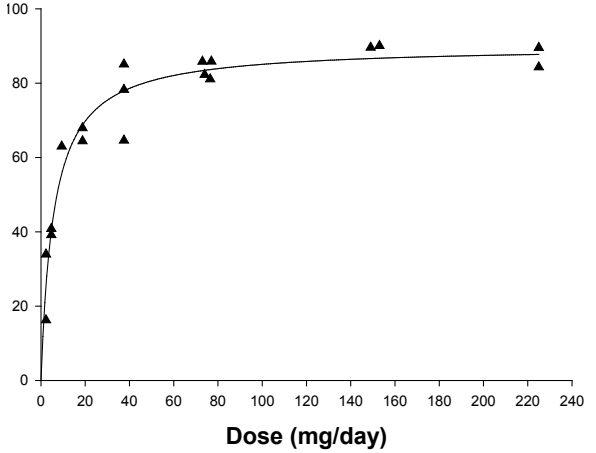
Paroxetine



Sertraline

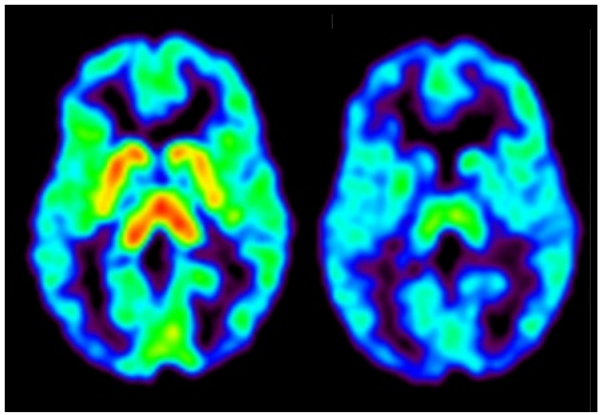


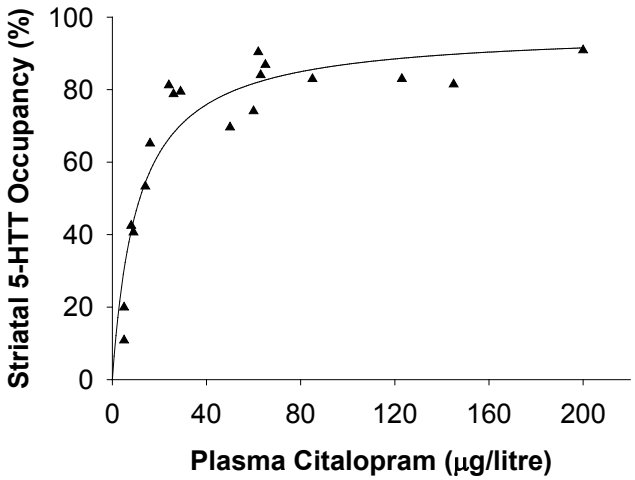
VenlafaxineXR

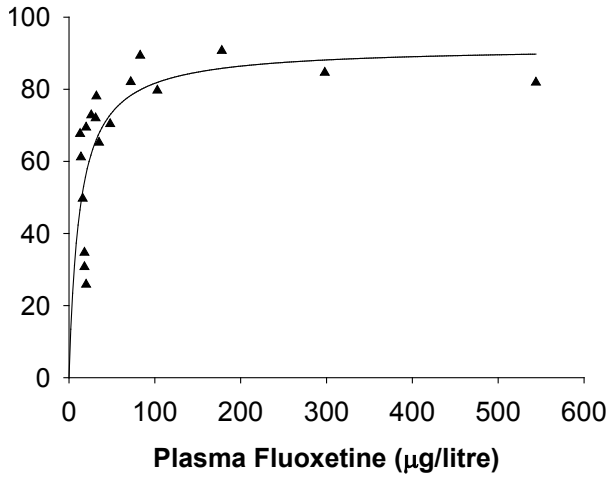


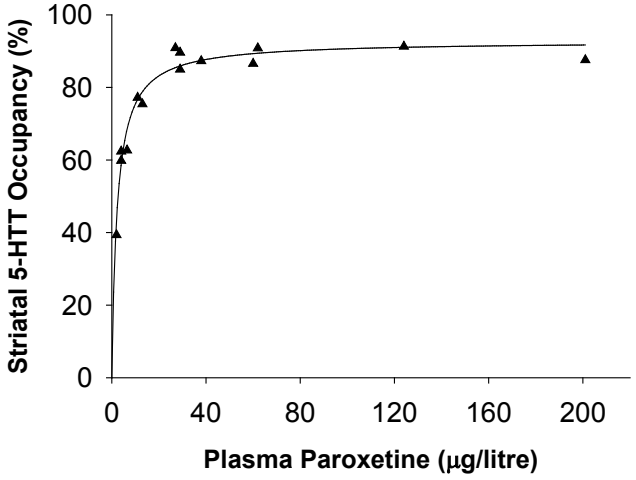
The data was fit using an equation of form f(x)=a*x/(b+x). Each fit was highly significant ($p<0.0002$ for all). Scanning occurred before treatment after four weeks of the treating dose. Occupancy = (baseline BP_{ND}-treatment BP_{ND})/baseline BP_{ND} **(Meyer et al. 2001, 2004)**

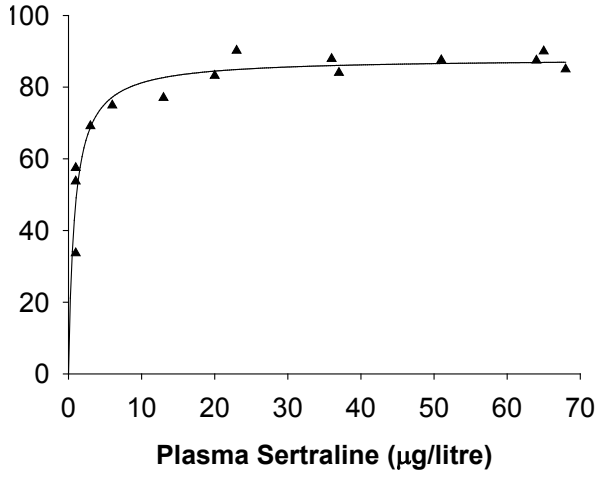
Plasma Level of SSRI Is Highly Influential Upon Occupancy

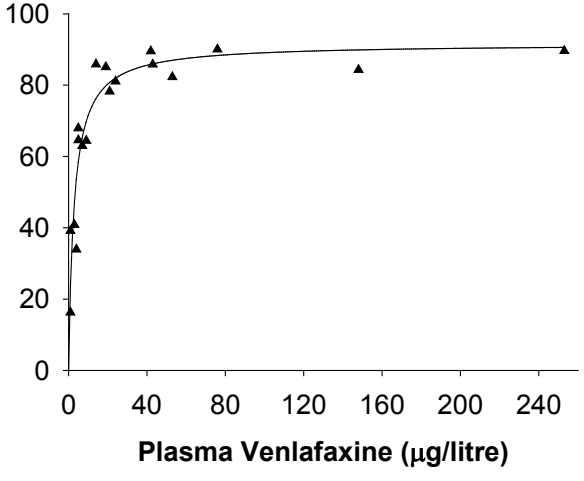








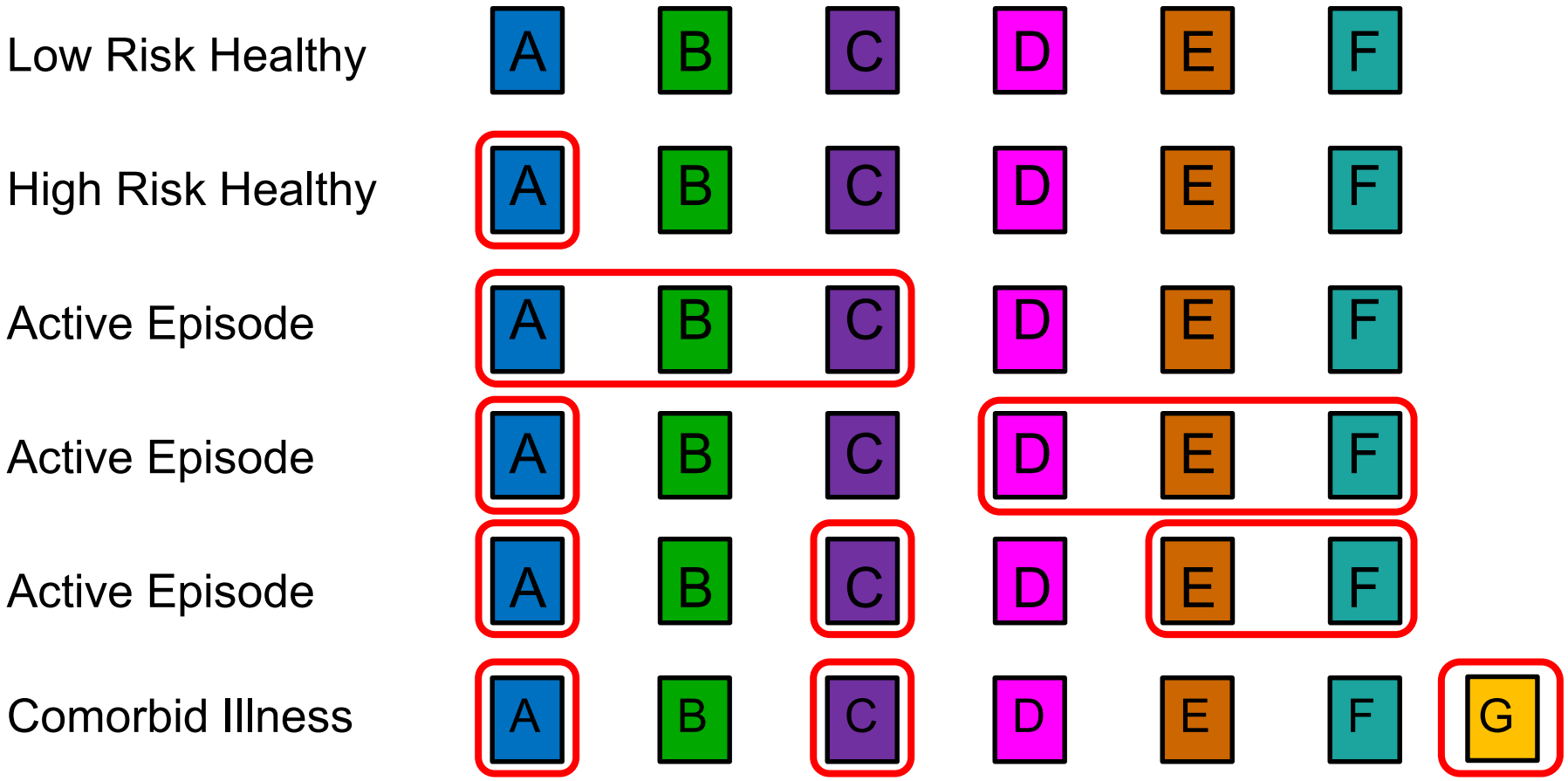




The data was fit using an equation of form f(x)=a*x/(b+x). Each fit was highly significant ($p<0.0002$ for all). Values for 'a', the theoretical maximum occupancy, ranged from 88 to 96%. Scanning occurred before treatment after four weeks of the treating dose. Occupancy is the per cent reduction in binding potential (BP_{ND}) i.e. Occupancy = (baseline BP_{ND}-treatment BP_{ND})/baseline BP_{ND}

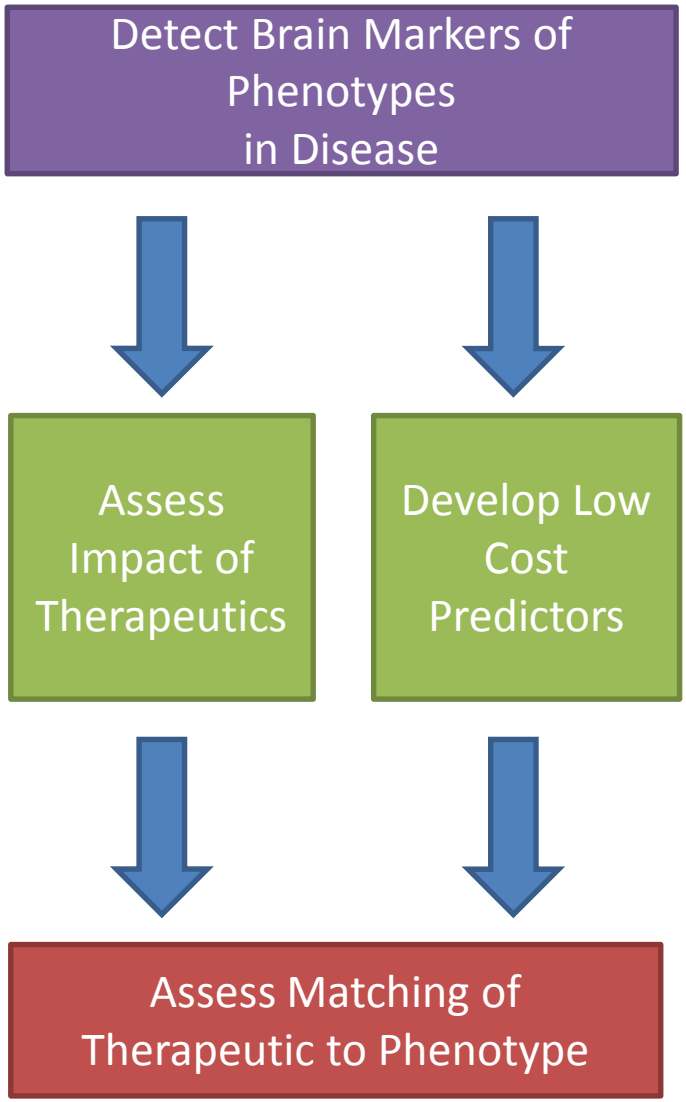
(Meyer et al. Am J Psych 2001, 2004)

Multiple Phenotype Model of Within Circuits of Psychiatric Illness



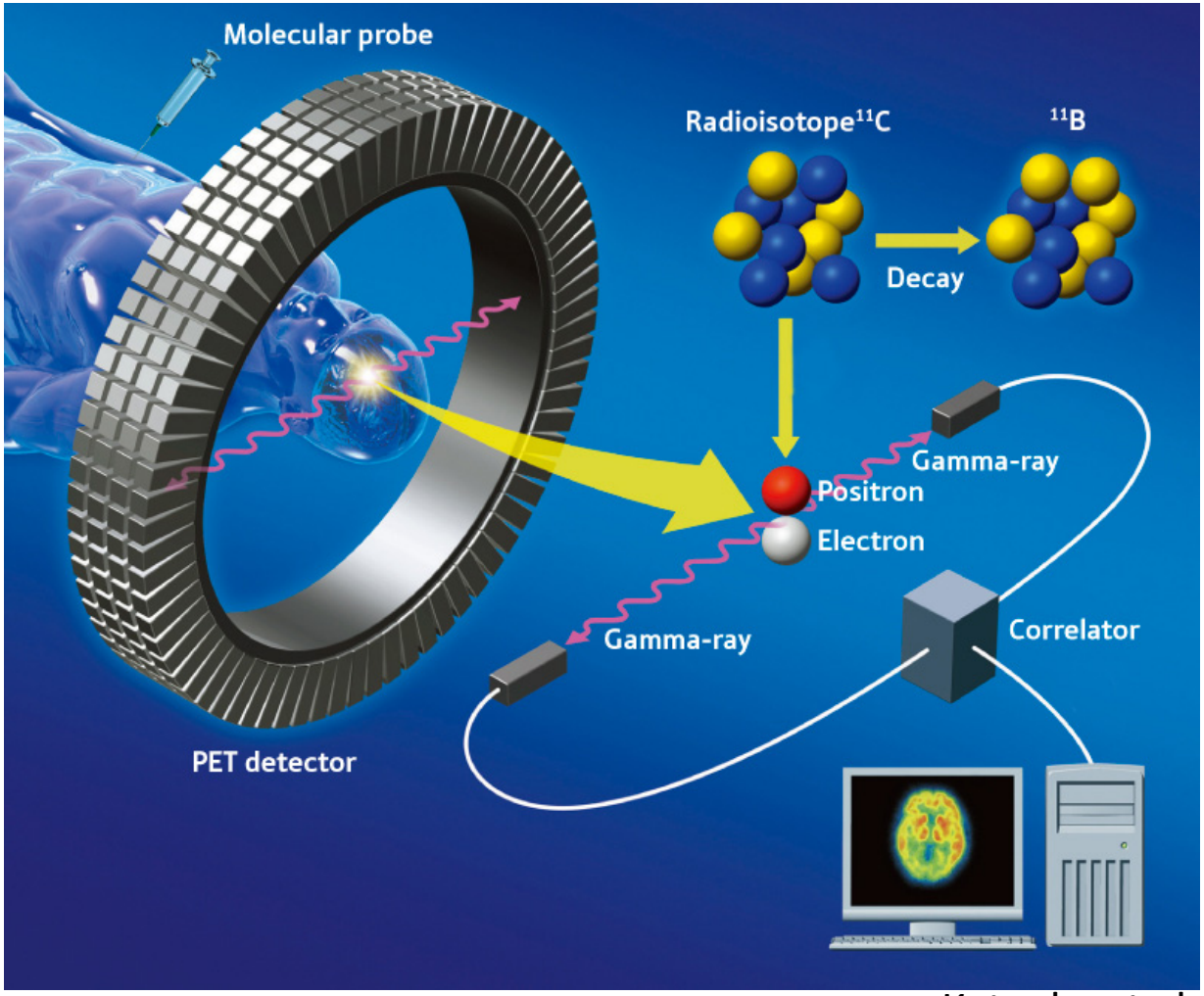
A through G represent markers of pathology.

PET-Radioligand Imaging to Understand/Improve Treatment



Positron Emission Tomography

- Ring of detector crystals
- Coincident imaging of 511 keV gamma rays
- Signal resolved in energy and time
- Detector activation defines a “line-of-response” (LOR)
- Events (decays) counted
- 3D (tomographic) image reconstructed



Kataoka et al.

Positron Emission Tomography has High Sensitivity

	PET	MRI
Spatial Resolution	2-6mm	<<1mm
Sensitivity	**10^{-12} M**	**10^{-4} M**
Temporal Resolution	minutes	<1 sec

from Innis RB

Positron Emission Tomography

- Thermoplastic mask
- Slide into scanner
- Transmission scan
- Radiotracer given
- Scanning for 90 min to 2h

What is Inflammation?

-inflammation is the bodily response to infection or trauma

-like the hot, painful, redness around a scrape to the skin

-our bodies can also use this response excessively at times even when not needed

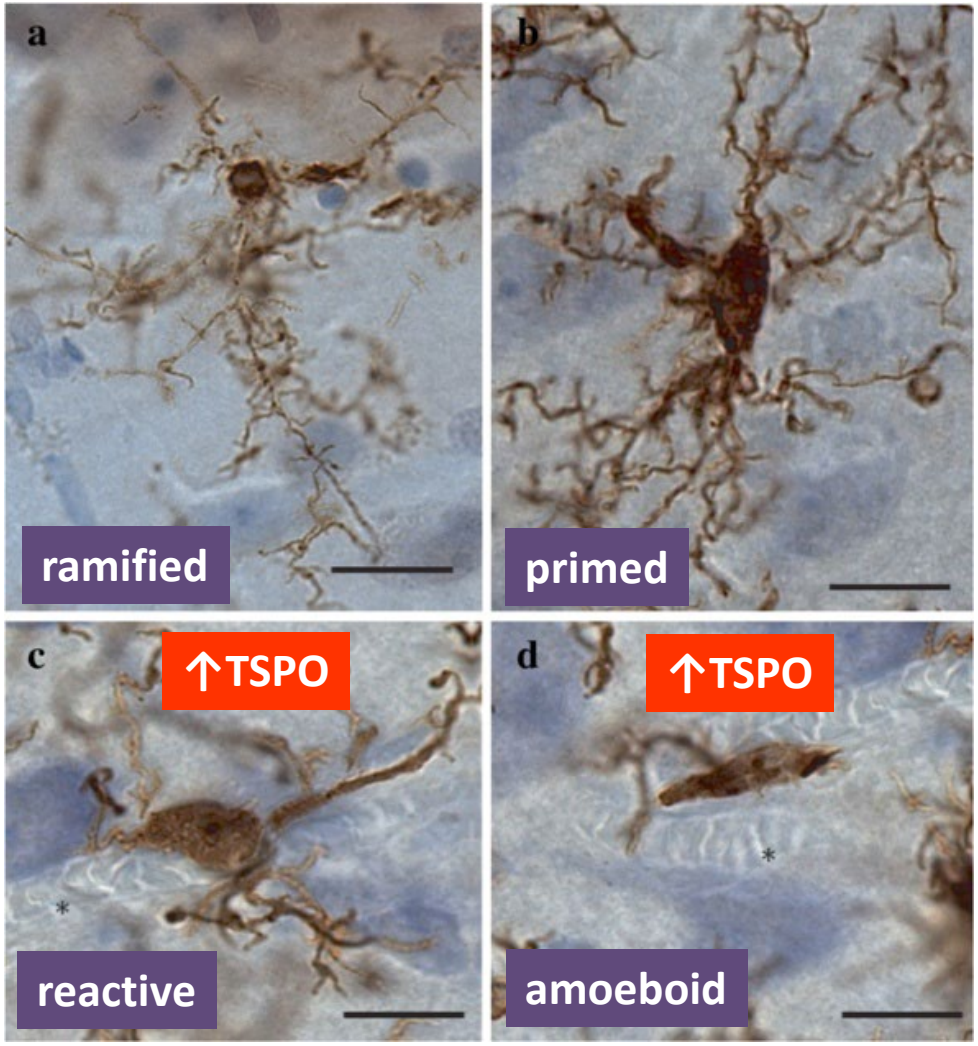
Microglia: Important Participants of Brain Inflammation

7 to 10% of the cells in the brain

Usually are in a **sensing detecting state** with a small body and long extensions scouting away

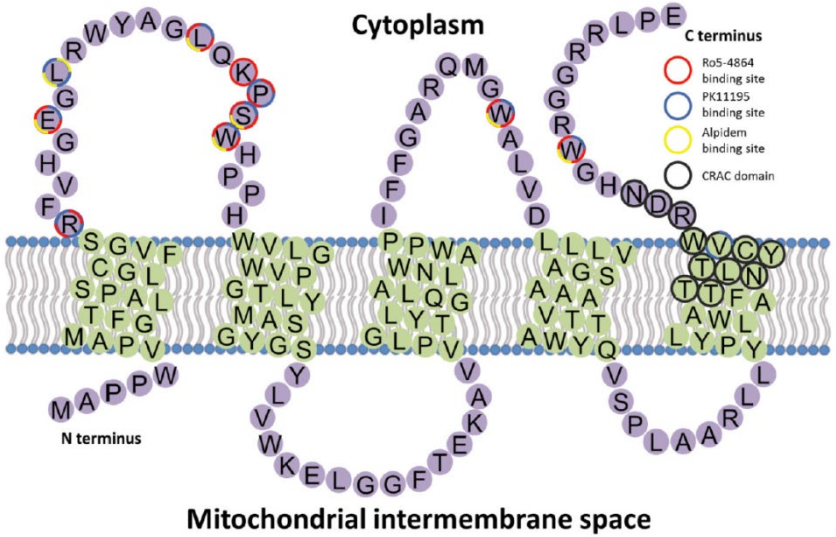
When **activated**
- cell bodies become larger
- extensions become shorter and thicker
- sometimes become little blobs like an amoeba

Increased density of TSPO when microglia are activated , an important component of neuroinflammation (Banati et al. 1997)



Torres- Platas et al. 2014; Scale bar 10µm

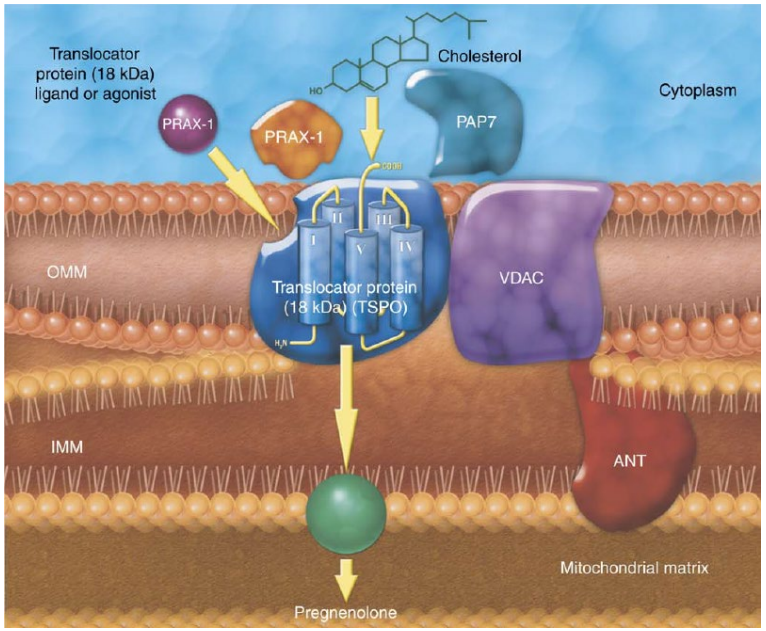
Translocator Protein



18KDa; 5 transmembrane alpha helices, 2 intra- and 2 extra-mitochondrial loops

Gene on chromosome 22q13.3

located on outer mitochondrial membrane



Hetero-oligomer with

VDAC (voltage dependent ion channel),
PRAX-1 (peripheral benzodiazepine receptor associated protein 1)
PAP7 (peripheral benzodiazepine receptor associated protein)
ANT (adenine nucleotide transporter)
DBI (diazepam binding inhibitor)
StAR (Steroidogeneic acute regulatory protein)
Or a monomer, or homo-oligomer

Papadopoulos et al., 2006, Liu et al. 2014

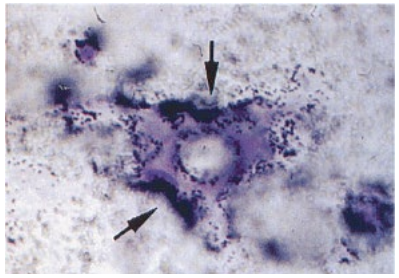
Elevated TSPO Level Mostly Specific to Microglial Activation

TSPO is found in several cell types microglia, astroglia, and endothelial cells, but during neuroinflammation, it mainly represents activated microglia (examples in human postmortem tissue: Cosenza-Nashat et al. 2009; Palzur et al. 2016).

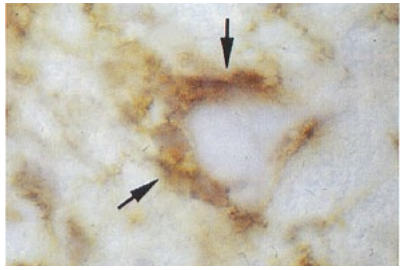
After toxin induced lesion, induced infarct and after LPS administration, changes in TSPO binding are associated with elevations in markers of microglial activation and not changes in astroglial activation (Banati et al. 1997; Martin et al. 2010, Hannestad et al 2012)

Elevated TSPO levels may occur in some models of astroglial activation, but this is probably at best a small contribution to the change detected, presumably due to a much lower density of TSPO in activated astrocytes (Banati et al. 2002)

TSPO has other roles - translocates cholesterol from outer to inner cell membranes and influences mitochondrial function (affecting apoptosis and respiration)



[11C]PK11195 Binding

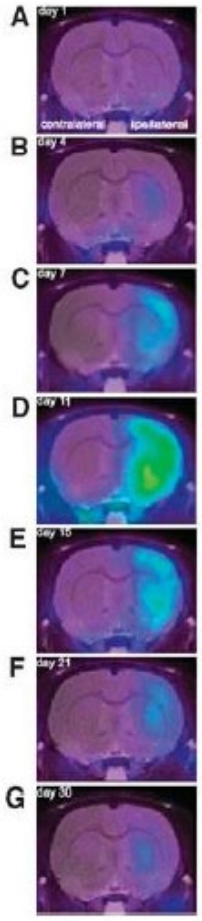


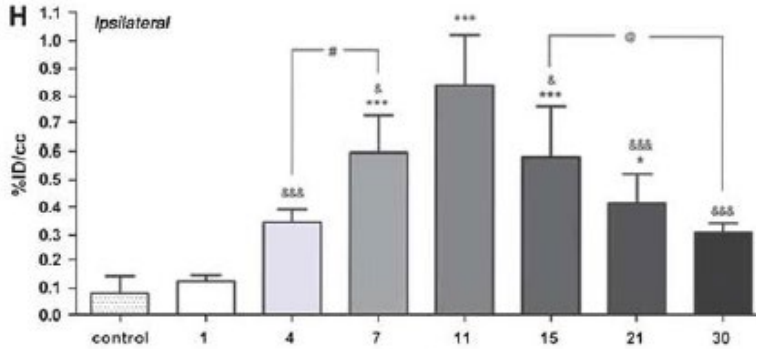
OX42 Binding and Morphologically Identified

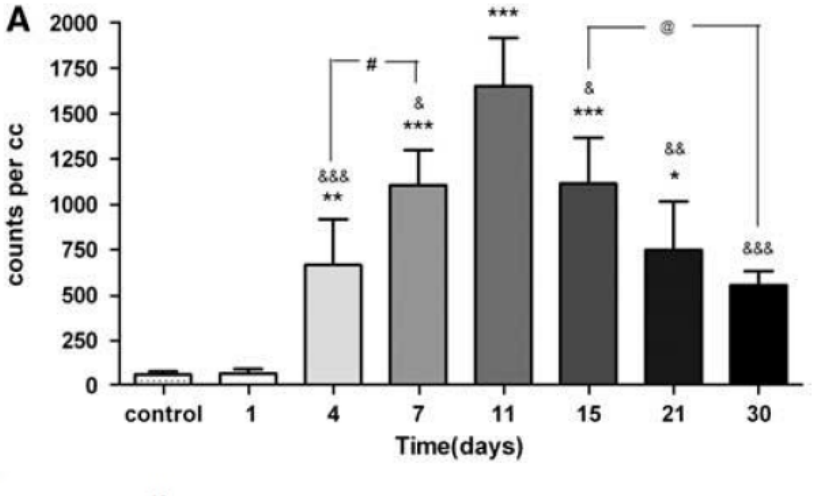
Banati et al. 1997

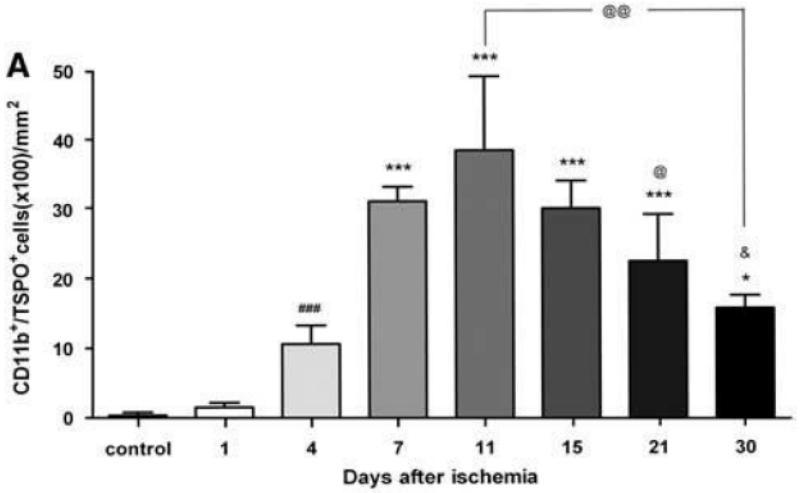
Specificity of TSPO for Microglial Activation

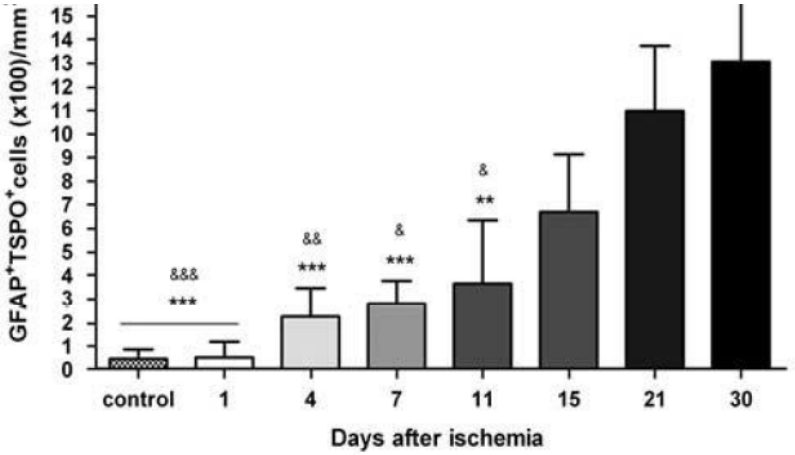
[^{18}F] DPA714 Uptake











Martin et al. 2010

[^{18}F]FEPPA PET- Validated Measure of Translocator Protein Binding

1. High affinity for TSPO (K_i=0.07nM)

2. Selective - Fully displaced in rodents with PK11195 and PBR28

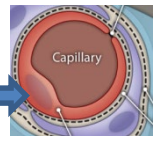
3. Metabolites not brain penetrant

4. Reversible kinetics in humans
(adding irreversible compartment not used since reduces identifiability)

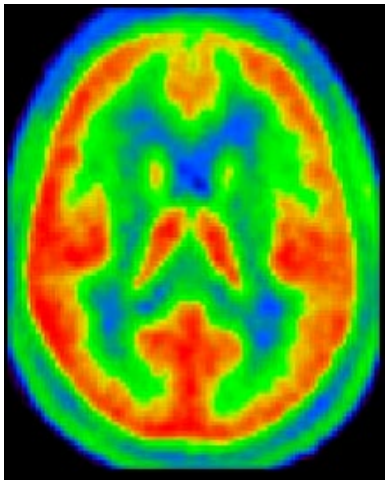
5. Regional TSPO V_T and TSPO V_S well identified with two tissue compartment model, and ratio of compartments ~ 5 in humans

6. Microglial activation induced by 6-hydroxydopamine associated with increased [^{18}F]FEPPA uptake

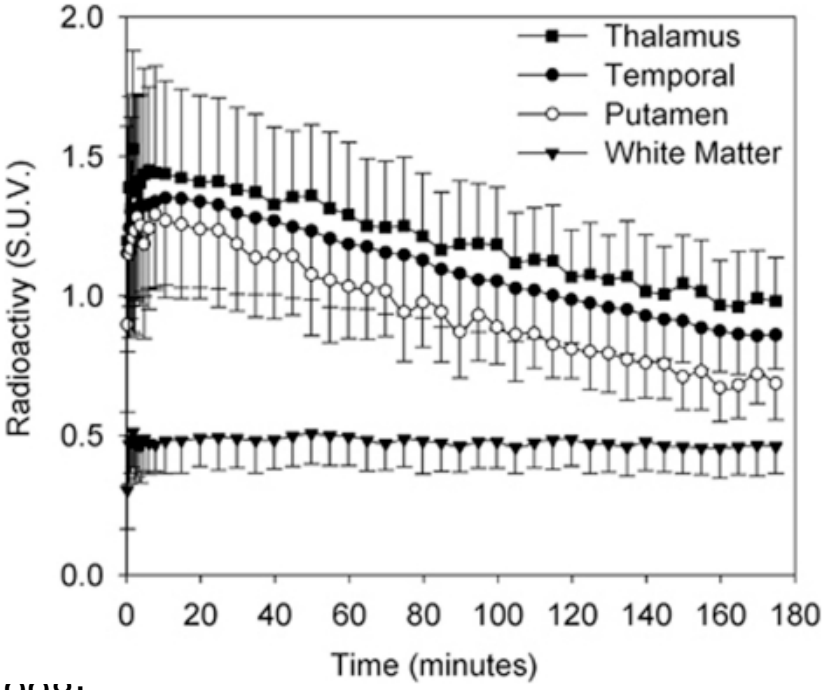
7. Time activity curves by volume are
96% tissue
4% blood volume
(endothelial wall is less)



(Wilson et al. 2008; Rusjan et al. 2010; Verma et al 1998; Kudo et al. 2008)



Transverse view of a healthy subject



Average Time Activity Curve (n=12)

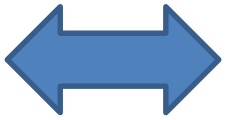
Translocator Protein Imaging In Major Depressive Disorder

Arguments for the Neuroinflammatory Theory in Major Depressive Disorder: Symptom Observations

1. Overlap of Symptoms

Sickness Behaviours

low mood
decreased social interest
anorexia and weight loss
sleep disturbances
reduced locomotor activity
lethargy
difficulty concentrating



Major Depressive Episode

depressed mood
decreased interest/pleasure
anorexia and/or weight loss/gain
insomnia or hypersomnia
psychomotor agitation or retardation
fatigue/loss of energy
difficulty concentrating

2. High Rate of MDE Symptoms in Disease with Neuroinflammation

lifetime prevalence of MDD is approximately 50% in diseases with neuroinflammation i.e.systemic lupus erythematosis, multiple sclerosis and head trauma *(Brey et al. 2002; Joffe et al. 1987; Rapoport 2012)*

3. Stimulation of Immune System is Associated with MDE Symptoms

induction of immune system is associated with depressed mood in humans
i.e. vaccinations, interferon therapy, LPS injection
(Reichenburg et al. 2001; Musselman et al. 2002; Brydon et al. 2008; Hannestad et al. 2012)

4. Elevated C-Reactive Protein and Cytokines Often Reported in MDD

Peripheral Markers of Neuroinflammation Associated with MDD

	IL-6	TNF-α	CRP
# positive studies (MDD > C)	12	11	6
# studies with no significant difference	4	4	6
# negative studies (MDD < C)	0	0	0
Total subjects in positive studies (MDD, C)	446, 344	316, 254	250, 205
Total subjects in studies with nsd* (MDD, C)	108, 86	252, 188	179, 164
Total subjects in negative studies (MDD, C)	n/a	n/a	n/a
Mean % change (SD) in positive studies (MDD vs. C)	↑188(223)	↑83(39)	↑108(64)
Mean % change (SD) in studies with nsd (MDD vs. C)	↑34(22)	↑26(83)	↑15(19)
Mean % change (SD) in negative studies (MDD vs. C)	n/a	n/a	n/a
Total studies = 30**			

Table 1. Evidence for Increased Peripheral Pro-inflammatory markers In Major Depressive Disorder (MDD) compared to controls (C) prior to 2014. Studies selected based on patient group with diagnosis of MDD, N ≥ 15 per group and total N ≥ 35. Studies with MDD > C, $p \leq 0.05$. IL-6, interleukin-6; TNF-α, tumor necrosis factor α; CRP, C-reactive protein. *nsd, no significant difference. **some studies evaluated more than one marker, hence adding the studies for the individual markers totals greater than 30

(reviewed 2014; inclusive Dowlati et al. 2010 and Miller et al 2009)

Postmortem Investigations of Microglial Activation or Highly Related Phenomena in Major Depressive Disorder and Suicide

	Diagnoses	Region	Marker	Result
Van Otterloo et al., 2005	10 MDD	OFC	LFA-1 as microglial marker	negative
Steiner et al., 2008	9 MDD (7 suicide) 16 SZ (6 suicide) 5 BD	DLPFC, ACC	HLA-DR expression (microglial marker)	↑ in suicide (no association with diagnosis)
Dean et al., 2010	10 MDD	DLPFC, ACC	tmTNF sTNF	↑ tm TNF in DLPFC; otherwise negative
Shelton et al., 2010	11 MDE of MDD 3 MDD	FP	cytokine transcripts (microarray)	↑ pro- and anti-inflammatory transcripts
Steiner et al., 2011	7 MDE of MDD 5 MDE of BD	ACC	quinolinic acid as microglial marker	↑ in MDE of MDD only
Pandey et al., 2012	8 MDD (24 suicide)	FP	IL1β, IL-6 and TNFα mRNA and protein	↑ in suicide (no association with diagnosis of MDD)
Torres-Platas et al. 2014	24 depressed suicide; 17 control	Dorsal ACC white matter	primed/ramified microglia (morphometry)	↑ depressed p=0.03 (one of four analyses positive)
Mahajan et al 2018	23 MDD; 23 control	hippocampus	whole transcriptome RNA sequencing	Altered genes with inflammatory and cytokine function
Wang et al. 2018	16 healthy, 21 MDE + suicide, 23 suicide; 12 healthy, 12 MDE, 14 MDE + suicide	DLPFC	TNFα mRNA	Increased in MDE Increased in MDE+suicide

OFC, orbitofrontal cortex; DLPFC, dorsolateral prefrontal cortex; ACC, anterior cingulate cortex;
FP, frontal pole; FC, frontal cortex; TC, temporal cortex; PC, parietal cortex; TH, thalamus; CB, cerebellum.

TSPO V_T During Major Depressive Episodes

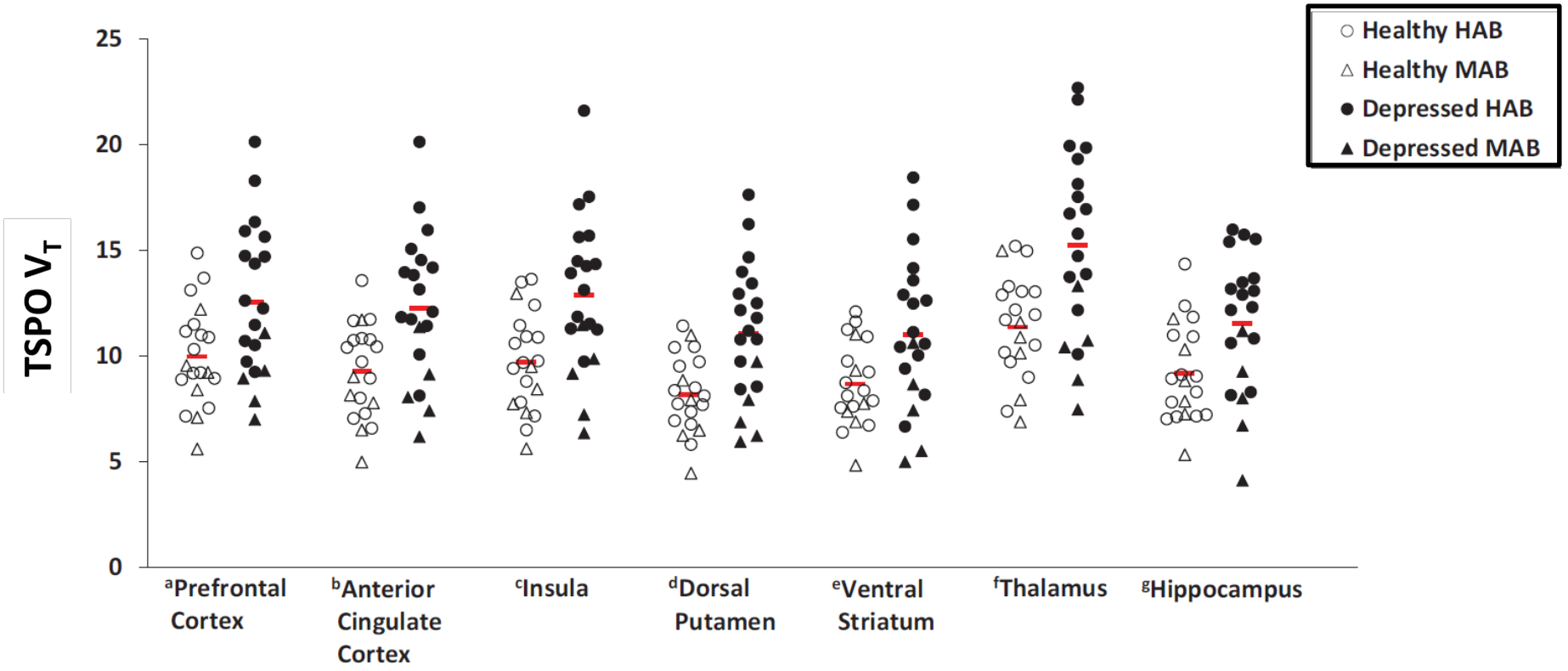


Figure 1. Elevated translocator protein density (TSPO V_T) during a major depressive episode (MDE) secondary to major depressive disorder (MDD). TSPO V_T was significantly greater in MDE of MDD (Depressed, N=20, 15 HAB, 5 MAB) compared to controls (Healthy, N=20, 14 HAB, 6 MAB): All second generation TSPO radioligands, such as [^{18}F]FEPPA, show differential binding according to the SNP rs6971 of the TSPO gene resulting in high affinity binders (HAB) and mixed affinity binders (MAB). Red bars indicate means in each group.

ANOVAs: [a]prefrontal cortex, $F_{1,37}$ = 8.07, P = 0.007; [b]anterior cingulate cortex, $F_{1,37}$ = 12.24, P = 0.001; [c]insula, $F_{1,37}$ = 12.34, P = 0.001; [d]dorsal putamen, $F_{1,37}$=14.1, P=0.001; [e]ventral striatum, $F_{1,37}$=6.9, P=0.013; [f]thalamus, $F_{1,37}$=13.6, P=0.001; [g]hippocampus, $F_{1,37}$=7.5, P=0.009.

JAMA Psychiatry 2015

Analysis of Variance of Regional TSPO V_T by Diagnosis and TSPO Genotype[a]

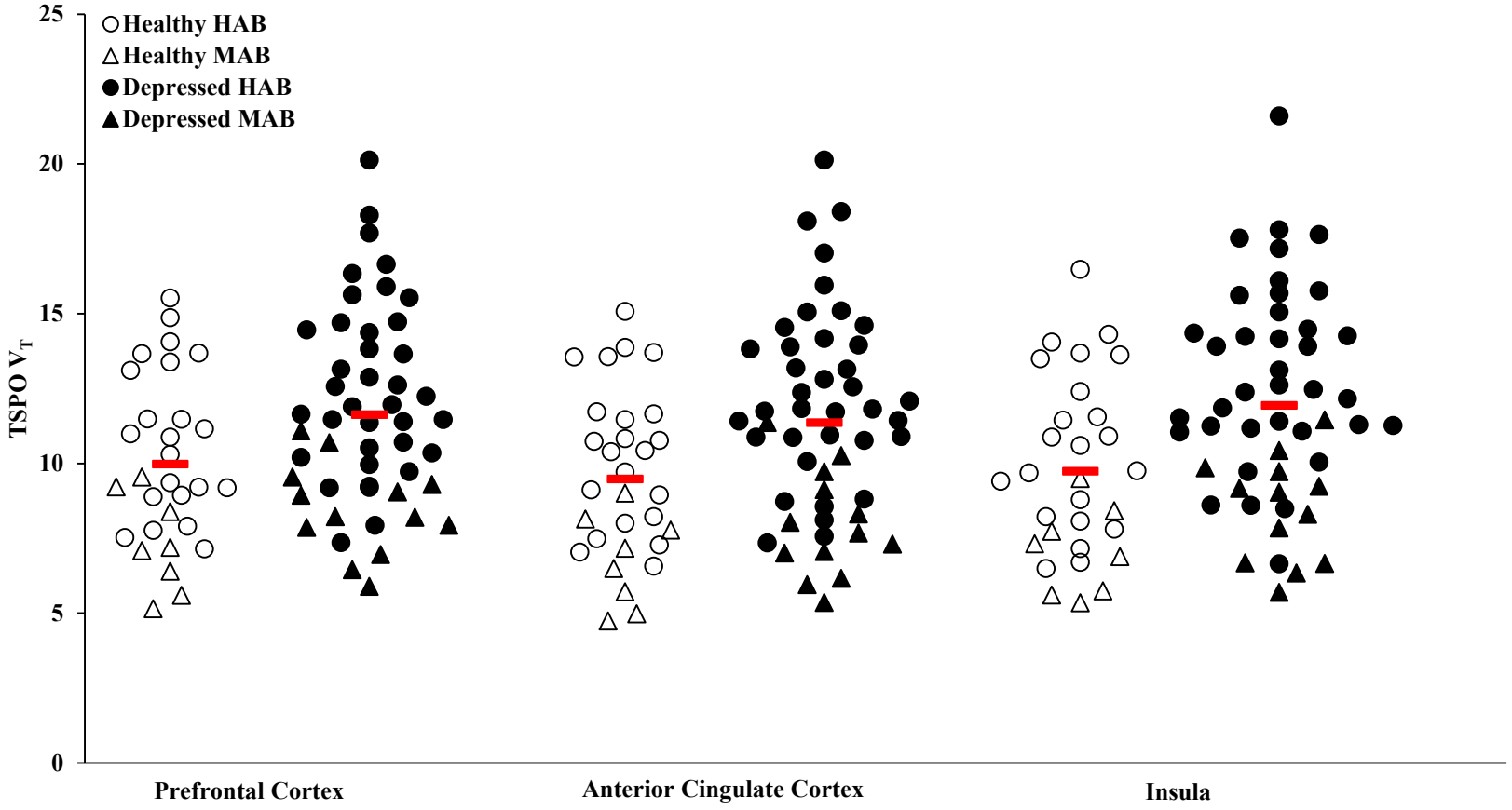
Region of Interest	Depressed (n=20) HAB (n=15)	Depressed (n=20) MAB (n=5)	Depressed (n=20) Total	Healthy (n=20) HAB (n=14)	Healthy (n=20) MAB (n=6)	Healthy (n=20) Total	Diagnosis Effect[b] $F_{1,37}$	Diagnosis Effect[b] P	Genotype Effect[b] $F_{1,37}$	Genotype Effect[b] P
MPFC	13.6 (3.1)	8.5 (2.0)	12.3 (3.6)	9.8 (2.1)	8.3 (2.4)	9.3 (2.2)	11.4	.002	11.2	.002
VLPFC	14.9 (2.9)	9.4 (1.7)	13.5 (3.6)	11.3 (2.4)	9.5 (2.6)	10.8 (2.5)	9.1	.005	13.5	.001
DLPFC	13.6 (3.2)	8.9 (1.3)	12.4 (3.5)	10.7 (2.3)	8.8 (2.5)	10.1 (2.5)	6.5	.015	11.6	.002
OFC	14.4 (2.9)	9.5 (2.7)	13.2 (3.6)	10.9 (2.4)	9.6 (2.8)	10.5 (2.5)	7.8	.008	9.4	.004
Frontal Pole	13.3 (3.0)	8.9 (2.0)	12.2 (3.3)	10.2 (2.1)	8.3 (2.3)	9.6 (2.3)	9.1	.005	11.8	.002
ACC	13.5 (2.9)	8.4 (2.0)	12.3 (3.5)	9.8 (2.0)	8.0 (2.3)	9.3 (2.2)	12.2	.001	14.2	.001
Insula	14.2 (3.0)	8.8 (2.1)	12.9 (3.7)	10.2 (2.2)	8.6 (2.5)	9.7 (2.3)	12.3	.001	12.6	.001
Temporal Cortex	14.4 (2.8)	8.7 (2.1)	12.9 (3.6)	10.9 (2.2)	9.0 (2.5)	10.3 (2.4)	8.7	.006	15.9	.000
Parietal Cortex	15.0 (3.1)	9.6 (2.0)	13.7 (3.7)	11.5 (2.2)	9.6 (2.5)	10.9 (2.4)	8.9	.005	13.8	.001
Occipital Cortex	14.5 (3.0)	8.4 (2.2)	12.9 (3.9)	11.0 (2.1)	9.3 (2.7)	10.5 (2.4)	7.0	.012	14.8	.000
Hippocampus	12.8 (2.5)	7.9 (2.7)	11.5 (3.3)	9.4 (2.3)	8.6 (2.3)	9.2 (2.3)	7.5	.009	9.4	.004
Thalamus	16.9 (3.6)	10.2 (2.2)	15.2 (4.4)	11.8 (2.2)	10.4 (2.9)	11.4 (2.4)	13.6	.001	12.5	.001
Dorsal Putamen	12.3 (2.6)	7.3 (1.5)	11.1 (3.2)	8.5 (1.6)	7.5 (2.3)	8.2 (1.8)	14.1	.001	12.4	.001
Dorsal Caudate	10.9 (2.6)	6.4 (1.8)	9.8 (3.1)	8.2 (1.9)	6.7 (2.1)	7.8 (2.0)	6.7	.013	13.4	.001
Ventral Striatum	12.2 (3.2)	7.4 (2.3)	11.0 (3.7)	9.0 (1.8)	7.9 (2.1)	8.7 (2.0)	6.9	.013	9.2	.004

[a] Values are expressed as mean (SD).

[b] Main effect of univariate ANOVA. MPFC, medial prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; DLPFC, dorsolateral prefrontal cortex; OFC, orbitofrontal cortex; ACC, anterior cingulate cortex. HAB, high affinity binders and MAB, mixed affinity binders refer to the single nucleotide polymorphism rs6971 of the TSPO gene known to influence [^{18}F]FEPPA binding

JAMA Psychiatry 2015

Elevated TSPO V_T in Major Depressive Disorder (n=50) Compared with Healthy (n=30)



Translocator protein distribution volume (TSPO V_T) was significantly greater in major depressive episode of major depressive disorder (depressed, N = 50, 37 HAB, 13 MAB) compared to controls (healthy, N = 30, 22 HAB, 8 MAB).

ANOVA: prefrontal cortex: effect of diagnosis $F_{1,77} = 7{\cdot}63$, $P = 0{\cdot}007$, effect of genotype $F_{1,77} = 38{\cdot}37$ $P < 0{\cdot}001$;
anterior cingulate cortex: effect of diagnosis $F_{1,77} = 9{\cdot}71$ $P = 0{\cdot}003$, effect of genotype $F_{1,77} = 42{\cdot}39$ $P < 0{\cdot}001$;
insula: effect of diagnosis $F_{1,77} = 11{\cdot}98$, $P = 0{\cdot}001$, effect of genotype $F_{1,77} = 38{\cdot}24$ $P < 0{\cdot}001$.

high affinity binders (HAB) and mixed affinity binders (MAB). Red bars indicate means in each group. Red horizontal bars indicate the mean for each group.

Lancet Psychiatry 2018

Comparison of Regional TSPO V_T Values Between Major Depressive Disorder and Healthy

Region of Interest	Effect (ANOVA)					
	MDD Versus Healthy		Genotype		R^2	
	$F_{1,77}$	P	$F_{1,77}$	P	Unadjusted	Adjusted
PFC	7·63	0·007	38·37	<0·001	0·38	0·36
MPFC	12·34	0·001	40·32	<0·001	0·41	0·39
VLPFC	8·91	0·004	39·51	<0·001	0·39	0·37
DLPFC	6·09	0·016	36·90	<0·001	0·36	0·34
OFC	8·29	0·005	39·56	<0·001	0·39	0·37
ACC	9·71	0·003	42·39	<0·001	0·41	0·39
Insula	11·98	0·001	38·24	<0·001	0·40	0·38
Temporal Cortex	6·66	0·012	42·74	<0·001	0·39	0·38
Parietal Cortex	6·44	0·013	43·58	<0·001	0·40	0·38
Occipital Cortex	5·61	0·020	41·87	<0·001	0·38	0·37
Hippocampus	5·59	0·021	25·45	<0·001	0·29	0·27
Thalamus	8·90	0·004	34·27	<0·001	0·36	0·34
Dorsal Putamen	10·90	0·001	39·47	<0·001	0·40	0·38
Dorsal Caudate	10·12	0·002	42·26	<0·001	0·41	0·39
Ventral Striatum	8·35	0·005	28·98	<0·001	0·33	0·31

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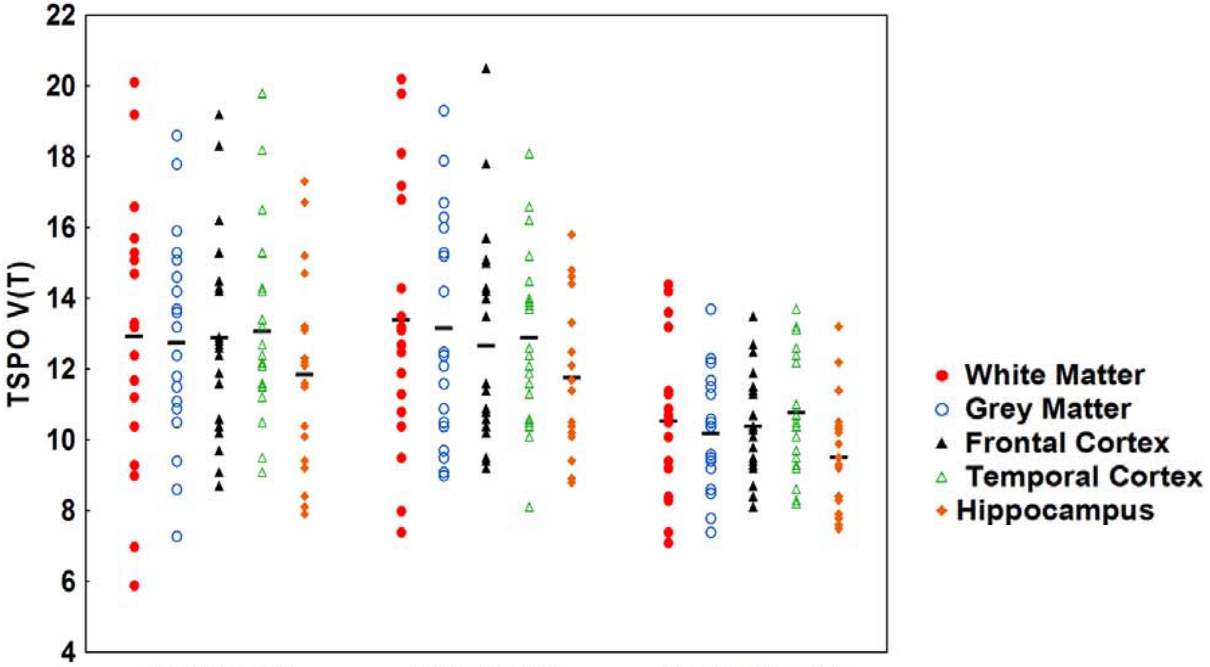
Replications of Elevated TSPO Binding During MDE

Four independent groups published ~30 % elevations in TSPO binding + 2 replications
(Li et al. 2017; Richards 2018; in ACC Holmes et al. 2018; Setiawan et al. 2018; Li et al. 2018)

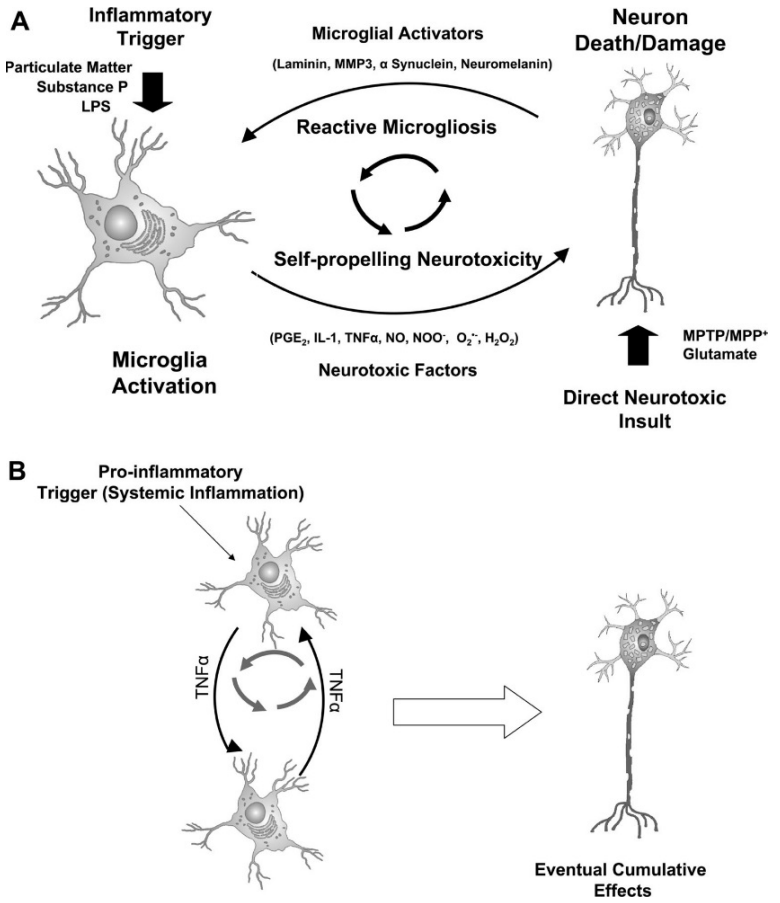
Initial negative study of 10 MDD subjects, some current depressed, some not
re-evaluated sample and found those with current MDE had elevated TSPO V_T
(Hannestad et al. 2013; Cosgrove personal communication)



Li et al. 2017

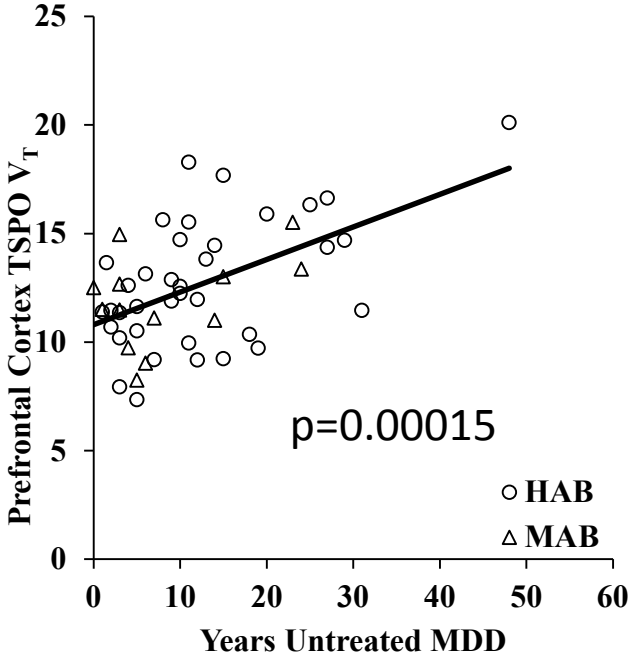
Clinical Phenomena and Microglial Activation

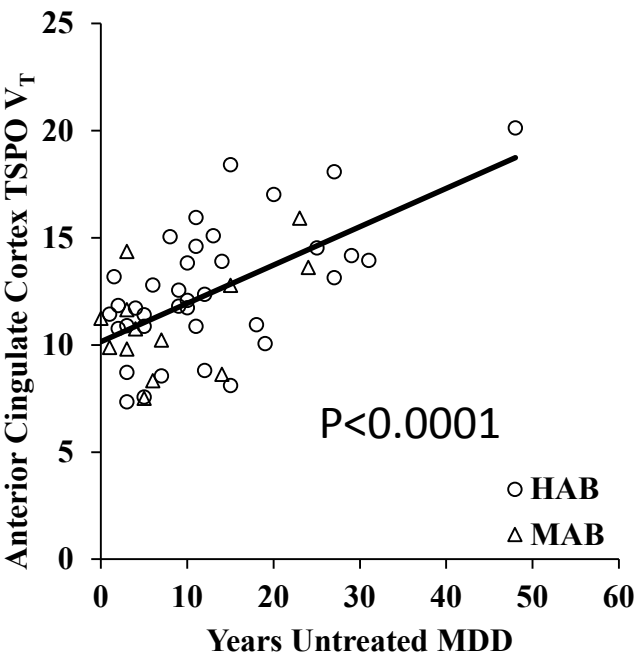
Neuroprogression
in neurodegenerative diseases like Alzheimer's disease, multisystem atrophy, Parkinsons Disease, Huntington's Disease, there is greater microglial activation with greater duration of disease

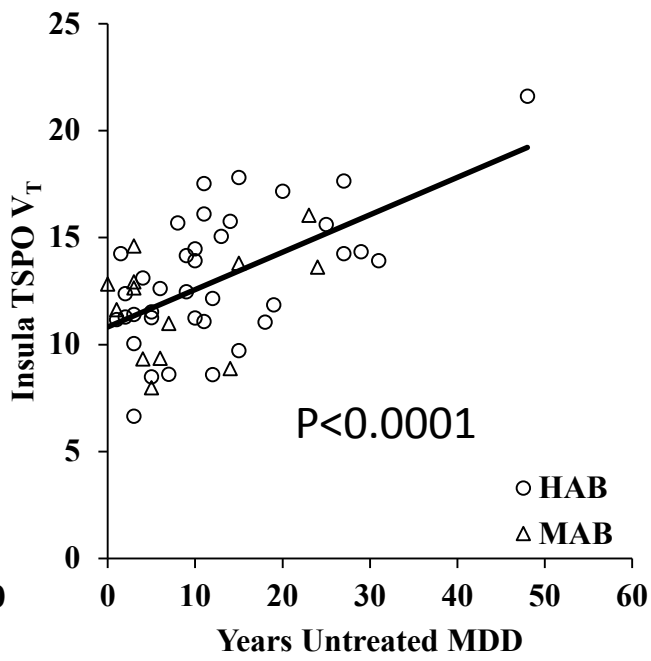


Antidepressants -SSRI in vitro, consistently, at typically high concentration reduce propensity of microglia to become activated after IFN-y or LPS administration (Horikawa et al. 2010, Liu et al. 2011 Tynan et al. 2012)

Relationship between Regional Translocator Protein Distribution Volume and Duration of Untreated Major Depressive Disorder







P values from ANOVA **for effect of duration of illness** , including rs6971 genotype as factor

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Duration of Untreated Major Depressive Disorder is Associated with TSPO V_T across Grey Matter Regions

Region of Interest	Effect (ANCOVA)							
	Duration of Untreated MDD			Genotype			R^2	
	$F_{1,47}$	P		$F_{1,47}$	P		Unadjusted	Adjusted
PFC	16·96	<0·001		23·06	<0·001		0·51	0·49
MPFC	22·28	<0·001		27·49	<0·001		0·57	0·55
VLPFC	14·55	<0·001		24·93	<0·001		0·51	0·49
DLPFC	13·42	0·001		20·51	<0·001		0·47	0·45
OFC	13·48	0·001		29·57	<0·001		0·53	0·51
ACC	24·13	<0·001		27·79	<0·001		0·58	0·56
Insula	21·92	<0·001		25·98	<0·001		0·56	0·54
Temporal Cortex	23·84	<0·001		31·15	<0·001		0·59	0·57
Parietal Cortex	21·51	<0·001		29·59	<0·001		0·57	0·55
Occipital Cortex	20·60	<0·001		33·32	<0·001		0·59	0·57
Hippocampus	7·69	0·008		18·33	<0·001		0·40	0·38
Thalamus	18·54	<0·001		26·26	<0·001		0·54	0·52
Dorsal Putamen	21·60	<0·001		33·76	<0·001		0·59	0·57
Dorsal Caudate	15·47	<0·001		29·39	<0·001		0·54	0·52
Ventral Striatum	11·50	0·001		18·40	<0·001		0·44	0·42

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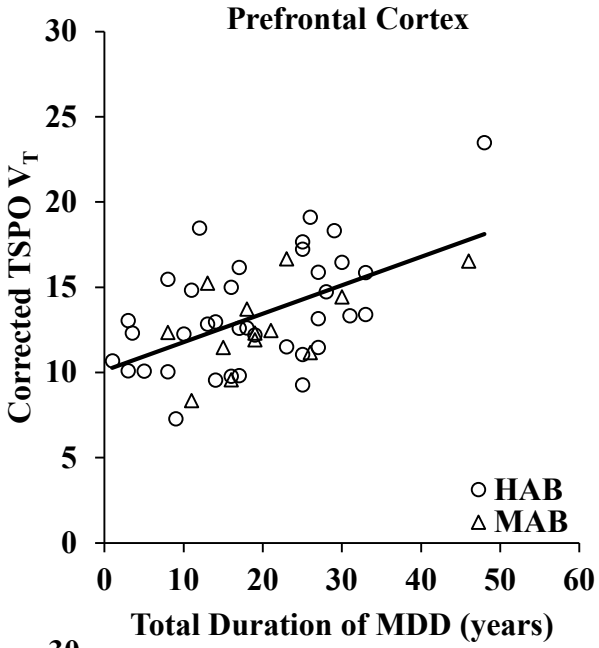
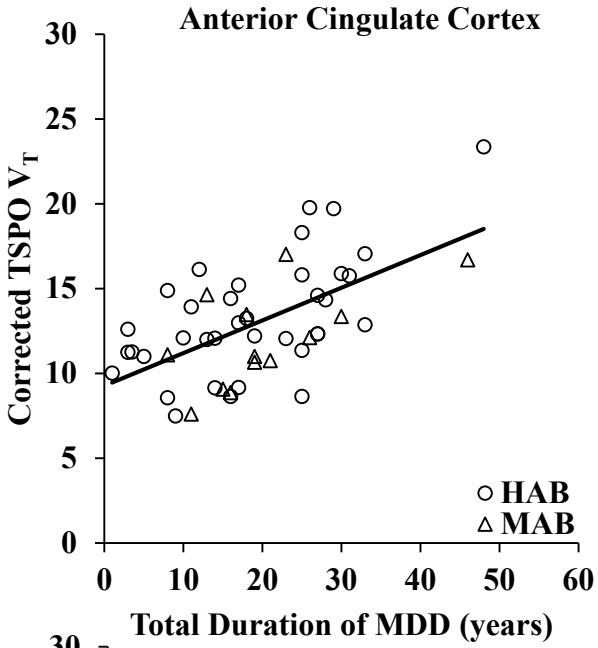
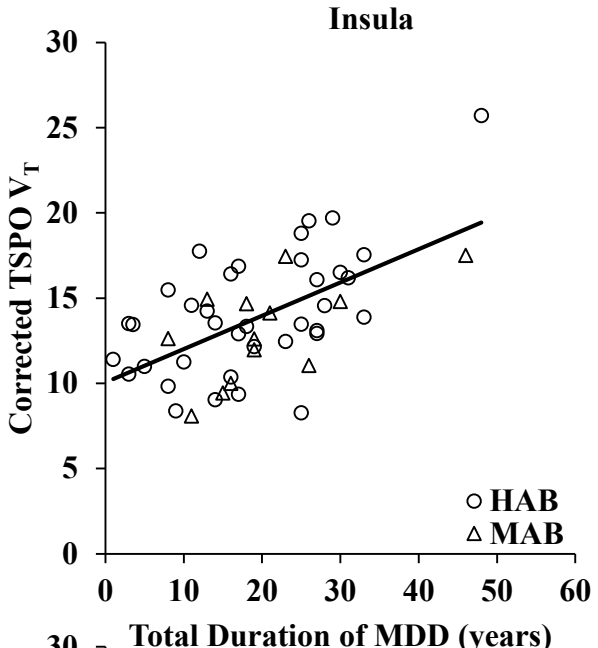
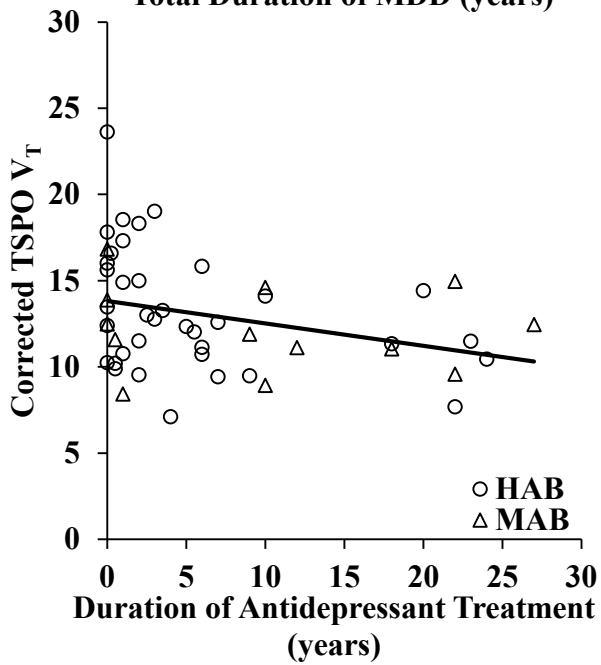
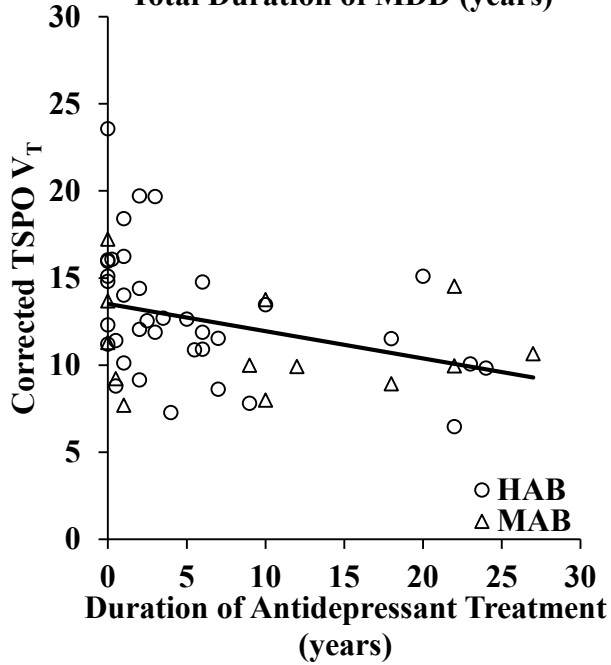
Duration of Major Depressive Disorder and Antidepressant Exposure are Opposite Predictors of TSPO V_T, but Similar in Magnitude

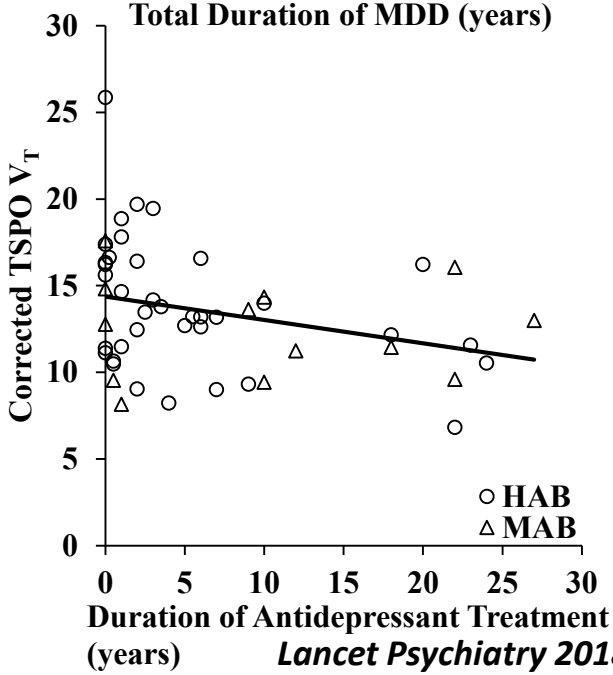












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SUPPLEMENTAL TABLE 1: Total Duration of Major Depressive Disorder and Antidepressant Exposure are Associated with TSPO V_T Across Grey Matter Regions

Region of Interest	Effect (ANCOVA)							
	Total Duration of MDD		Duration of Antidepressant Exposure		Genotype		R^2	
	$F_{1,46}$	P	$F_{1,46}$	P	$F_{1,46}$	P	Unadjusted	Adjusted
PFC	9·36	0·004	7·16	0·010	22·01	<0·001	0·48	0·44
MPFC	14·22	<0·001	10·53	0·002	26·73	<0·001	0·55	0·52
VLPFC	7·35	0·009	7·06	0·011	23·33	<0·001	0·48	0·44
DLPFC	7·92	0·007	6·02	0·018	19·91	<0·001	0·45	0·41
OFC	8·16	0·006	8·82	0·005	28·05	<0·001	0·52	0·49
ACC	15·4	<0·001	7·73	0·008	27·64	<0·001	0·54	0·51
Insula	11·25	0·002	9·45	0·004	24·22	<0·001	0·51	0·48
Temporal cortex	12·64	0·001	10·00	0·003	28·97	<0·001	0·55	0·52
Parietal cortex	11·22	0·002	12·17	0·001	27·31	<0·001	0·55	0·52
Occipital cortex	10·32	0·002	9·44	0·004	30·62	<0·001	0·55	0·52
Hippocampus	1·60	0·212	5·63	0·022	16·13	<0·001	0·38	0·34
Thalamus	8·22	0·006	9·37	0·004	23·82	<0·001	0·50	0·47
Dorsal putamen	10·64	0·002	11·86	0·001	30·77	<0·001	0·56	0·54
Dorsal caudate	10·99	0·002	10·94	0·002	26·65	<0·001	0·55	0·52
Ventral striatum	10·99	0·002	10·94	0·002	28·65	<0·001	0·55	0·52

ANCOVA with TSPO V_T as the dependent variable, and total duration of MDD, duration of antidepressant exposure and the rs6971 genotype that influences binding of second generation radiotracers for TSPO as the predictor variables. R^2 refers to the proportion of variance attributable to the model, one adjusted for number of predictors.

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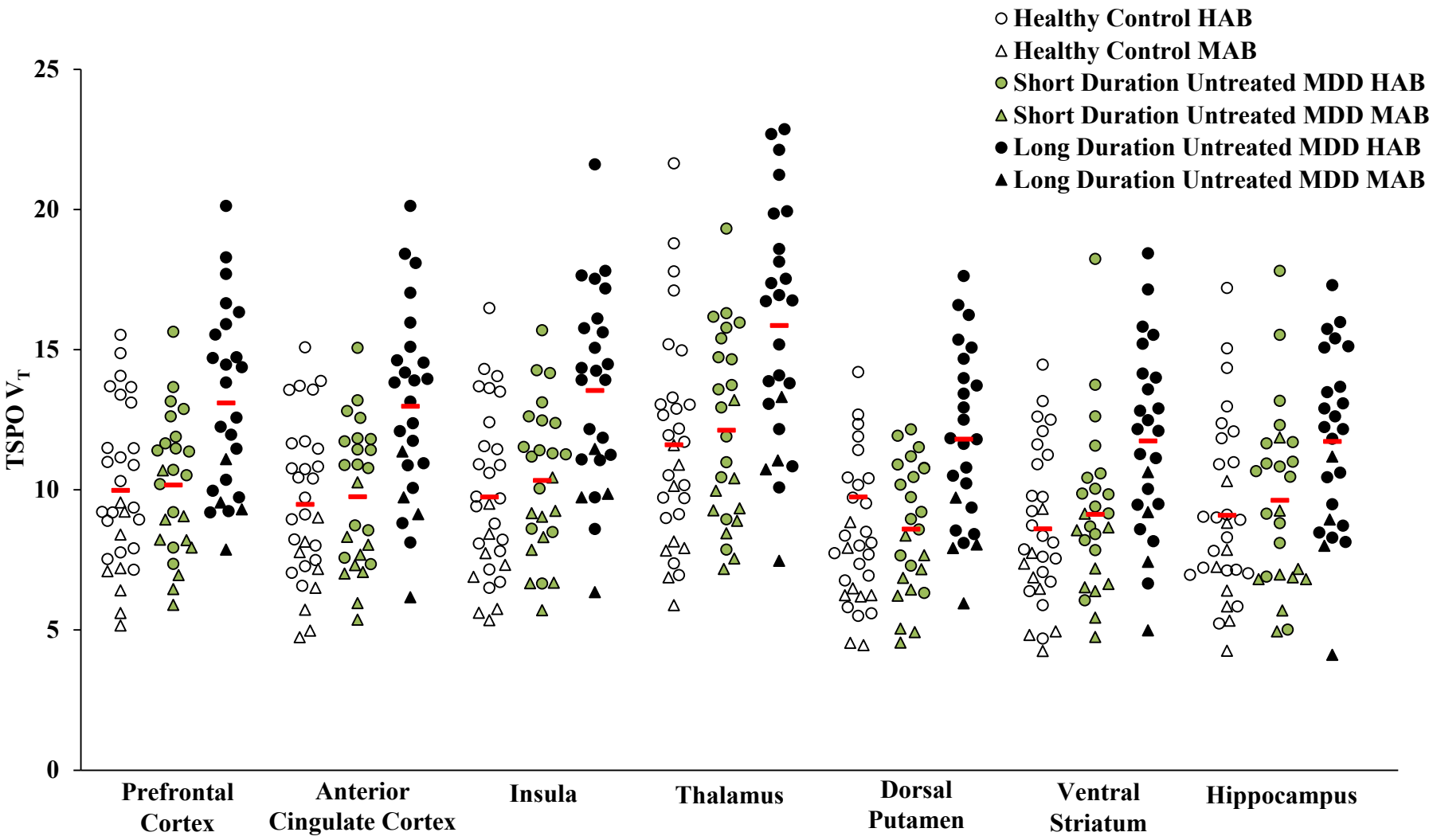
Translocator Protein Density Greater with More Years of Untreated MDD Compared to Short Duration of Untreated MDD and Healthy Controls



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SUPPLEMENTAL TABLE 2. Regional TSPO V_T Values Grouped by Years of Being Untreated and Diagnosis

	Depressed (<10 yrs untreated) N = 25		Depressed (≥10 yrs untreated) N = 25		Healthy Controls N = 30		Effect of Group	Effect of Genotype	Long Duration Untreated versus Healthy	Long Duration Versus Short Duration Untreated
Region of Interest	Mean	SD	Mean	SD	Mean	SD	P	P	P	P
PFC	10·2	2·5	13·1	3·3	10·0	2·8	<0·001	<0·001	<0·001	0·004
MPFC	9·9	2·6	13·0	3·3	9·4	2·6	<0·001	<0·001	<0·001	0·002
VLPFC	11·2	2·7	13·8	3·2	10·7	3·0	0·001	<0·001	0·001	0·011
DLPFC	10·1	2·4	13·0	3·3	10·1	2·9	0·001	<0·001	<0·001	0·005
OFC	10·6	3·0	13·5	3·3	10·3	2·9	<0·001	<0·001	<0·001	0·008
ACC	9·7	2·5	13·0	3·4	9·5	2·8	<0·001	<0·001	<0·001	0·002
Insula	10·3	2·6	13·5	3·5	9·7	3·0	<0·001	<0·001	<0·001	0·003
Temporal Cortex	10·2	2·5	13·6	3·4	10·3	3·1	<0·001	<0·001	<0·001	<0·001
Parietal Cortex	10·8	2·7	14·2	3·4	10·9	3·0	<0·001	<0·001	<0·001	0·001
Occipital Cortex	10·3	2·5	13·7	3·7	10·4	3·2	<0·001	<0·001	0·001	0·001
Hippocampus	9·6	3·2	11·7	3·2	9·1	3·1	0·016	<0·001	0·005	0·103
Thalamus	12·1	3·4	15·9	4·3	11·6	3·8	<0·001	<0·001	<0·001	0·005
Dorsal Putamen	8·6	2·3	11·8	3·1	8·3	2·5	<0·001	<0·001	<0·001	<0·001
Dorsal Caudate	8·0	2·1	10·3	2·7	7·6	2·4	<0·001	<0·001	<0·001	0·005
Ventral Striatum	9·1	2·9	11·7	3·3	8·6	2·7	0·001	<0·001	<0·001	0·021

Analyses of variance with regional TSPO V_T as the dependent variable was done and the least significant difference test was applied towards differences in TSPO V_T between the long duration group and the other two groups.

Translocator Protein Imaging in Obsessive Compulsive Disorder

Rationale for Neuroinflammation in Obsessive Compulsive Disorder

1. **Case Series of OCD Symptoms** (Pediatric Autoimmune Neuropsychiatric Disease Associated With Group A Beta-Hemolytic Streptococci; PANDAS; or Pediatric Acute Neuropsychiatric Syndrome; PANS)

   -exposure also associated with Sydenham's chorea
   -Sydenham's chorea of CNS origin; cross reactivity of gangliosides in bacterial cell wall with basal ganglia neurons implicated
   -reports of anti-basal ganglia antibodies in OCD with exposure
   -reports of reduced symptoms in such cases after plasmapheresis, intravenous immunoglobin, predisone, antibiotic treatment (Swedo et al. 1994; Aleen et al 1995; Swedo et al. 1998; Lee et al., 2009; Kiessling et al. 1994; Dale et al. 2005; Murphy et al. 2002; Snider et al. 2005)

   Represent a small proportion of OCD cases, and there are reports of no relationship between group A beta-hemolytic streptococci and exacerbation of OCD symptoms (Luo et al. 2004) nor association with onset of OCD symptoms after exposure to this streptococci (Perrin et al. 2004)

2. **Higher Rate of Anxiety and OCD in Autoimmune Disorders**

   -prevalence of anxiety disorder 30 to 40% in large controlled studies of multiple sclerosis and systemic lupus erythematosis
   prevalence of OCD ~20 to 30% in case series of systemic lupus erythematosis
   -prevalence of OCD ~15% in case series of multiple sclerosis
   (Slattery et al. 2004, Uquz et al. 2013; Uquz et al. 2008; Foroughipour et al 2012)

Methods: Participants

Table 1. Demographic Characteristics of Study Participants

Characteristic	OCD (n = 20)	Healthy (n = 20)
TSPO genotype, No.[a]		
HAB	13	13
MAB	7	7
Age, mean (SD), y	27.4 (7.1)	27.6 (6.6)
Women, No. (%)	11 (55)	8 (40)
BMI, mean (SD)	22.8 (2.9)	24.4 (2.2)
Y-BOCS score, mean (SD)	23.0 (6.2)	NA
Age at OCD onset, mean (SD), y	13.7 (7.1)	NA

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HAB, high-affinity binding; MAB, mixed-affinity binding; NA, not applicable; OCD, obsessive-compulsive disorder; TSPO, translocator protein; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

[a] Indicates single-nucleotide polymorphism rs6971 of the *TSPO* gene known to influence binding of second-generation radioligands, including fluorine F 18–labeled *N*-(2-(2-fluoroethoxy)benzyl)-*N*-(4-phenoxypyridin-3-yl)acetamide.

Range of severity:
0-7 subclinical;
8-15 mild;
16-23 moderate;
24-31 severe;
32-40 extreme.

Age of onset
<12y (n=12)
<18 (n=18)

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Methods: Participant Symptoms

eTable 1. Yale-Brown Obsessive Compulsive Scale Symptoms

Y-BOCS Symptom	OCD (n=20)	
	No.	%
Obsessions		
Aggressive	13	65
Contamination	16	80
Sexual	5	25
Religious	8	40
Magical	4	20
Somatic	12	60
Compulsions		
Cleaning, Washing	15	75
Checking	15	75
Repeating	13	65
Counting	7	35
Ordering	12	60
Hoarding	11	55
Ritualized Eating	7	35
Superstitious	3	15

Percentage does not add up to 100 percent, because it indicates the percentage of participants experiencing particular obsessive-compulsive symptoms.

Abbreviations: No., number; OCD, obsessive compulsive disorder; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

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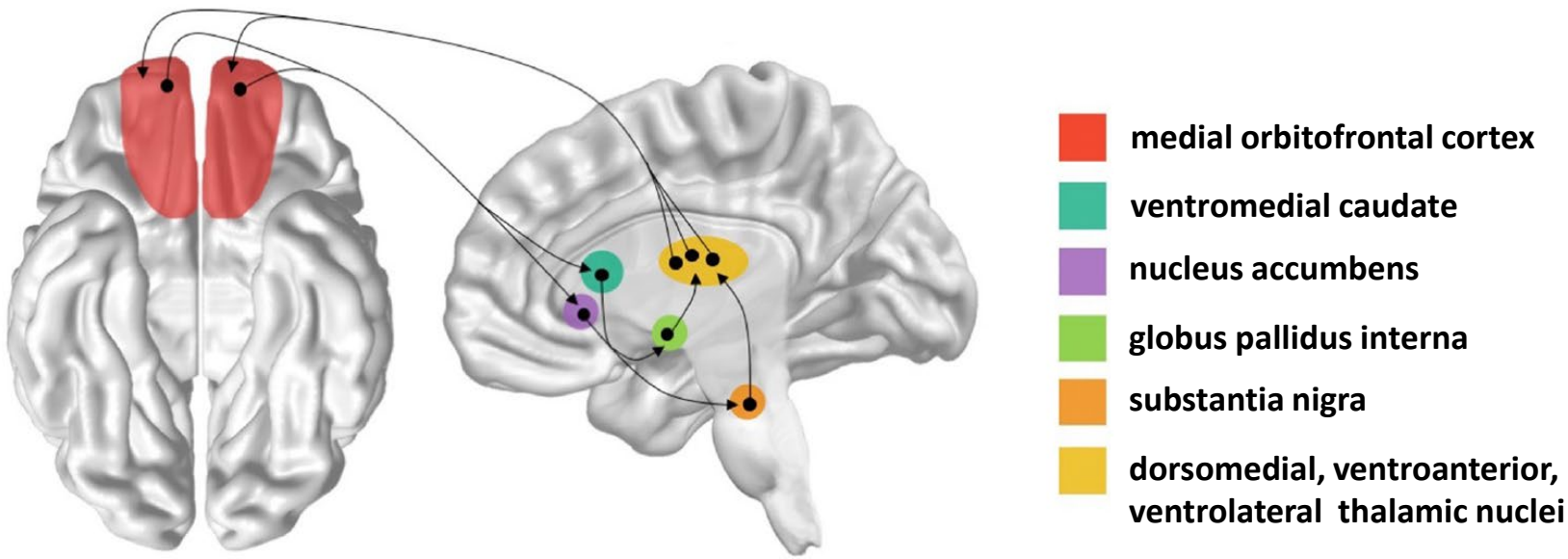
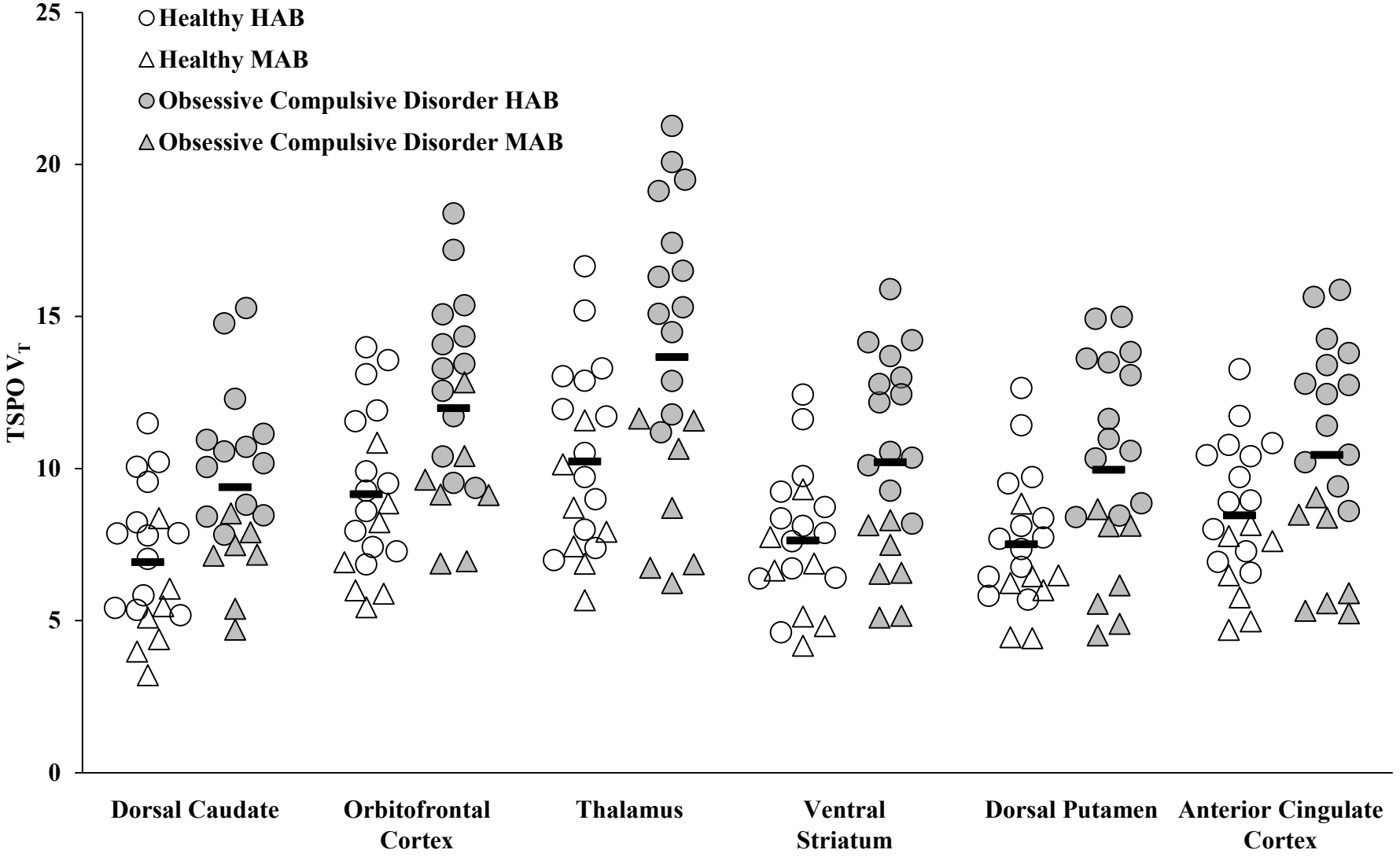
Corticostriatal Circuitry of Obsessive Compulsive Disorder

-caudate, orbitofrontal cortex, basal ganglia, ventral striatum and thalamus
highly implicated in the corticostriatal circuitry of OCD
across neurochemical, metabolic, and functional imaging studies



modified from Fettes et al. 2017

Elevated TSPO V_T in Obsessive Compulsive Disorder



ANOVA, effect of diagnosis across regions, $F_{1,37}$=9.5 to 15.5, p=0.004 to p<0.001

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Greater TSPO V_T Associated With OCD Diagnosis

	Mean (Standard Deviation)							Effect			
	Obsessive Compulsive Disorder			Healthy			Percent Difference	Diagnosis		Genotype	
Region of Interest	HAB (n=13)	MAB (n=7)	Total (n=20)	HAB (n=13)	MAB (n=7)	Total (n=20)		$F_{1,37}$	*P*	$F_{1,37}$	*P*
Dorsal Caudate	10.7 (2.3)	6.9 (1.4)	9.4 (2.7)	7.8 (2.1)	5.2 (1.7)	6.9 (2.3)	35.6	15.5	<.001	23.9	<.001
OFC	13.4 (2.8)	9.3 (2.1)	12.0 (3.2)	10.1 (2.5)	7.5 (2.0)	9.2 (2.6)	30.9	13.5	.001	17.5	<.001
Thalamus	16.2 (3.2)	8.9 (2.4)	13.7 (4.6)	11.3 (3.0)	8.3 (2.0)	10.2 (3.0)	33.5	13.2	.001	26.5	<.001
Ventral Striatum	12.1 (2.2)	6.8 (1.3)	10.2 (3.2)	8.3 (2.1)	6.4 (1.8)	7.6 (2.2)	33.8	14.4	.001	25.6	<.001
Dorsal Putamen	11.8 (2.4)	6.6 (1.7)	10.0 (3.3)	8.3 (2.1)	6.1 (1.5)	7.5 (2.1)	32.6	12.8	.001	26.2	<.001
ACC	12.4 (2.3)	6.9 (1.7)	10.5 (3.4)	9.5 (2.0)	6.5 (1.4)	8.5 (2.3)	23.5	9.5	.004	40.3	<.001
MPFC	12.8 (2.4)	7.1 (1.7)	10.8 (3.5)	9.4 (2.1)	6.7 (1.3)	8.4 (2.2)	27.5	11.9	.001	34.8	<.001
DLPFC	13.0 (2.1)	7.3 (1.9)	11.0 (3.4)	10.0 (2.0)	7.1 (1.8)	9.0 (2.3)	22.0	9.1	.005	38.5	<.001
VLPFC	13.9 (2.6)	8.2 (1.8)	11.9 (3.6)	10.7 (2.2)	7.7 (2.0)	9.6 (2.5)	23.9	10.0	.003	31.8	<.001
INS	13.3 (2.6)	7.5 (1.8)	11.3 (3.6)	9.9 (2.3)	6.9 (1.5)	8.8 (2.5)	27.7	11.4	.002	33.0	<.001
Temporal Cortex	13.5 (2.5)	7.8 (2.1)	11.5 (3.6)	10.4 (2.3)	7.2 (1.8)	9.3 (2.6)	24.3	9.5	.004	33.5	<.001
Inferior Parietal Cortex	14.1 (3.1)	8.1 (1.8)	12.0 (4.0)	10.9 (2.2)	7.9 (1.9)	9.8 (2.6)	22.2	7.5	.009	29.8	<.001
Occipital Cortex	13.9 (2.6)	7.8 (2.1)	11.8 (3.8)	10.6 (2.4)	7.4 (1.9)	9.5 (2.7)	23.8	8.9	.005	33.9	<.001
Hippocampus	12.2 (2.3)	6.9 (2.0)	10.3 (3.3)	8.7 (2.5)	6.8 (2.0)	8.0 (2.5)	28.9	9.4	.004	20.3	<.001

Abbreviations: ACC, anterior cingulate cortex; ANOVA, analysis of variance; DLPFC, dorsolateral prefrontal cortex; HAB, high-affinity binding; INS, insula; MAB, mixed-affinity binding; MPFC, medial PFC; OFC, orbitofrontal cortex; SD, standard deviation; TSPO, translocator protein; TSPO V_T, translocator protein density measured by distribution volume; VLPFC, ventrolateral PFC.

[a] Indicates binding to the single-nucleotide polymorphism rs6971 of the TSPO gene known to influence binding of second-generation TSPO radioligands, including [^{18}F]FEPPA.

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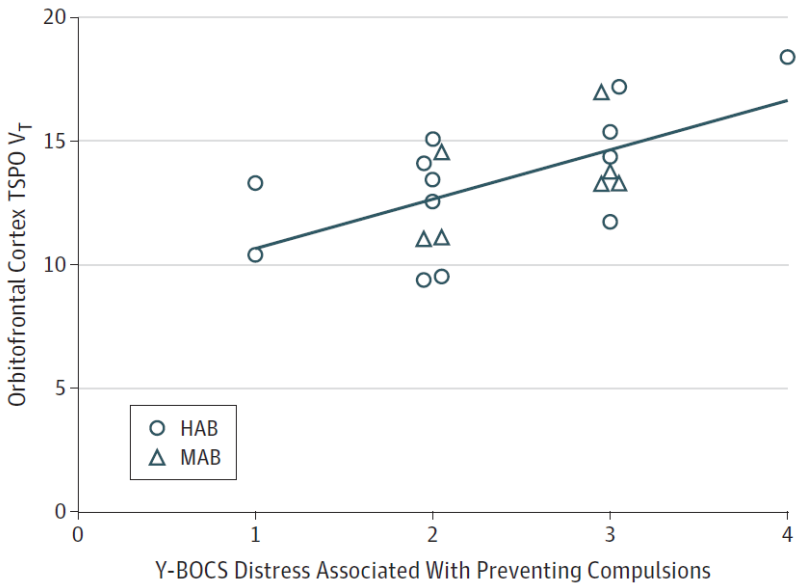
Relationship of TSPO V_T To OCD Symptoms

Figure 2. Greater Translocator Protein (TSPO) Distribution Volume (V_T) in Orbitofrontal Cortex Is Correlated With Distress Associated With Preventing Compulsive Behaviors



Greater TSPO V_T was significantly correlated with greater distress associated with preventing compulsive behaviors as reported on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS).

Y-BOCS Subscale Correlations[a] Controlling for rs6971 Genotype	Dorsal Caudate		Orbitofrontal Cortex	
	r	*P*[b]	r	*P*[b]
Time Spent Performing Compulsions	0.30	.17	0.38	.11
Interference Due to Compulsions	0.21	.38	0.32	.18
Distress Associated with Compulsions	*0.48*	*.04*	*0.62*	*.005*
Resistance Against Compulsions	0.06	.80	0.03	.90
Degree of Control Over Compulsions	-0.04	.88	-0.09	.71
Total Compulsion Severity	0.28	.25	0.33	.17
Total Obsession Severity	0.20	.41	0.23	.35
Overall Severity	0.25	.30	0.29	.23

Abbreviations: Y-BOCS, Yale-Brown Obsessive Compulsive Scale.
[a] Indicates binding to the single-nucleotide polymorphism rs6971 of the translocator protein (TSPO) gene known to influence binding of second-generation TSPO radioligands, including [^{18}F]FEPPA.
[b] P-value derived from uncorrected Pearson partial correlation coefficient controlling for rs6971 genotype.

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Interpretations, Implications and Potential for Improving Clinical Care

Magnitude and Regional Distribution of TSPO V_T Elevation During Major Depressive Episodes and OCD

The magnitude of ~30%+ on average - Is it meaningful?

Well established that microglial activation occurs in Alzheimer's disease

Elevated TSPO V_T occurs in Alzheimer's disease (Kreisl et al. 2013; Suridjan et al. 2015)

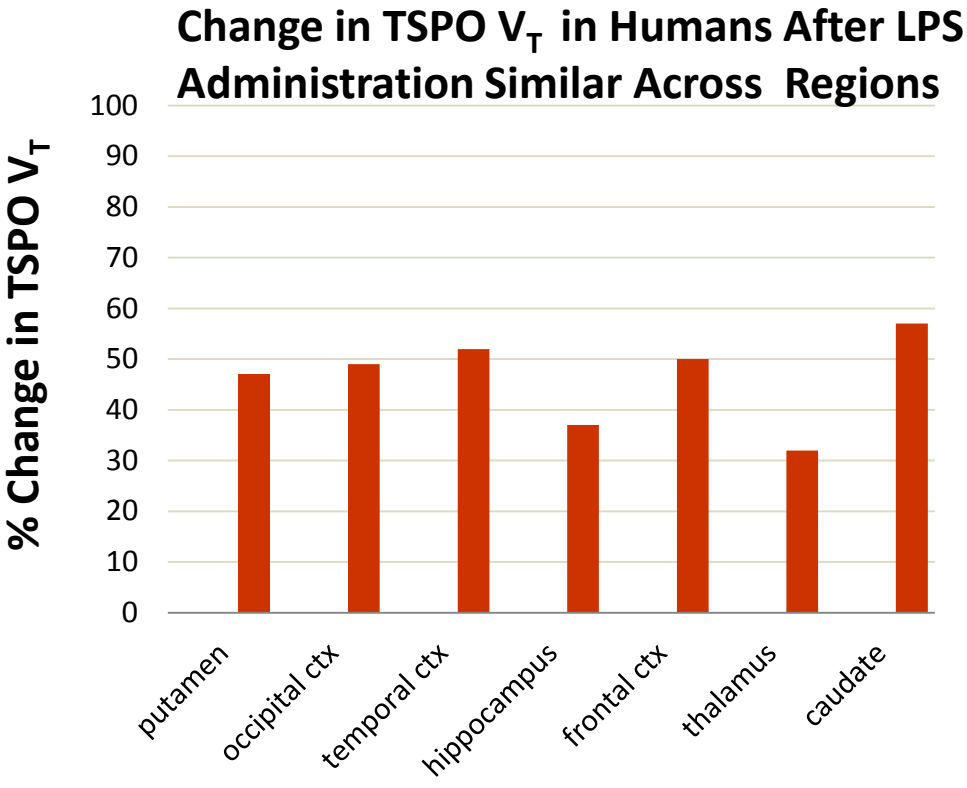
In mild-moderate Alzheimer's disease, mean increase in TSPO V_T in with same [^{18}F]FEPPA PET technique across cerebral cortex, cerebellar cortex and hippocampus is 20-55% (Suridjan et al 2015)

Magnitude and Regional Distribution of TSPO V_T Elevation During Major Depressive Episodes and OCD

Elevation of TSPO V_T not regionally specific in MDD, modest specificity in OCD

lack of strong regional specificity of elevated TSPO V_T in MDD consistent across studies

modest regional specificity in OCD but not significantly more different in one region versus another, just more prominent differences in implicated regions



Coefficient of variation approximately 0.2-0.3 for each mean.

Adapted from Sandiego et al. 2015

Distribution of Elevated TSPO V_T is Inclusive of Circuitry Implicated in Major Depressive Disorder

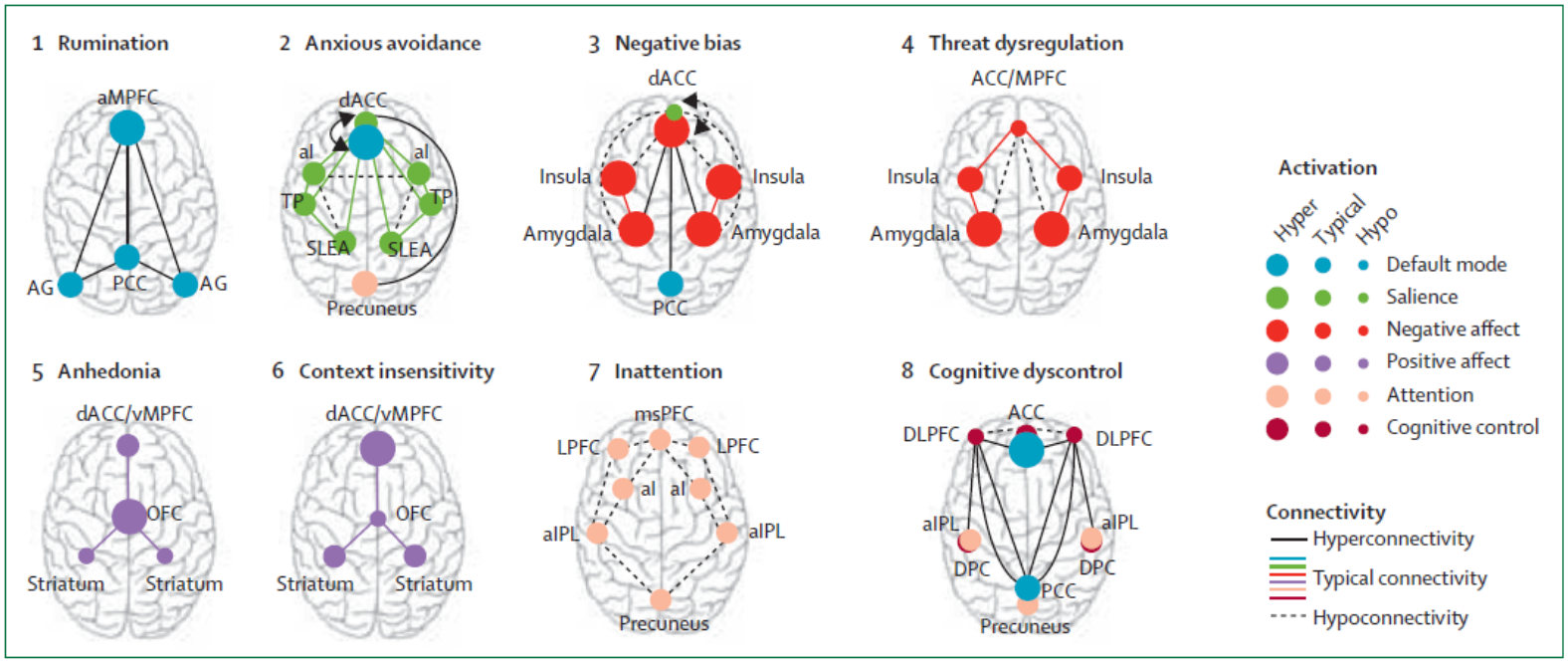


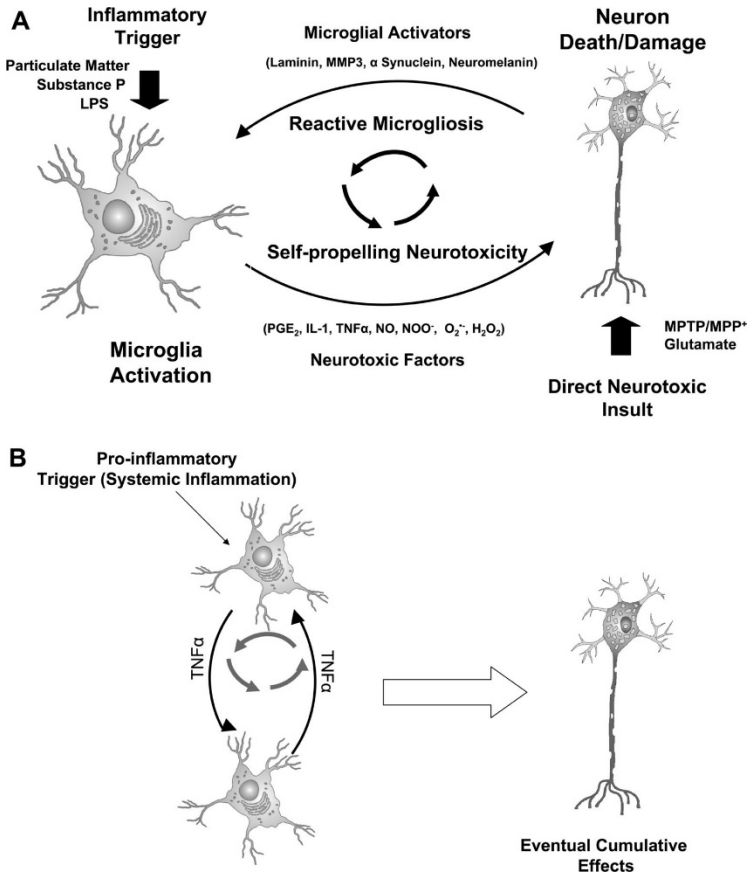
Figure 2: **Proposed taxonomy of putative biotypes of neural circuit dysfunction for depression and anxiety based on published work**

The proposed phenotype associated with each proposed neural dysfunction is mentioned above each type of dysfunction. aMPFC=anterior medial prefrontal cortex. AG=angular gyrus. PCC=posterior cingulate cortex (includes precuneus). dACC=dorsal anterior cingulate cortex. al=anterior insula. TP=temporal pole. SLEA=sublenticular extended amygdala. ACC/MPFC=dorsal medial prefrontal cortex (includes dorsal ACC and vMPFC, including ventral—subgenual and pregenual—and rostral ACC). msPFC=medial superior prefrontal cortex. LPFC=lateral prefrontal cortex. aIPL=anterior inferior parietal lobule. MPFC=medial prefrontal cortex. vMPFC=ventromedial prefrontal cortex. OFC=orbitofrontal cortex. ACC=anterior cingulate cortex. DLPF=dorsoateral prefrontal cortex (includes anterior prefrontal cortex and inferior frontal cortex). PCG=precentral gyrus. DPC=dorsal parietal cortex.

Williams et al. 2016

Distribution of Elevated TSPO V_T Favors Circuitry Implicated in Obsessive Compulsive Disorder

Region of Interest	Percent Difference	Effect: Diagnosis $F_{1,37}$	Effect: Diagnosis *P*
Dorsal Caudate	35.6	15.5	<.001
OFC	30.9	13.5	.001
Thalamus	33.5	13.2	.001
Ventral Striatum	33.8	14.4	.001
Dorsal Putamen	32.6	12.8	.001
ACC	23.5	9.5	.004
MPFC	27.5	11.9	.001
DLPFC	22.0	9.1	.005
VLPFC	23.9	10.0	.003
INS	27.7	11.4	.002
Temporal Cortex	24.3	9.5	.004
Inferior Parietal Cortex	22.2	7.5	.009
Occipital Cortex	23.8	8.9	.005
Hippocampus	28.9	9.4	.004



(Block et al. Nat Neurosci Rev 2007, and Biochem Soc Trans 2008)

Cause of Microglial Activation

Our studies do not identify cause

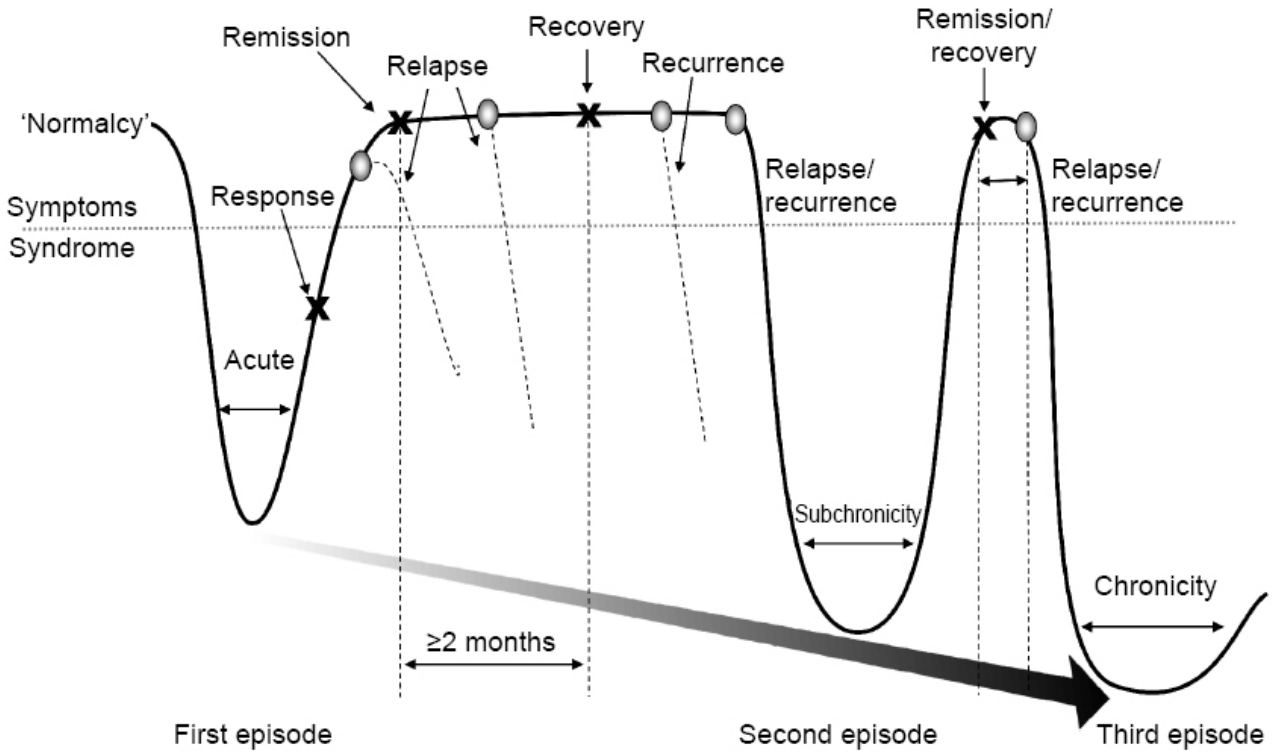
- **Exposure to inflammatory stimuli (trauma, infection)**
- **Stress stimulating microglial activation and priming**
- **Persistence mechanisms**
- **Injury to Neurons**

Duration of Untreated Major Depressive Disorder and Microglial Activation

-sometimes MDE has progressively worse outcome with greater durations of MDE and refractoriness to treatment

-but we have not identified progressive biological changes of large magnitude

-rare striking example of a strong relationship between greater change in clinical depression and duration of clinical depression



Kupfer et al. 1991
Sibille et al. 2013

Duration of Untreated Major Depressive Disorder and Microglial Activation

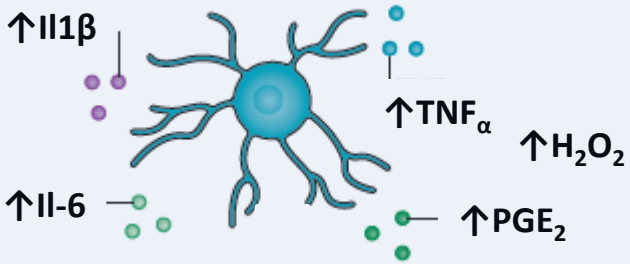
-also argues for a later phase of major depressive disorder where it may be best to orient development of inflammatory modulating treatments

-relationship of antidepressant treatment to TSPO V_T suggests a halting of progressive microglial activation

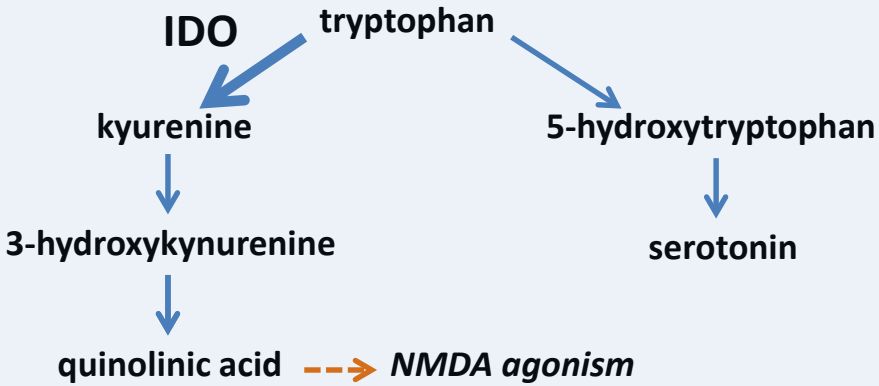
Role of Microglial Activation in Disease

Pathological

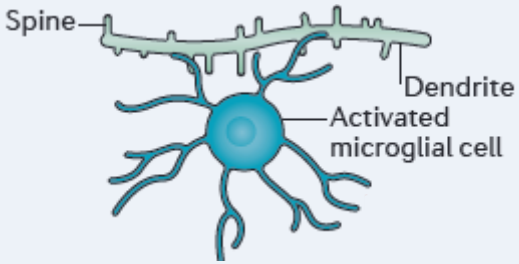
Increase Pro-Inflammatory Cytokines and Prostaglandins; H_2O_2



Divert Tryptophan Metabolism

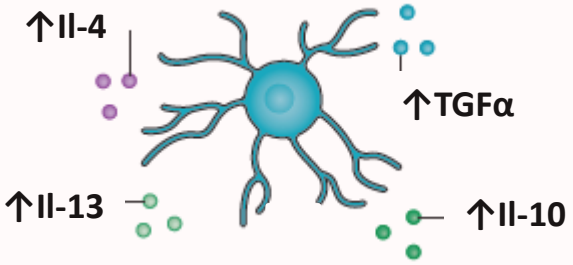


Excessive Synaptic Pruning

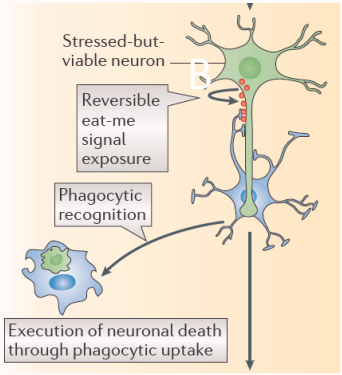


Protective

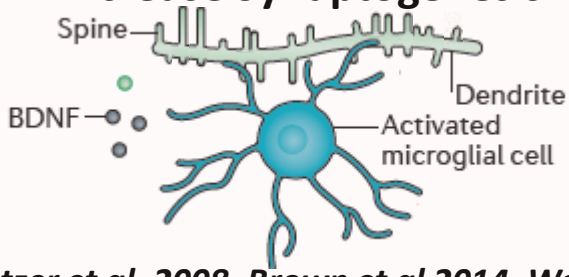
Increase Cytokines Implicated in Promoting Curative Roles



Phagocytose and Remove Debris



Increase Synaptogenesis



Dantzer et al. 2008, Brown et al 2014, Wohleb et al. 2016

Role of TSPO and Symptoms

Elevated TSPO binding associated with morphological changes of microglial activation but degree of pro-inflammatory versus curative roles still under investigation

- microglial cell culture polarized towards older terminology of M1 (pro-inflammatory; post LPS versus M2 (more curative; post IL4) reported greater TSPO mRNA expression in M1 only (Beckers et al. 2018)

Microglial activation contributing to symptoms?
Favor causality based on relationship of induction of microglial activation to depression and anxiety

Conditions/diseases with greater microglial activation such as multiple sclerosis and traumatic brain injury have several fold higher prevalence of comorbid MDD, OCD and anxiety with prevalence rates of 30 to 50%
(Grados et al. 2009; Marrie et al. 2015, Uguz et al. 2008)

Stimulation of immune system, with vaccinations or LPS, the latter which induces microglial activation are associated with MDE symptoms
(*Reichenburg et al. 2001; Musselman et al. 2002; Brydon et al. 2008;* Hannestad et al. 2012, 2015)

Therapeutic Implications

Case for New Therapeutic Development

Induction of microglial activation associated with greater depression and anxiety

Greater TSPO V_T, mainly a marker of microglial activation occurs within circuits of major depressive disorder and obsessive compulsive disorder

Does modulating microglial activation lead to reduction of symptoms?

Case for new therapeutic development

Reduce microglial proliferation
i.e. P2X7 inhibitors

Prevent Consequences of Microglial Proliferation
i.e. inhibit 2,3 indoleamine dioxygenase

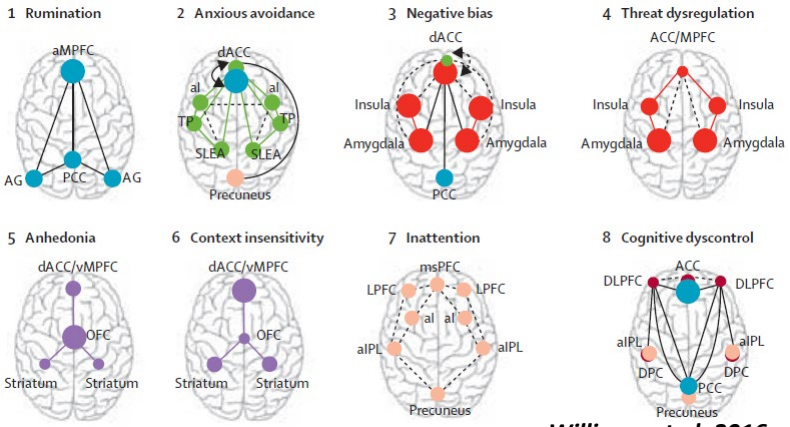
Case for repurposing medications

Reduce microglial activation/shift microglia to curative roles
i.e. minocycline

Prevent Consequences of Microglial Proliferation
i.e. COX2 inhibitors

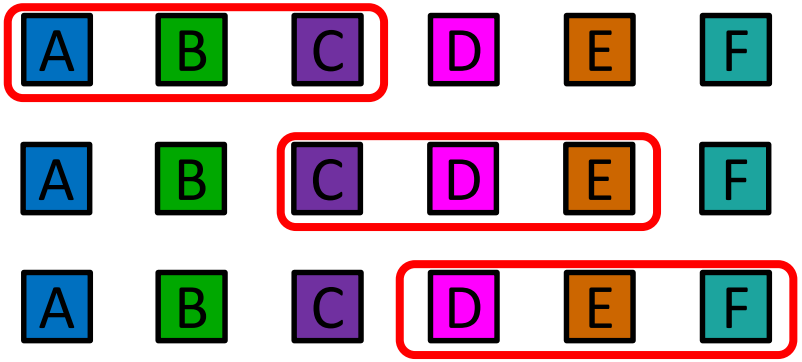
Stratify Illness for Clinical Trials and Eventually Clinical Treatment

Key Brain Systems Affected by Illness



Williams et al. 2016

Multiple Possible Phenotypes Affecting Key Brain Systems



Conventional pharmacotherapy will reach some targets

Which cases would benefit from a microglial targeting therapeutic?

- identify with symptoms
- blood predictors

Peripheral Inflammation Influences Brain Inflammation in Rodents During Sickness

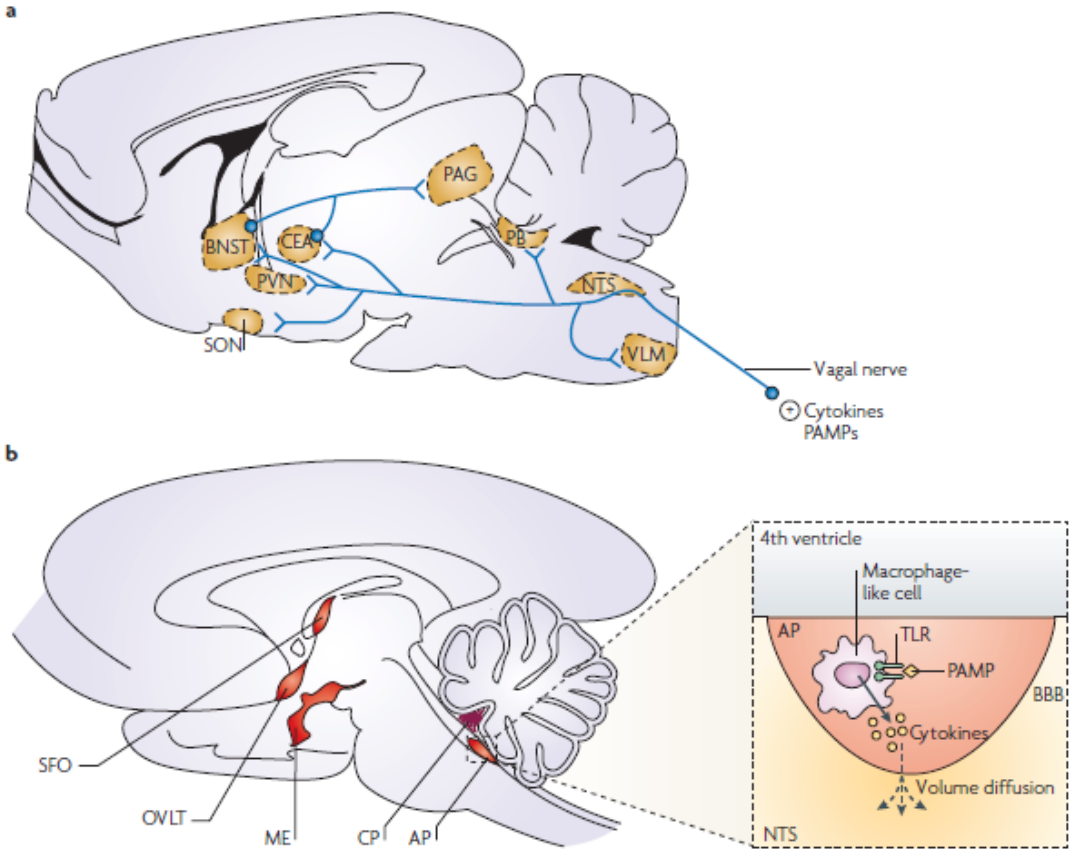


Figure 1 | **Pathways that transduce immune signals from the periphery to the brain.** The brain and the immune system communicate through different pathways. **a** | In the neural pathway, peripherally produced pathogen-associated molecular patterns (PAMPs) and cytokines activate primary afferent nerves, such as the vagal nerves during abdominal and visceral infections[8,9] and the trigeminal nerves during oro-lingual infections[10]. Vagal afferents project to the nucleus tractus solitarius (NTS), and from there to the parabrachial nucleus (PB), the ventrolateral medulla (VLM), the hypothalamic paraventricular and supraoptic nuclei (PVN, SON), the central amygdala (CEA) and the bed nucleus of the stria terminalis (BNST). These last two structures form part of the extended amygdala, which projects to the periaqueductal grey (PAG). **b** | The humoral pathway involves circulating PAMPs that reach the brain at the level of the choroid plexus (CP) and the circumventricular organs[11], including the median eminence (ME), organum vasculosum of the laminae terminalis (OVLT), area postrema (AP) and suprafornical organ (SFO). In the circumventricular organs, PAMPs induce the production and release of pro-inflammatory cytokines by macrophage-like cells expressing Toll-like receptors (TLRs). As the circumventricular organs lie outside the blood–brain barrier (BBB), these cytokines still need to reach the brain. They do so by mechanisms that are still unknown, but involve volume diffusion[12].

Models of influence of peripheral inflammation on central inflammation (cytokine stimulation of peripheral nerves, macrophage like cells proximal to the ventricles secreting cytokines, cytokine transporters at the blood brain barrier) are described during active bodily illness (Dantzer et al. nature reviews 2007)

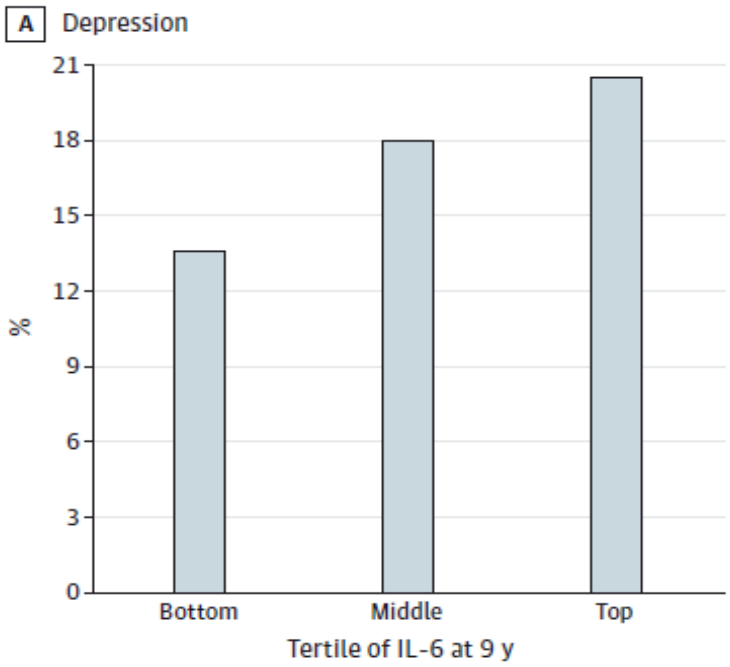
Results: TSPO and Peripheral Markers

Table 3. Lack of Positive Correlation Between Regional TSPO V_T and Peripheral Inflammatory Markers in Major Depressive Episodes

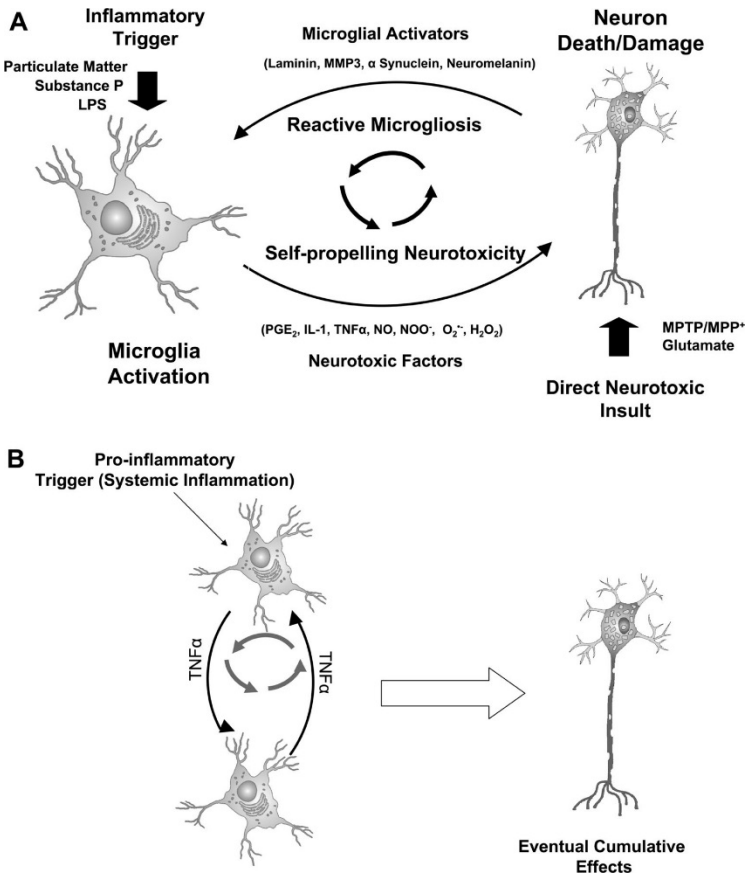
Marker	Prefrontal Cortex	Anterior Cingulate Cortex	Insula
IL-1β	-0.35 (0.13)[a]	-0.39 (0.09)	-0.35 (0.14)
IL-6	-0.20 (0.39)	-0.04 (0.88)	-0.09 (0.70)
TNFα	-0.29 (0.21)	-0.34 (0.14)	-0.36 (0.12)
CRP	-0.27 (0.25)	-0.16 (0.51)	-0.26 (0.27)
Correlations Controlling for rs6971 Genotype			
IL-1β	-0.39 (0.10)	-0.45 (0.05)	-0.40 (0.09)
IL-6	-0.29 (0.24)	-0.08 (0.75)	-0.15 (0.53)
TNFα	-0.33 (0.16)	-0.40 (0.09)	-0.44 (0.06)
CRP	-0.52 (0.02)	-0.40 (0.09)	-0.54 (0.02)
Correlations Controlling for Body Mass Index			
IL-1β	-0.18 (0.46)	-0.21 (0.38)	-0.14 (0.56)
IL-6	-0.12 (0.62)	0.09 (0.71)	0.03 (0.89)
TNFα	0.18 (0.46)	0.16 (0.52)	0.18 (0.46)
CRP	-0.15 (0.54)	0.01 (0.98)	-0.12 (0.63)
Correlations Controlling for Both rs6971 Genotype and Body Mass Index			
IL-1β	-0.25 (0.31)	-0.31 (0.21)	-0.23 (0.36)
IL-6	-0.22 (0.39)	0.04 (0.87)	-0.04 (0.89)
TNFα	0.05 (0.84)	0.01 (0.97)	0.03 (0.90)
CRP	-0.42 (0.08)	-0.25 (0.31)	-0.43 (0.07)

JAMA Psychiatry 2015

In Humans, Behavioral Effects May Occur Years After Elevation of Peripheral Inflammation



IL-6 serum at 9y predicts
major depressive episode at 18 years
in 422 of 2447 participants
(Khandaker et al., JAMA Psych 2014)



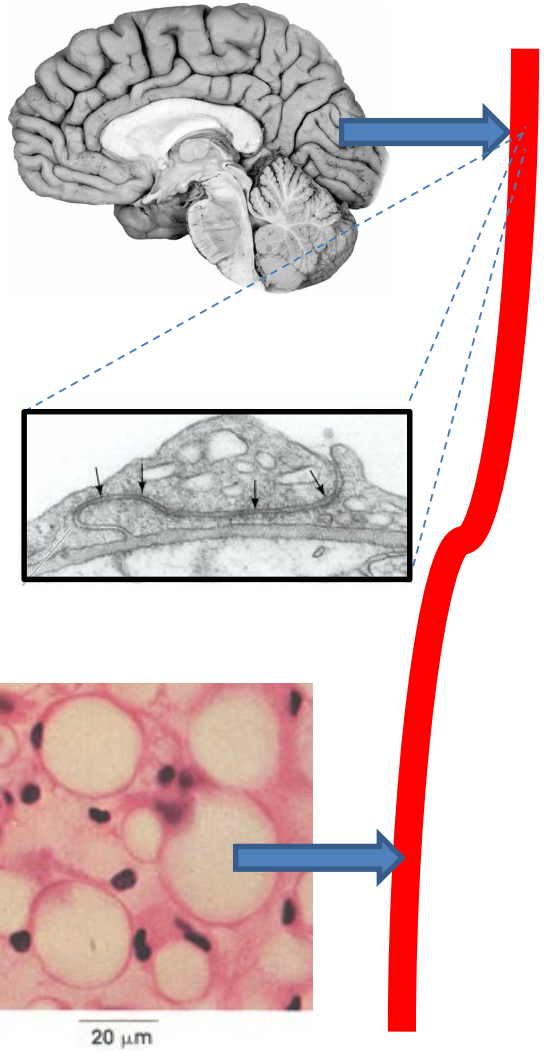
(Block et al. Nat Neurosci Rev 2007, and Biochem Soc Trans 2008)

Approach to Designing Peripheral Markers of Microglial Activation

1. Think about molecule going from **brain to periphery** since peripheral inflammation may no longer dominate inflammatory processes in brain

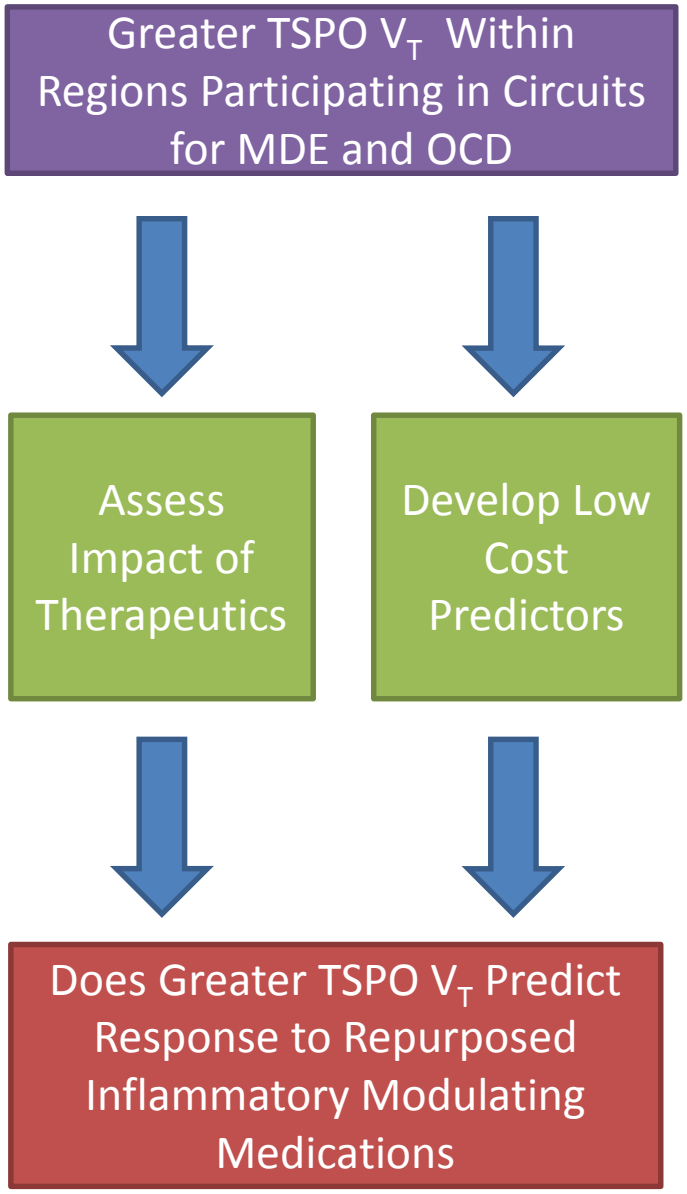
2. Choose markers that can cross the blood brain barrier
   BUT from brain to periphery

3. Apply a strategy to **control for peripheral (often adipose) contributions** since most inflammation related molecules from CNS are also created by adipose



Pictures from Salamon et al; Peters et al.; Bergman et al.;

PET-Translocator Protein Imaging to Understand/Improve Treatment



PET Radioligands In Development Related to Neuroinflammation

Molecular Target	Cellular Expression	Expression in Neuroinflammation	Radiotracers Investigated
TSPO	Microglia and astrocytes	Upregulated	[^{11}C]PK11195, [^{18}F]FEPPA, [^{18}F]PBR06, [^{18}F]FEDAA1106, [^{11}C]PBR28, [^{11}C]ER176, [^{18}F]DPA-714
GSK-3	Microglia and astrocytes	Upregulated	[^{11}C]PF-367, [^{11}C]SB-216763,
MAO-B	Astrocytes >> microglia	Upregulated	[^{11}C]SL25.1188, [^{11}C]-*L*-deprenyl, [^{11}C]-*L*-deprenyl-D_2, [^{18}F]fluorodeprenyl-D_2, [^{18}F]fluororasagiline-D_2,
ROS	Microglia	Upregulated	[^{11}C]hydromethidine, [^{11}C]**1**, [^{18}F]ROStrace, [^{11}C]ascorbic acid
I_2BS	Astrocytes	Upregulated	[^{11}C]BU99008
COX-1	Microglia	Upregulated	[^{11}C]Ketoprofen-methyl ester, [^{11}C]PS13, [^{18}F]PS2
COX-2	Microglia	Upregulated	[^{11}C]MC1
Arachidonic acid	Microglia and astrocytes	Upregulated	[^{11}C]Arachidonic acid
S1P1	Microglia >> astrocytes	Upregulated	[^{18}F](R)-1-[[3-(6-fluorohexyl)-phenyl]amino-4-oxobutyl]phosphonic acid, [^{11}C]TZ3321, [^{18}F]TZ35110, [^{18}F]TZ43113, [^{18}F]TZ35104, [^{18}F]TZ4877, [^{18}F]TZ4881
CB2	Microglia and astrocytes	Downregulated	[^{11}C]NE40, [^{11}C]MA2, [^{18}F]MA3
CX3CR1	Microglia Lymphocytes	Upregulated	–
Purinergic receptor: $P2X_7$	Microglia >> astrocytes	Upregulated	[^{11}C]A-740003, [^{11}C]SMW139, [^{11}C]JNJ-54173717, [^{11}C]GSK1482160
Purinergic receptor: $P2Y_{12}$	Microglia (M2)	Downregulated	[^{11}C]**2**
RAGE	Microglia	fIRAGE: upregulated; sRAGE: downregulated	[^{18}F]RAGER, [^{18}F]FPS-ZM1
MerTK	Microglia and astrocytes	Upregulated	[^{18}F]JHU16907
TREM1	Microglia	Upregulated	[^{64}Cu]TREM1-mAb

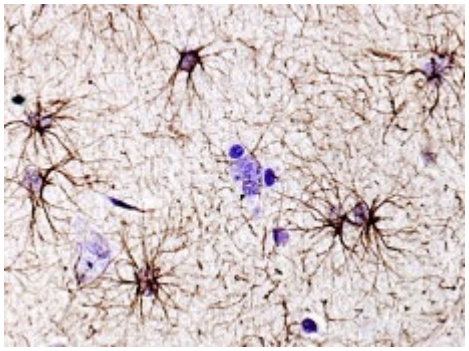
Abbreviations: CB2: cannabinoid-2 receptor; COX: cyclooxygenase; GSK-3: glycogen synthase kinase 3; I_2BS: imidazoline-2 binding sites; MAO-B: monoamine oxidase-B; MerTK: Mer tyrosine kinase; RAGE: the receptor for advanced glycation end products; ROS: reactive oxygen species; S1P1: sphingosine-1-phosphate receptor 1; TSPO: translocator protein-18 kDa; TREM1: triggering receptor expressed on myeloid cells-1.

Narayanaswami et al 2018

[^{11}C] SL25.1188 Radiotracer for Monoamine Oxidase B

Astrocytes

- ~20% of brain cells
- activate in response to infection or trauma and in neurodegenerative disease



GFAP stain (Abcam)

monoamine oxidase B

astroglia and serotonin releasing neurons
glucocorticoid and inflammatory response
DA and NE metabolism, oxidative stress, apoptosis

[^{11}C] SL25.1188 Radiotracer for Monoamine Oxidase B

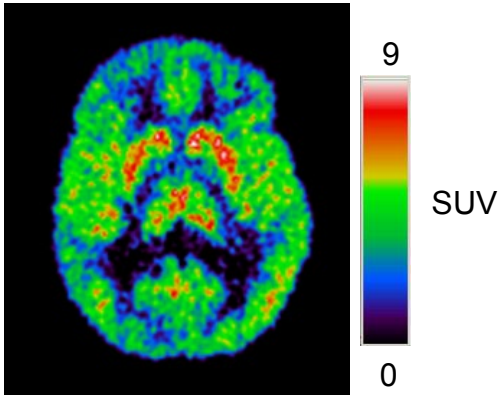
1. High affinity for MAO-B (K_i=3nM)

2. Selective

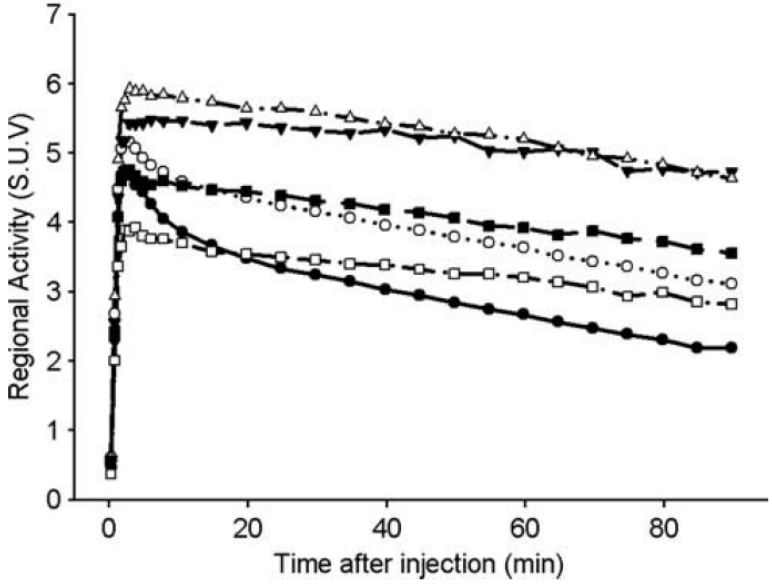
3. Metabolites not brain penetrant

4. Reversible kinetics in humans

5. Regional MAO-B V_T well identified with two tissue compartment model, and ratio of modeled compartments ~ 7 to 12 in humans



Transverse view of a healthy subject



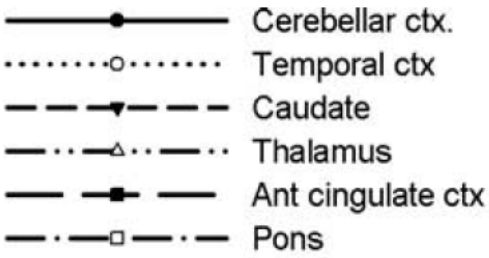


Figure 2. Average ($n = 14$) regional time-activity curve (standard uptake value, SUV) obtained after injection of [^{11}C]SL25.1188. Prefrontal cortex and putamen are omitted because they highly overlap with the temporal cortex and the thalamus, respectively.

Bramoulle et al. 2008, Saba et al. 2011, Vasdev et al. 2011, Rusjan et al. 2014

Main Points

1. Translocator Protein PET Imaging mainly reflects microglial activation, an important component of neuroinflammation.

2. Greater TSPO V_T throughout grey matter in clinical depression (which includes mood influencing brain circuits) is well replicated.

3. TSPO V_T is highest in clinical depression with long duration of untreated illness
   It is a prominent example of neuroprogression in clinical depression.

4. Greater TSPO V_T also occurs in OCD throughout grey matter, but most prominently in the corticostriatal thalamic circuit.

5. Imaging findings make a case for developing new therapeutics to target sequelae of microglial activation and/or microglial activation itself.

6. Future directions include:
   i) further development of blood markers and symptom measures to predict TSPO V_T
   ii) assessing predictiveness of TSPO V_T for response to inflammatory modulating interventions
   iii) development and application of new markers to target other aspects of neuroinflammation and further characterize changes in microglia

Neurochemical Imaging Program in Affective Disorders

Radioligand Development

Sylvain Houle
Alan Wilson
Armando Garcia
Neil Vasdev
Pablo Rusjan
Alvina Ng
Jun Parkes
Terry Bell
Peter Bloomfield

Research Co-ordinators & Current/Past Trainees

Laura Miler
Cynthia Xu
Brittany Matthews
Lina Chiuciarello
Ingrid Bacher
Alex Soliman
Sofia Raitsin
Aristotle Voineskos
Vivien Rekkas
Julia Sacher
Nathan Kolla
Yekta Dowlati
Elaine Setiawan
Andrea Tyrer
Sophia Attwells
Sho Moriguchi

Collaborators

Mars Innovation
Ken Evans
Rob Levitan
Arun Ravindran
Robert Cook
Trevor Young
Michael Bagby
Jeff Daskalakis
Peggy Richter
Lakshmi Ravindran
Paul Links
Shelley McMain
Donna Stewart
Meir Steiner
Tony George
Peter Selby
Grazyna Rajkowska
Steve Kish
Junchao Tong