Moderat

Steven G. F

Ranga Kris

- 2) MEASURES A SURRO
  DIRECTLY RELATED TO
  MAYBE LIKE A SYMPTO
  DEPRESSION

NOT A SOLE MEA

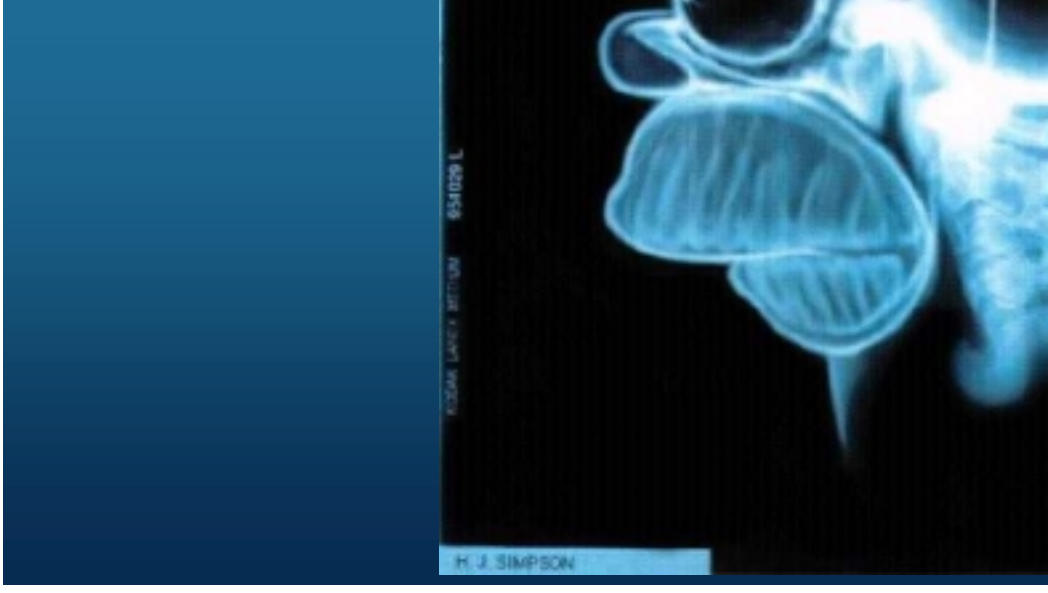
WMAY CUT TIME L
INSUFFICIENT B

Structural: MRI

Functional: FDG PET, ligand

Value: proof of principal, co
endpoints

Future: primary or co-prima

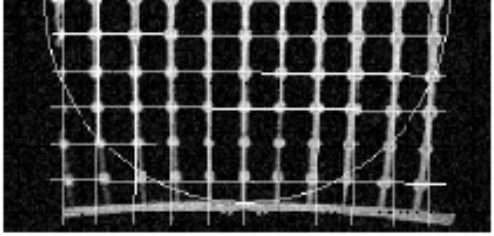

H. J. SIMPSON

- fMRI: studies of brain blood
  tasks
- PET: blood flow, metabolis
- MEG: studies of brain elec
  high temporal resolution

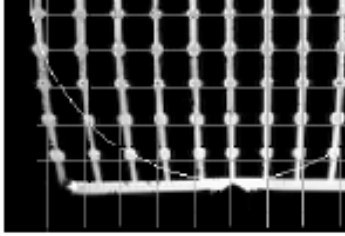
understand the norm
disease states, and t
by treatment.

the question bein

Combining tools t
synergistic

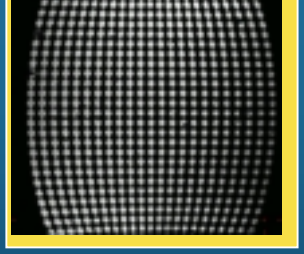


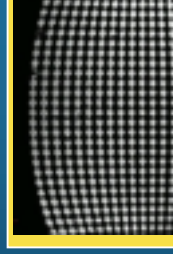
Siemens Sonata

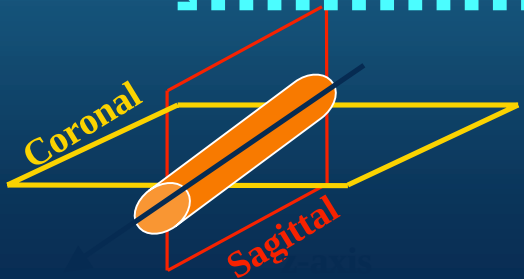


GE Signa C

Coronal

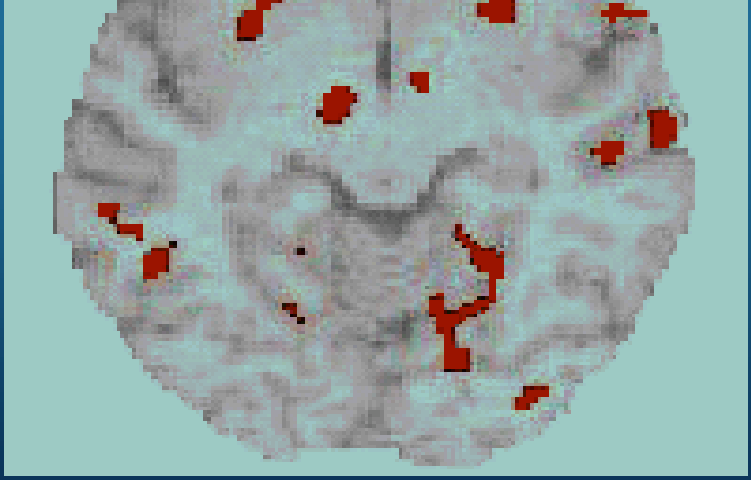


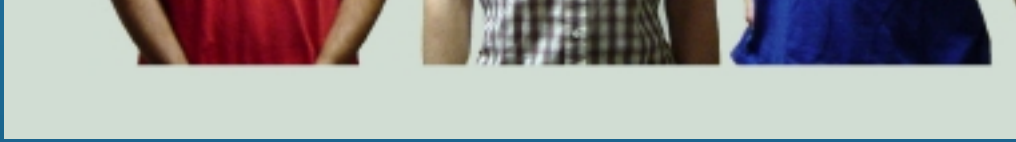




Within subjec
not eliminate
equipment ch

BOLD reflects changes in blood flow
associated with changes in neural





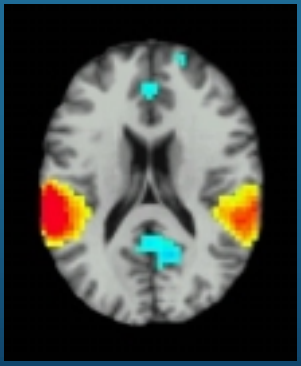
At Each Site:

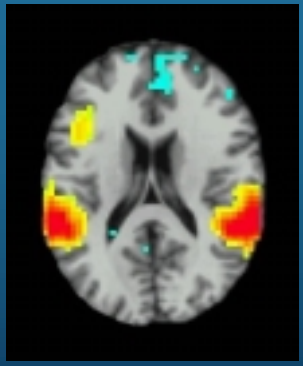
1. Cog SIRP or MMN
2. Cog
3. SM
4. Rest
5. BH
6. SM
7. BH
8. Rest
9. SM

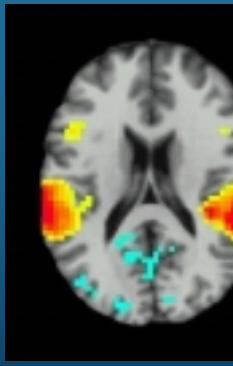
Multi-ce
demons
imaging

Different scanners = diffe
raw images

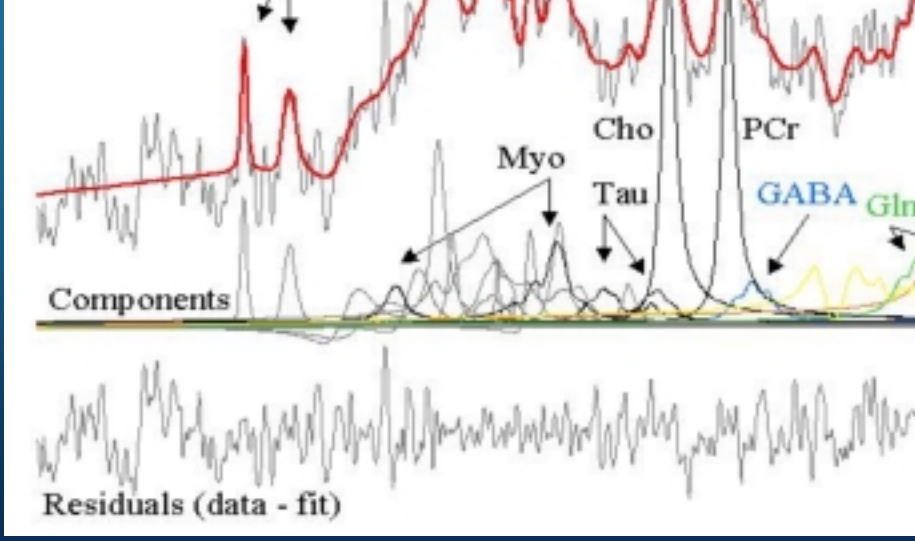
SMOOTHED





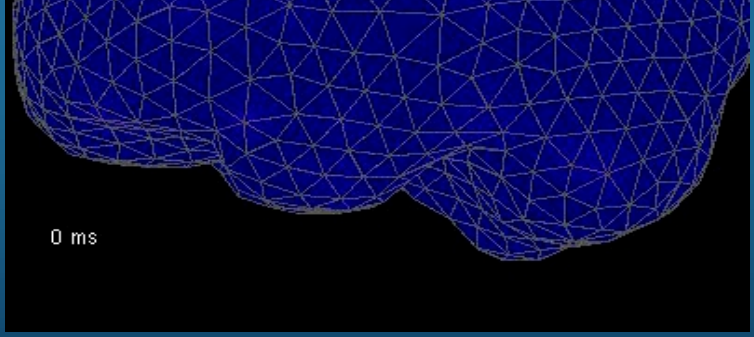


Analysis performed by Lee Friedman, U New Me


Cho
PCr
Myo
Tau
GABA
Components
Residuals (data - fit)

circuits (with 300 array

- Cons
- Difficult to analyze and
- Very weak signal
- Expensive and not wide
- Poor resolution of subc



Normal

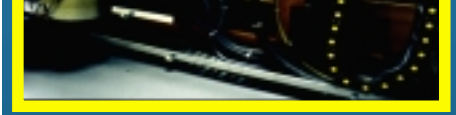
UNM

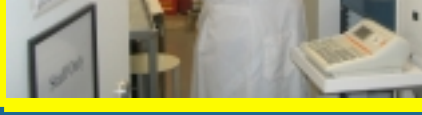
Radioactive decay (F^{18}) with p
electron producing coincidence

Great flexibility in tasks

E.g., attention; memory; & sleep

Lower spatial resolution than FDG





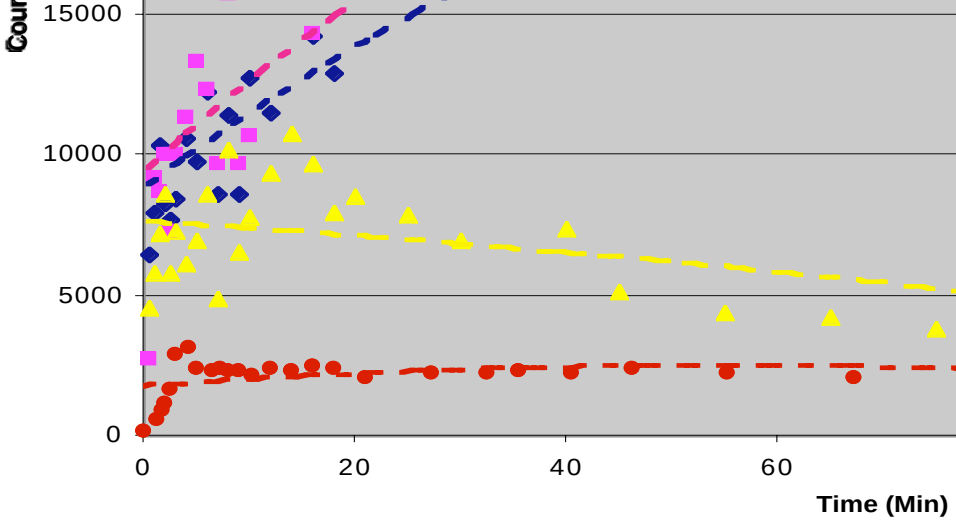
Cyclotron

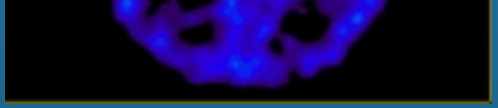
^{18}F synthesis

Radio-pharmaco chemistry

^{18}F NCQ-115 synthesis

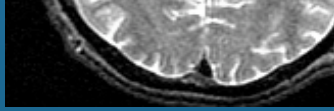
Data Ana


15000
10000
5000
0
0
20
40
60
Time (Min)

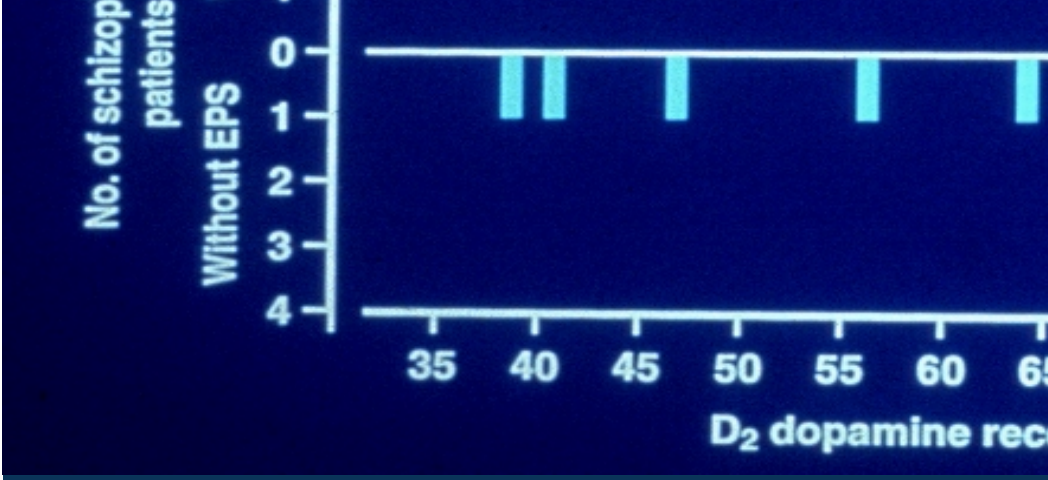


^{11}C-Raclopride
PET Scan

Before
Treatment



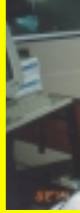
Coregistered
MRI Scan


No. of schizop
patients
Without EPS
0
1
2
3
4
35
40
45
50
55
60
D2 dopamine rec

^{18}F synthesis

Radio-pharmaco-chemistry

^{18}FDG synthesis

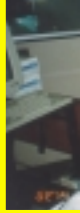


Rad

^{18}F synthesis

Radio-pharmaco-chemistry

^{18}FDG synthesis



Rad

PET Imaging

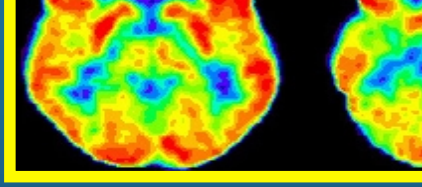


Image
Reconstructi

- Quantitative blood flo
- Receptor & reporter m

Cons

- Radiation exposure
- Lower temporal resolu
- Less widely available

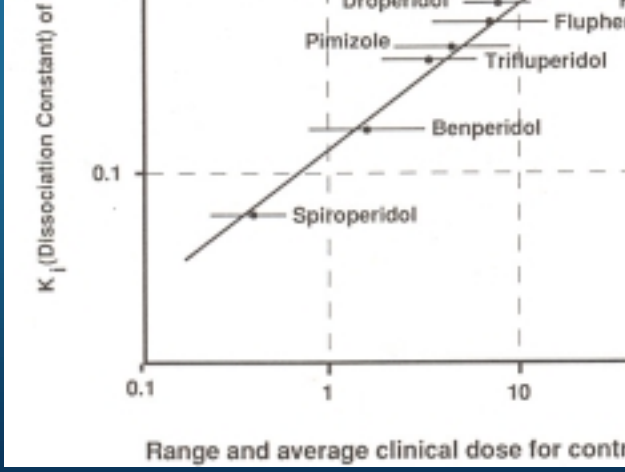
Steven G. Potkin, M.D.

Professor and Director of Clinical R
Psychiatry and Human Behavior

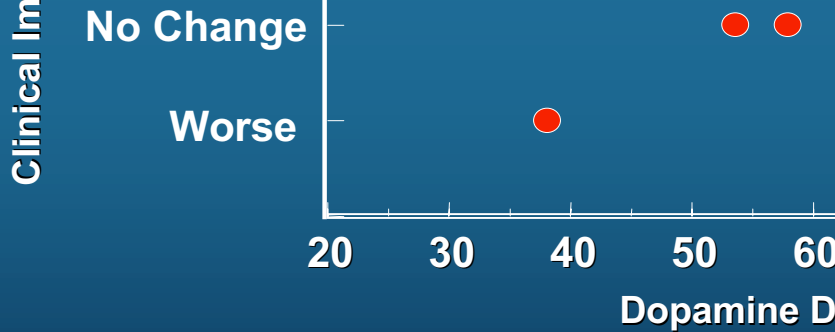
Robert R. Sprague Director, UCI Bra
University of California, Irvine

at a variety of neuro
receptors

- But, only at dopami
  is there a close corre
  efficacy and recepto

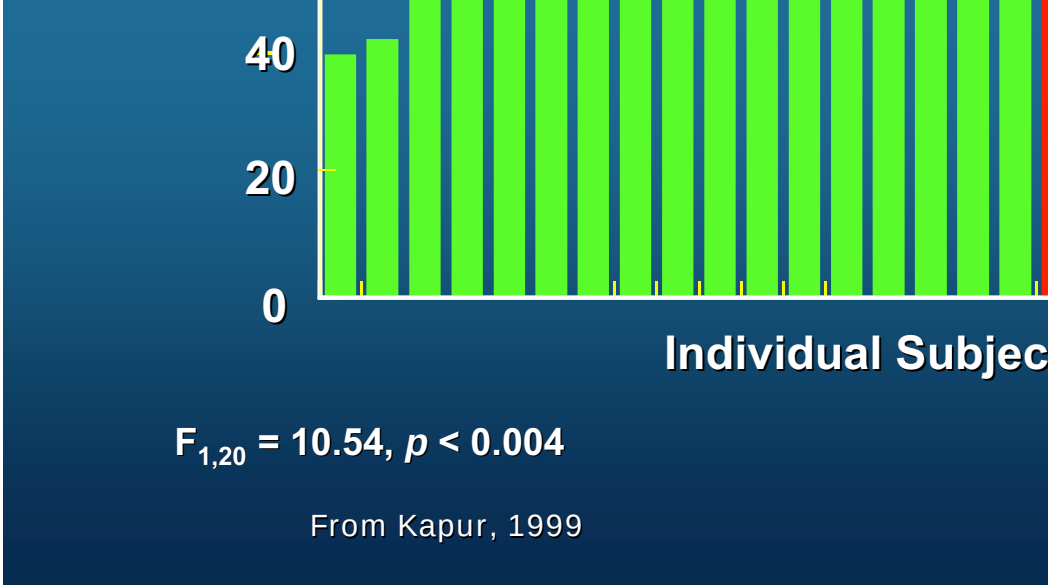


Seeman P et al Nature 261:717,1



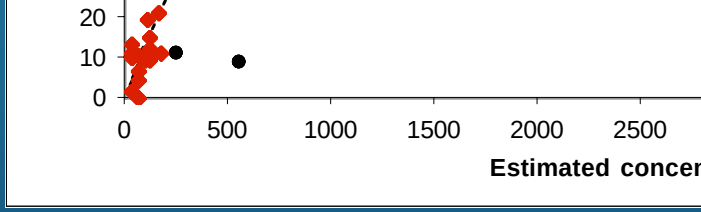
D_2 occupancy predicts response on CGI
D_2 predicts change in positive symptoms
D_2 does not predict change in negative symptoms, despite im

From Kapur, 1999



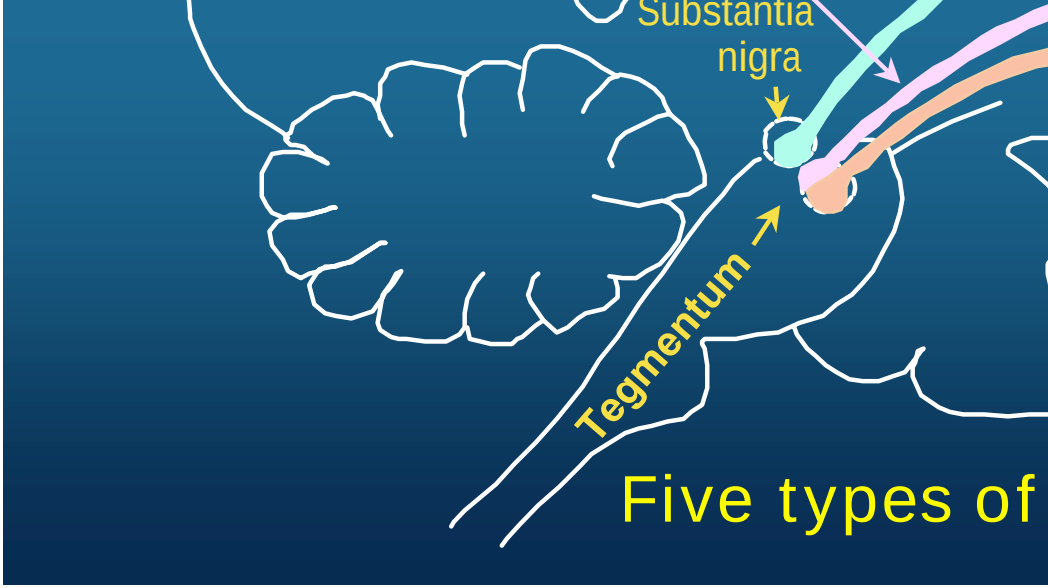
$F_{1,20} = 10.54, p < 0.004$

From Kapur, 1999



Best used to choose dose range

Occupancy necessary to insure
efficacy trial but does not imply


Substantia
nigra
Tegmentum
Five types of

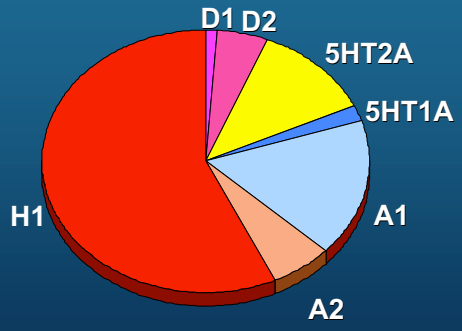
Using fallypride to develop new antipsychotic treatments and depot formulations

UC

5HT2A

A1

Quetiapine

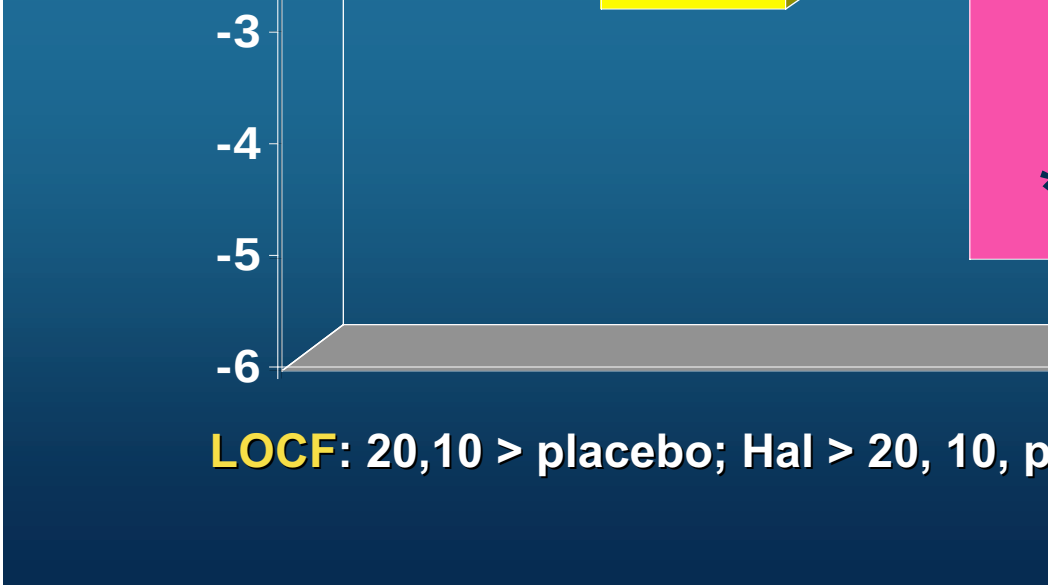


From Goldstein. Emerging Drugs (1999) 4:127-151

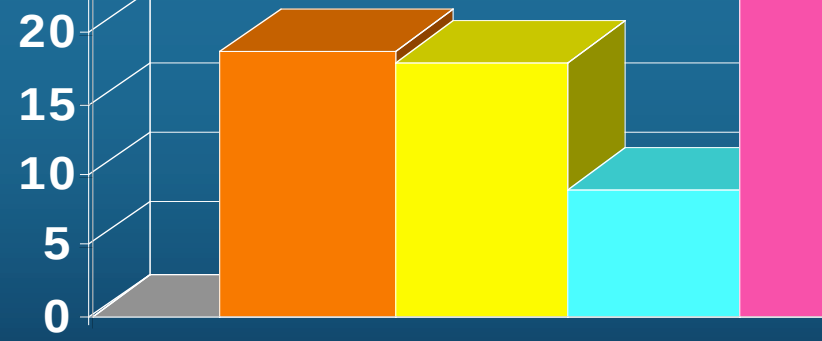
- M100907 10 mg
- M100907 20 mg

W66% schizophrenia; 3

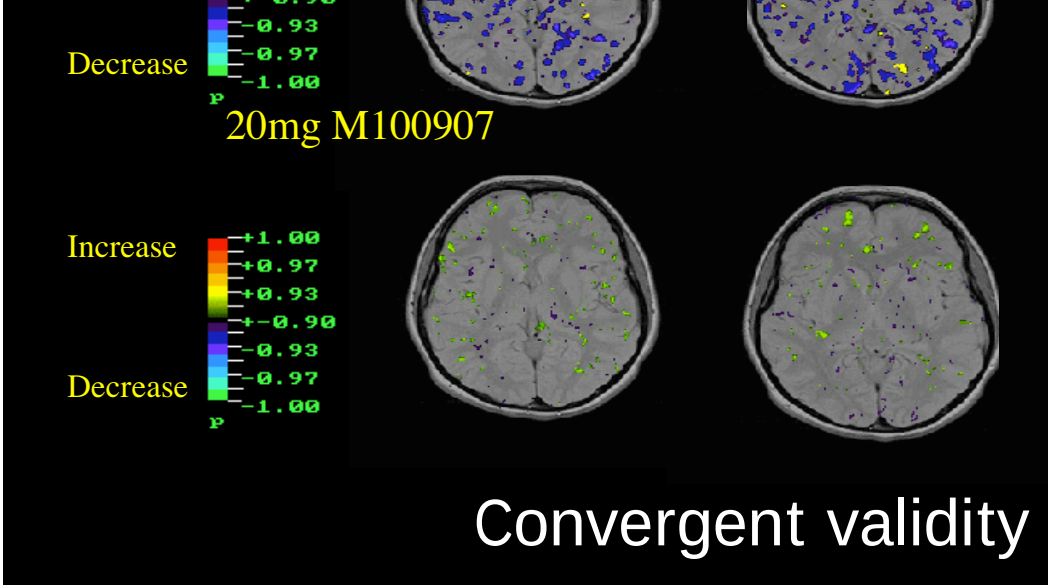
W6 week study



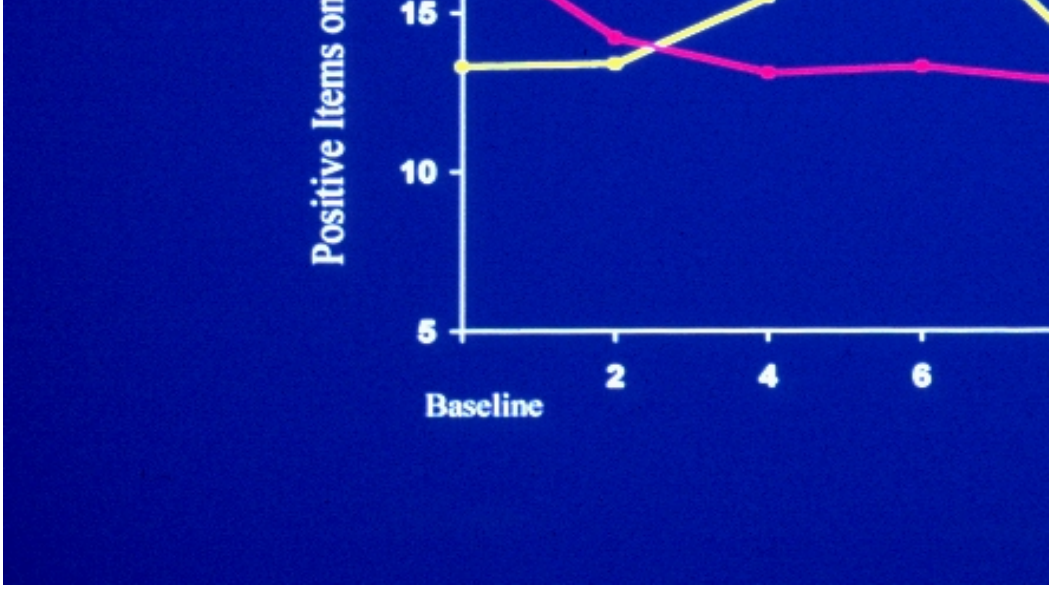
LOCF: 20,10 > placebo; Hal > 20, 10, p

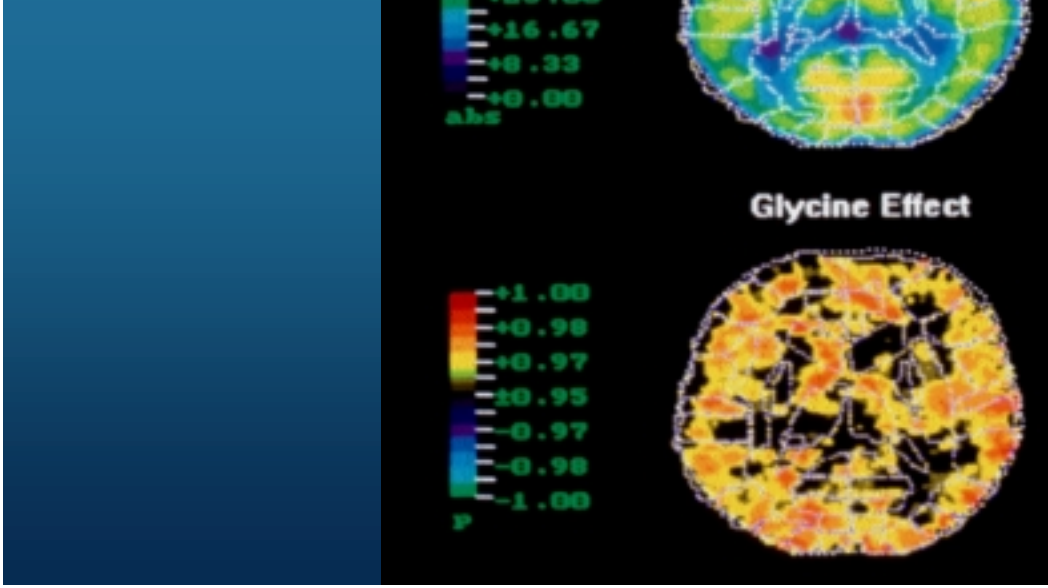


No change in body wei


Decrease
-0.93
-0.97
-1.00
P
20mg M100907
Increase
+1.00
+0.97
+0.93
+-0.90
Decrease
-0.93
-0.97
-1.00
P
Convergent validity

- Neuregulin mutants reve
- DARPP-32 regulates G p
- RGS4
- Reelin – extra cellular prote gabaergic layers


Positive Items on
15
10
5
2
4
6
Baseline


+16.67
+8.33
+0.00
abs
Glycine Effect
+1.00
+0.98
+0.97
±0.95
-0.97
-0.98
-1.00
p

WUse of FDG PET as P
as biological marker
validity

inferior prefrontal cortex

- Gender
  - Cingulate metabolism lowered in fe
- Methodology
  - Compared to normal controls, no ba
  - Auditory discrimination task

Cohen RM et al. Neuropsy

- Metabolic response was blunted
  symptom scores before treatmer
  of dopamine manipulation upon
  thalamic circuits)

medial frontal cortex

- No change in basal ganglia or in
- No differences in global metabol
- No increase in metabolism follow

Lane CJ et al. F

- Decreased activity in motor area
- Decreased in positive symptoms

Molina V et al. Schizop

improvement in negative s

- Increased in occipital cort
  improvement in positive sy

Molina

- Increase in right DLPFC cor
  in positive symptoms
- Decrease orbital frontal cor
  in positive symptoms.

- After 30 drug-free days, d
  the basal ganglia and thal
  frontal and anterior cingul
- Unclear if pk or lack of tre

Holcomb HH e

were all given a 10 mg/d haloperido

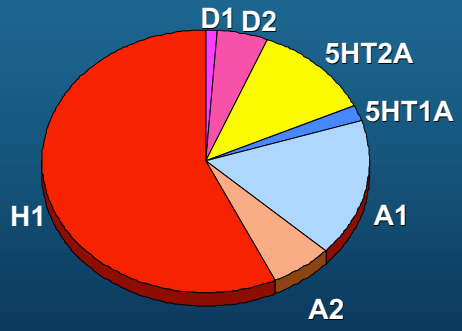
- Patients with first-episode psychosi similar in all parameters as compare
- Decreased prefrontal gray matter w hippocampal activity in schizophren importance of considering both stru

Molina V et al. J Ps

5HT2A

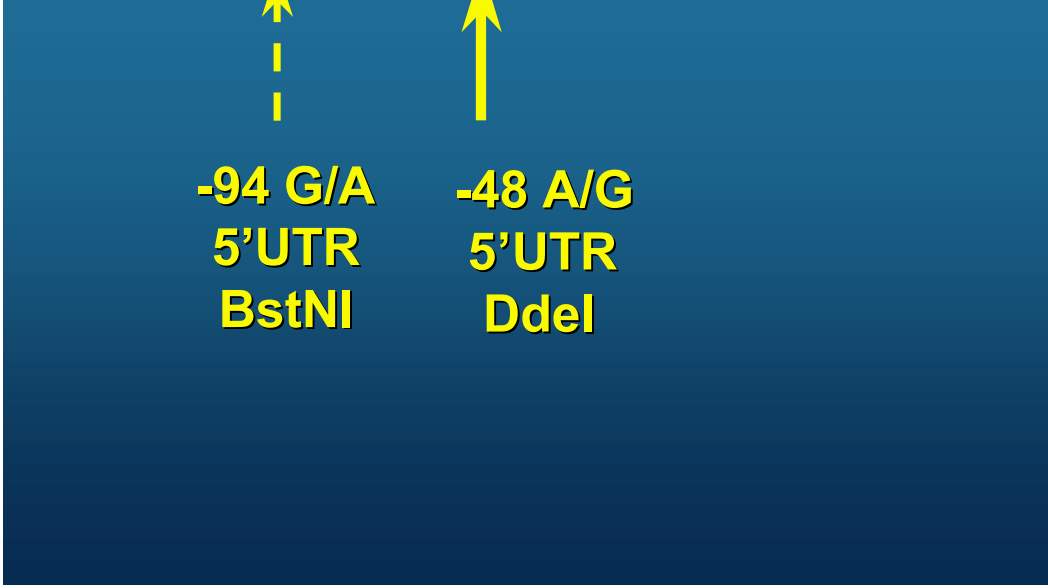
A1

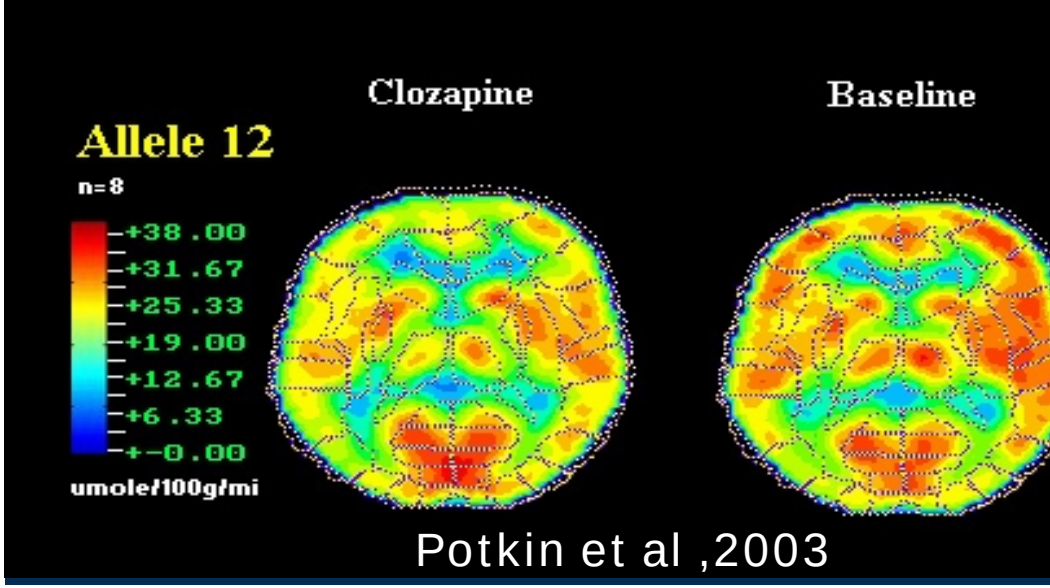
Quetiapine



From Goldstein. Emerging Drugs (1999) 4:127-151


D1
D5
D

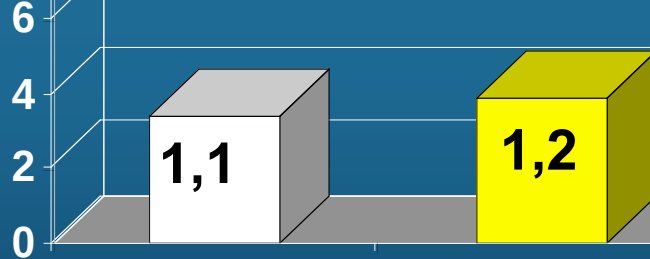

-94 G/A
5'UTR
BstNI
-48 A/G
5'UTR
DdeI



Potkin et al ,2003

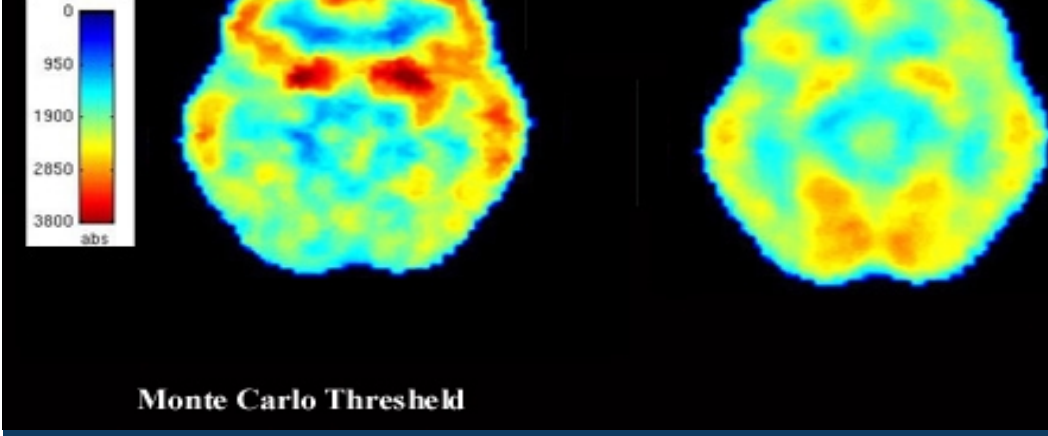
Are any of the genetic
DRD1, DRD2, DRD3 or D
associated with conver
induced

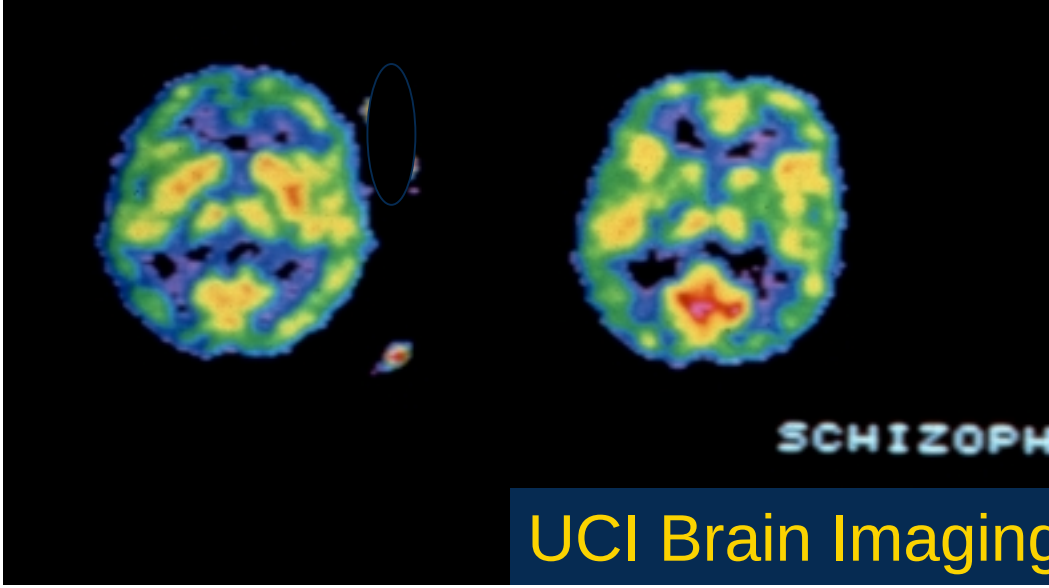
score



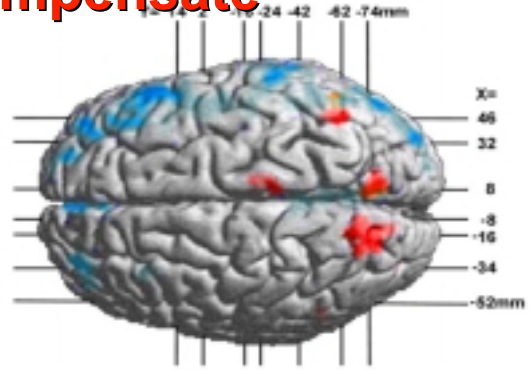
DRD3 Geno

F[2,95] = 8.25, p < 0.0005, Power = 0.5

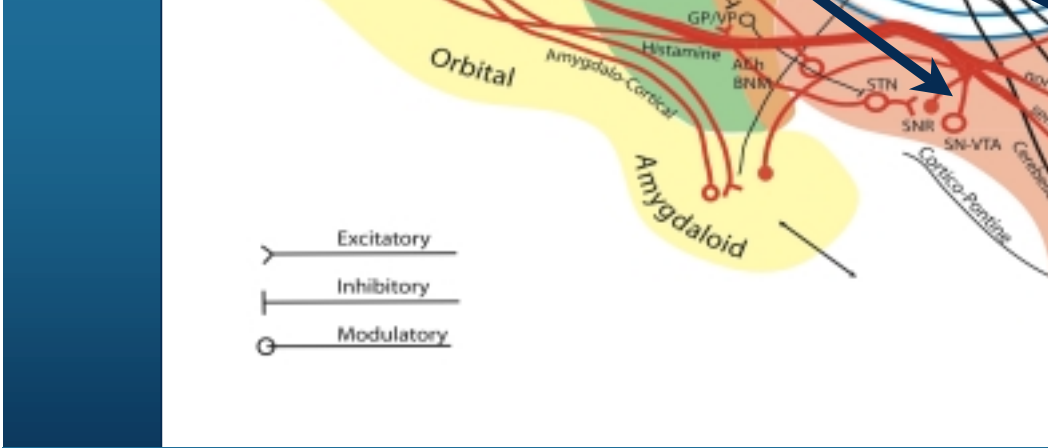

0
950
1900
2850
3800
abs
Monte Carlo Threshold


SCHIZOPH
UCI Brain Imaging

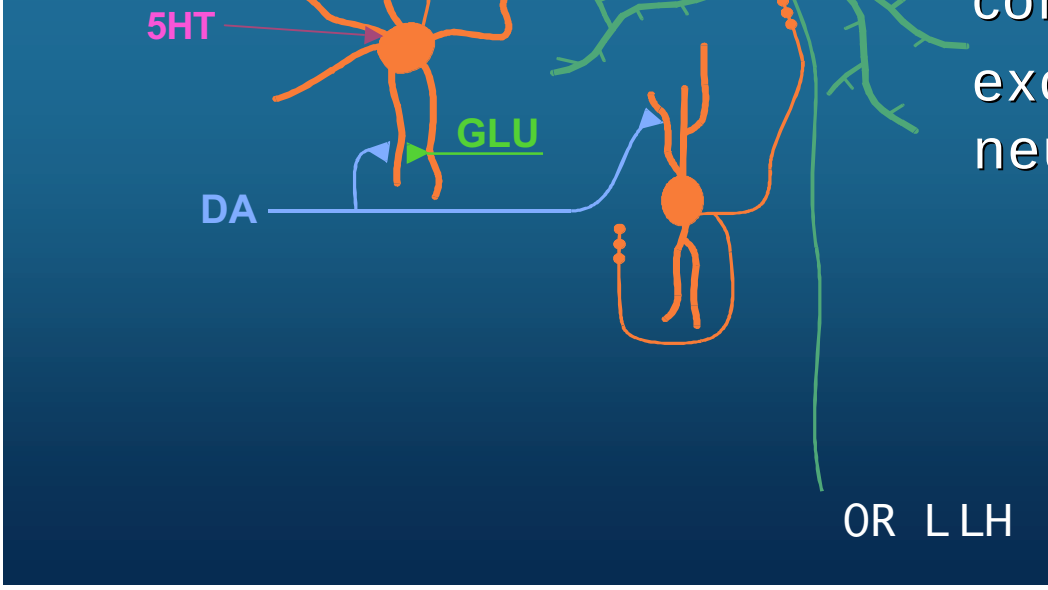
Cerebellar attempt to compensate



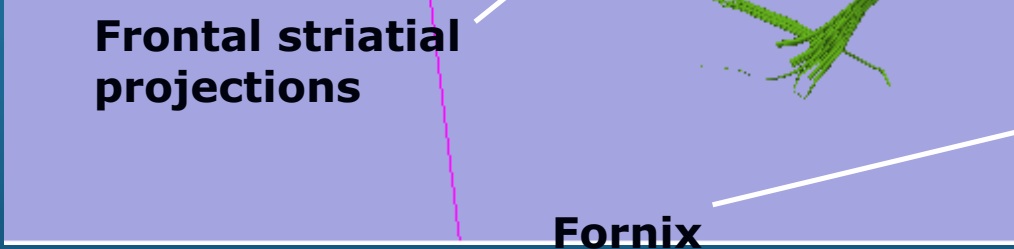
R LH DO



Convergence of abnormal circuits in schizop
pathway on the PFC pyramidal neuron (ellip


5HT
GLU
DA
OR L LH

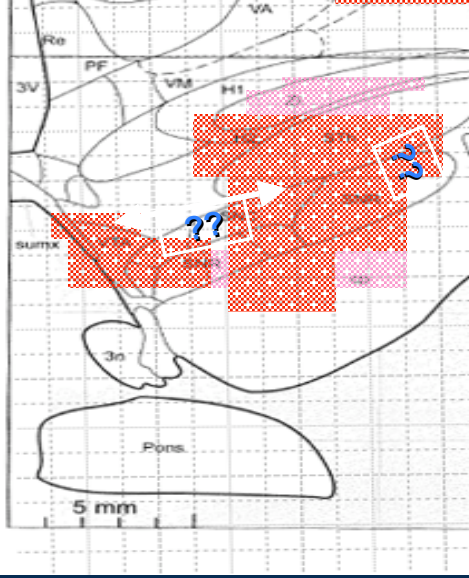
- Negative symptom schizo
  by greater deficits in these
  predominately positive sy
  - Decreased ability to activate

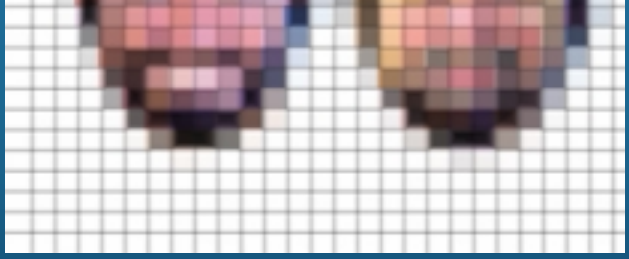


Actual white matter tracks in schizophrenic patient revealed by DTI (colors and location by J. Fallon)

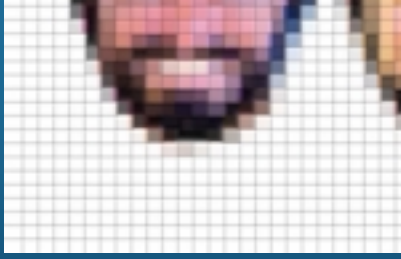
Limitations of current imaging technology in resolving brain circuits involved in negative symptoms and cognition

Unable to distinguish cognitive from motor areas in thalamus & midbrain

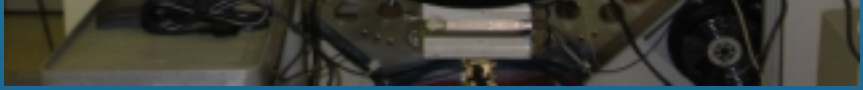


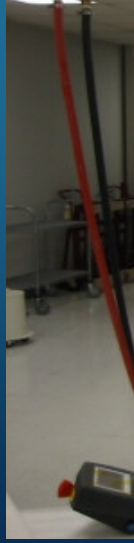


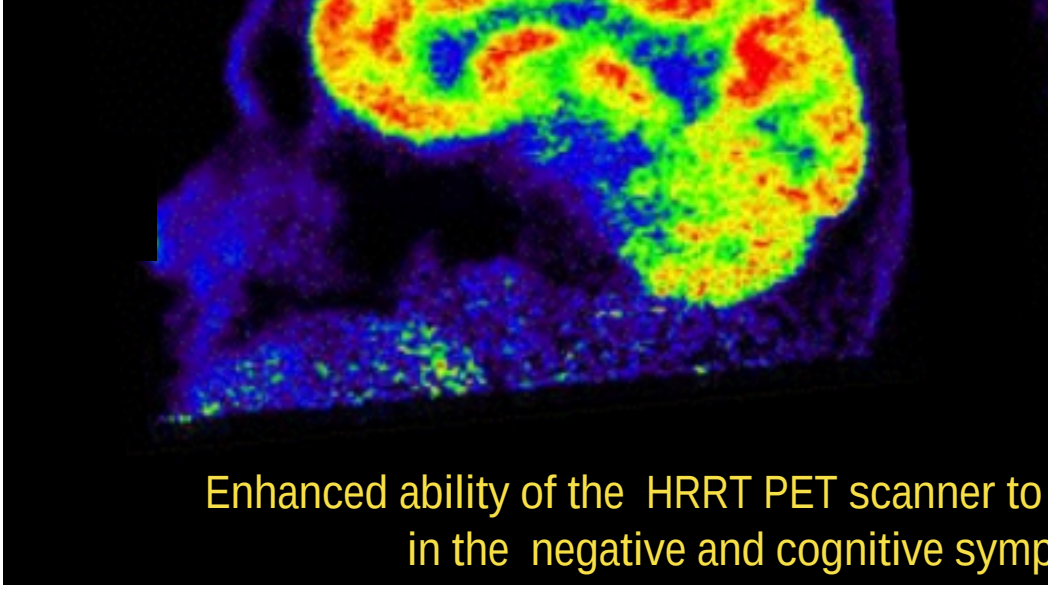
Original Technology



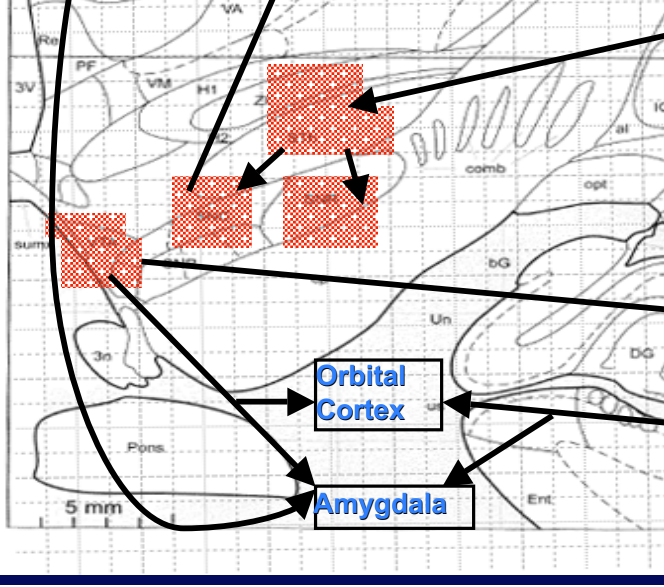
Current Tech

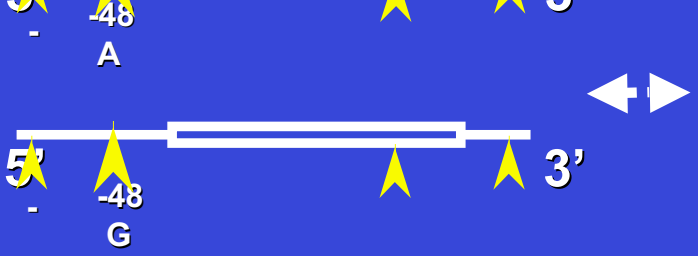




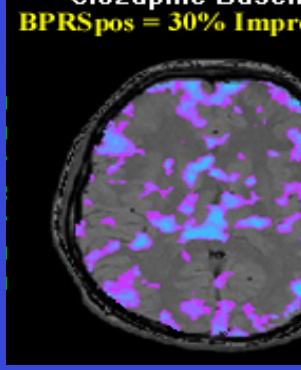


Enhanced ability of the HRRT PET scanner to
in the negative and cognitive symp

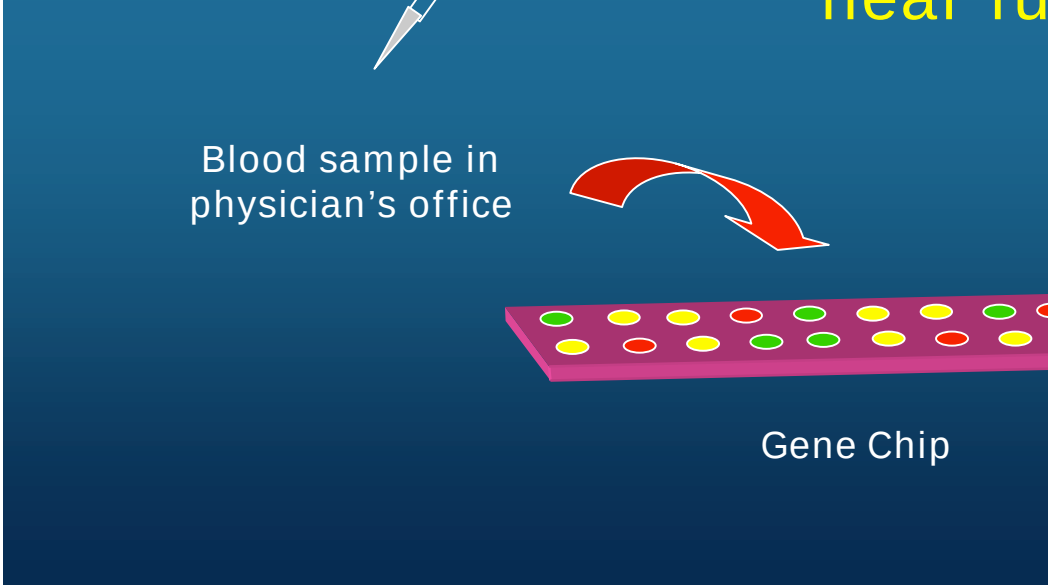

VA
Re
PF
3V
VM
H1
comb
opt
bG
Un
DG
3o
Orbital Cortex
Pons
Amygdala
Ent
5 mm



Inherited genotype



Neuroimag


Blood sample in
physician's office
Gene Chip

	Efficacy	Negative	Cognitive	DM	Weight
Clozapine	90	80	25	50	85
Asenapine	90	80	50	10	15
Olanzapine	80	70	20	70	90
Ziprasidone	85	75	30	20	10

- Washout and baseline long?
- Distinguishing drug response

pathophysiology, clinic
development of side e

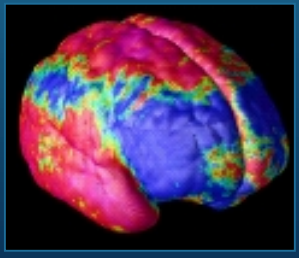
- Convergent validity by
  subjects
- Co-primary clinical tria

- Need standardizat
  - reliability, task, ba
  - placebo-control, c
  - clinical change an

Wrapper

PET

Wrapper



Structure

Wrapper

Receptor Densit