Early identification of neurobiological markers of remission

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Outline

- Why study remission?
- Defining remission
- Data collection
- Results
  – neurocognition
  – neuroimaging: sMRI & fMRI
- Conclusions & Future Direction

Why study remission?

- heterogeneity of outcome (Emsley et al, 2011, *Curr Opin Psychiatry*)
- inability to predict response early on
  (Menezes et al, 2006, *Psychol Med*)

  → trial-and-error treatment strategy
  - ongoing assessments
  - careful monitoring of response and side-effects

    (Tandon et al, 2010, *Schizophr Res*)

- the challenge: to better understand the heterogeneity of outcome following a first-episode of psychosis
  → identify markers of remission

Remission in schizophrenia

PANSS

level : mild or less

1 Absent
2 Minimal
3 Mild
4 Moderate
5 Moderately Severe
6 Severe
7 Extreme

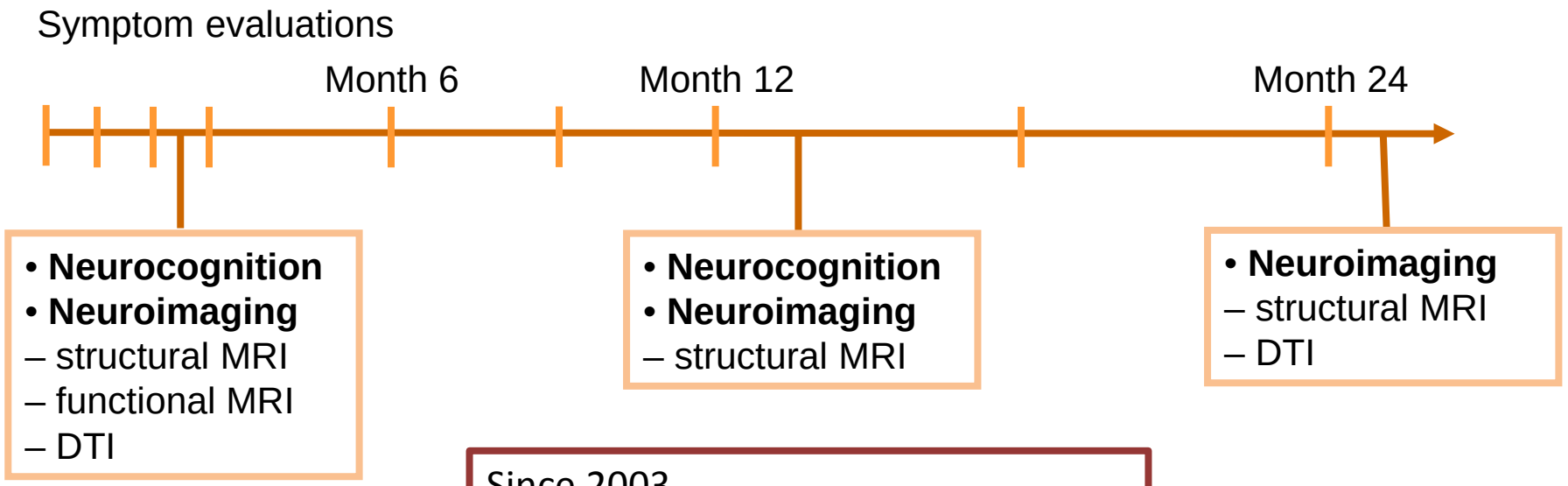
(Andreasen et al, 2005, *Am J Psychiatry*)

on all 8 core symptoms

- delusions
- hallucinatory behavior
- unusual thought content
- blunted affect
- passive or apathetic social withdrawal
- lack of spontaneity & flow of conversation
- mannerisms & posturing
- conceptual disorganization

sustained for at least 6 months

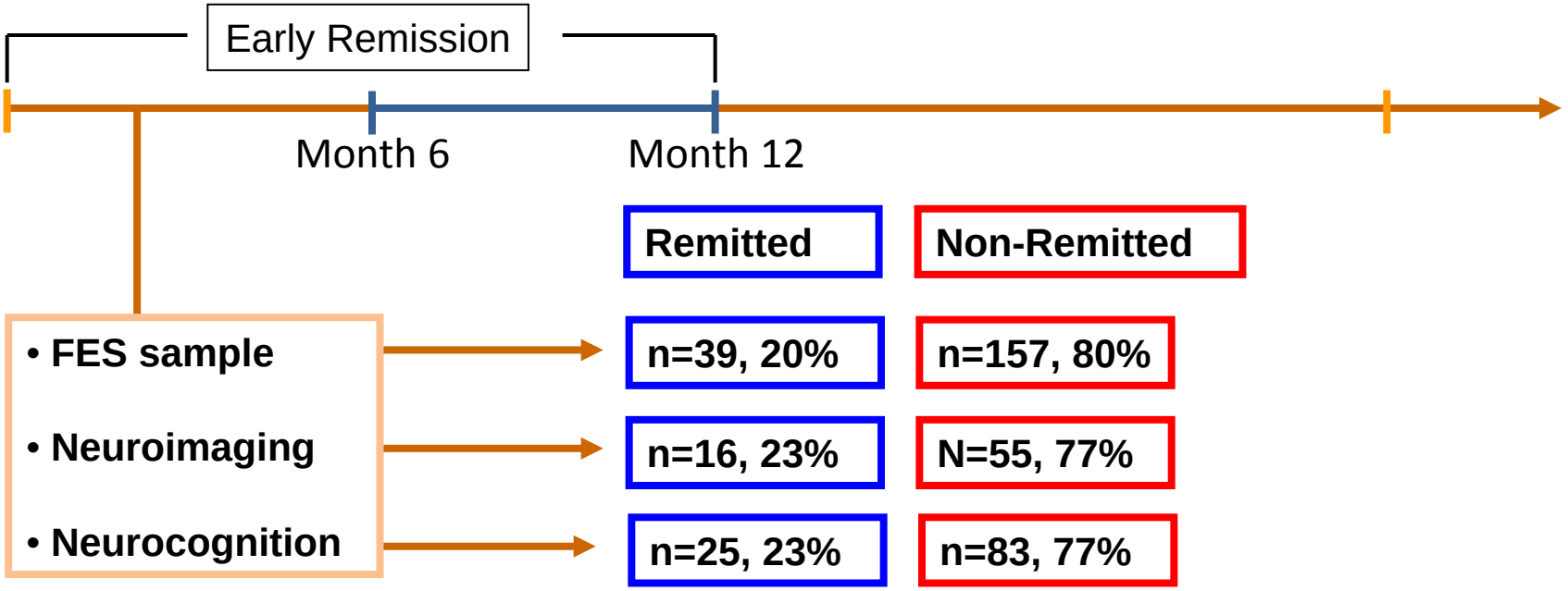
Data Collection



Since 2003
- 500+ clients treated

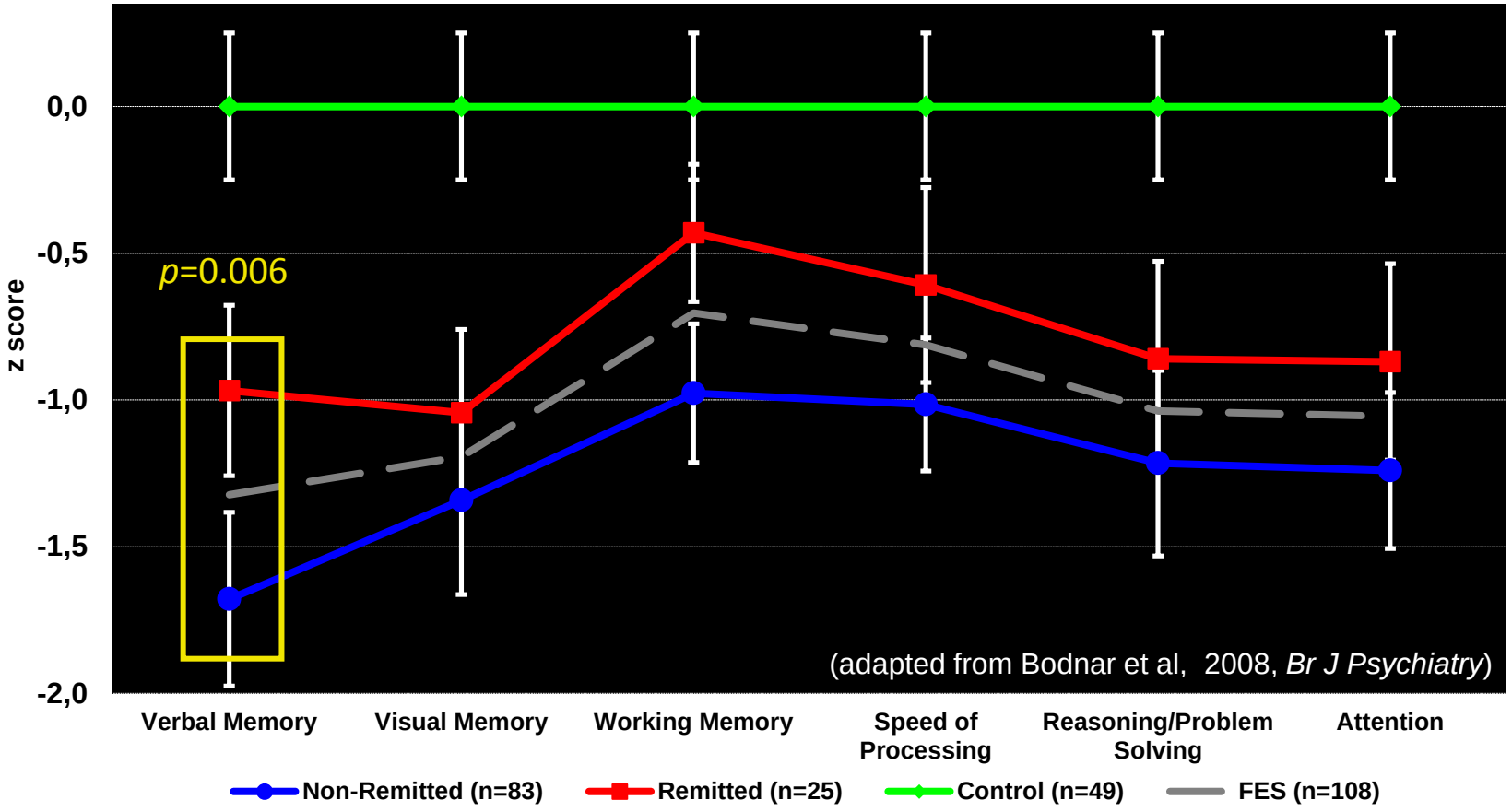
Since 2004
- sMRI: 135 initial, 68 fup1, & 47 fup2

Remission Rates



- Percentages in line with other studies (Emsley et al, 2011, *Curr Opin Psychiatry*)
  – rates varied from 19% to 88%

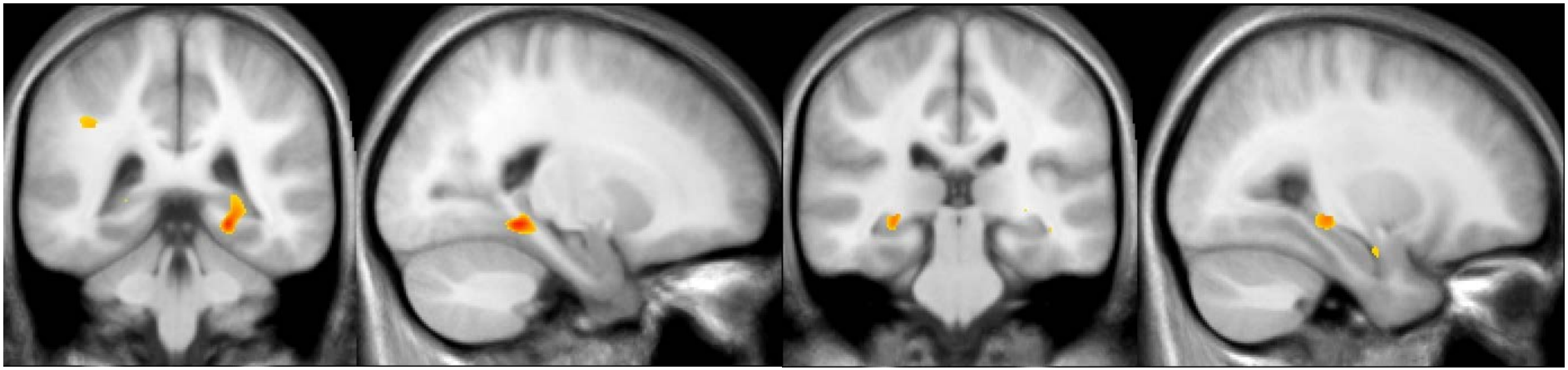
Neurocognition



MATRICS – Measurement and Treatment Research to Improve Cognition in Schizophrenia (Nuechterlein et al, 2004, *Schizophr Res*)

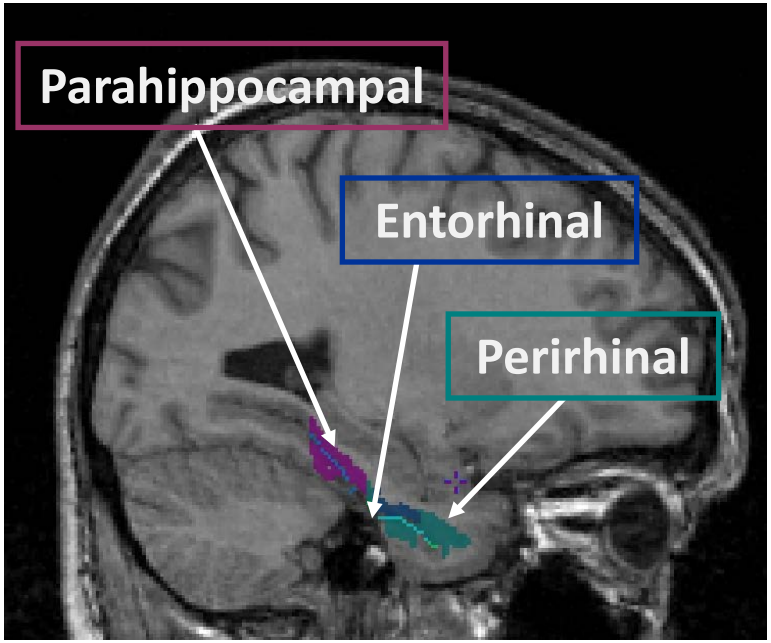
Automated whole-brain analysis (VBM8)

right parahippocampal gyrus **left hippocampus**

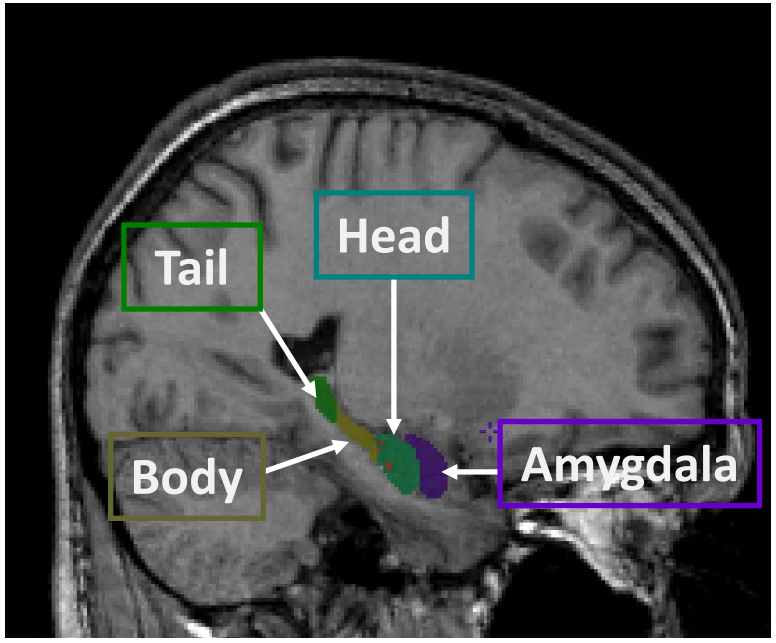


Areas with lower grey matter in non-remitted (n=41) compared to remitted (n=17) (p<0.001, uncorrected)
(adapted from Bodnar et al, 2011, *Clin Schizophr Related Psychoses*)

Parahippocampus & Hippocampus

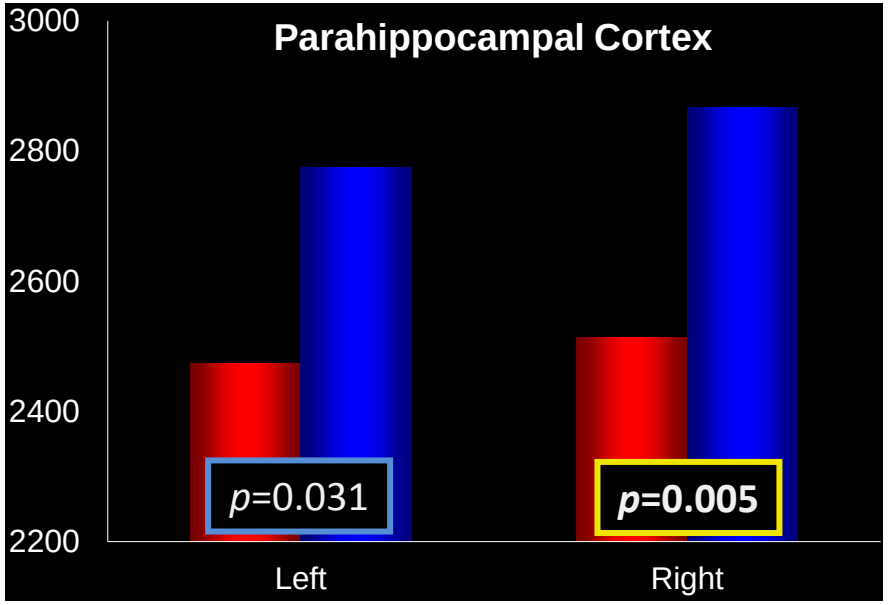


(Pruessner et al, 2002, *Cereb Cortex*)

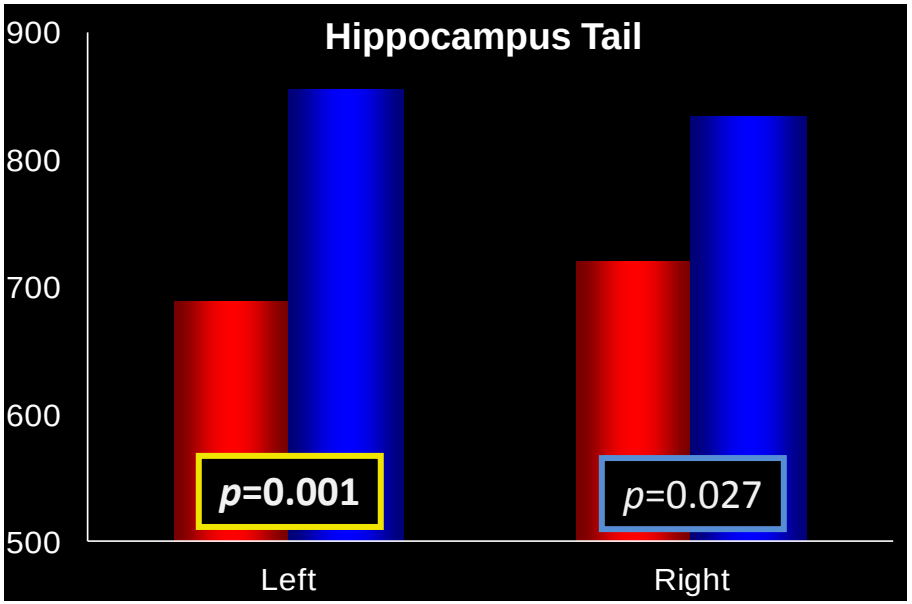


(Pruessner et al, 2000, *Cereb Cortex*)
(Bodnar et al, 2010, *Schizophr Res*)

Verifying the VBM results...



(adapted from Bodnar et al, 2012, *Psychiatry Res*)



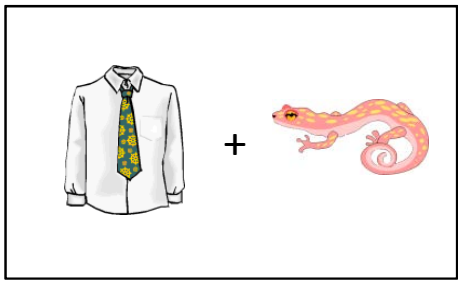
(adapted from Bodnar et al, 2010, *Schizophr Res*)

Correlation, Right Side
Social Withdrawal: -0.351, *p*=0.008
Verbal Memory: 0.349, *p*=0.009

There were no significant or trend-level correlations.

Non-Remitted (n=41) Remitted (n=17)

fMRI Behavioral Task



Which one is bigger?

Encoding Strategy

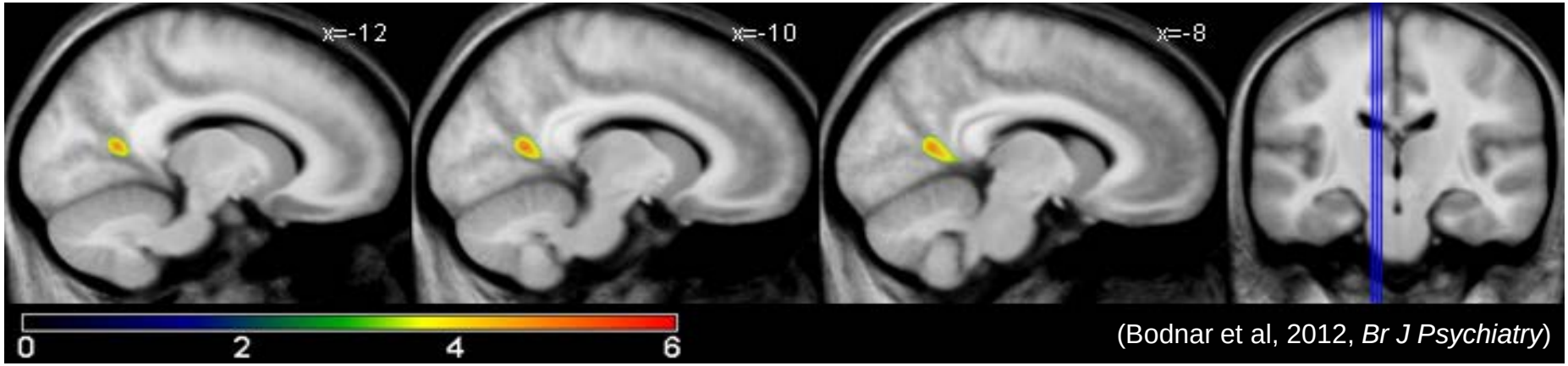
	Associative	Item-Oriented
Related	Associative-related	Item-related
Unrelated	Associative-unrelated	Item-unrelated

Semantic Relatedness

(Achim et al, 2007, *JAMA Psychiatry*)

2x2 design

Related > Unrelated: Non-Remitted > Remitted



(Bodnar et al, 2012, *Br J Psychiatry*)

Posterior cingulate in schizophrenia:

- remains overactive when mentally engaged
  (Garrity et al, 2007, *Am J Psychiatry*; Meda et al, 2009, *PLoS One*; Whitfield-Gabrieli et al, 2009, *Proc Natl Acad Sci USA*)

- hyper-activity → worse memory
  (Meda et al, 2009, *PLoS One*; Whitfield-Gabrieli et al, 2009, Proc Natl Acad Sci USA)

- PCC fails to "turn off" leading to over-sampling and unfocused attention → poorer memory (Broyd et al, 2009, *Neurosci Biobehav Rev*; Mannell et al, 2010, *Hum Brain Mapp*)

Non-Remitted Remitted

Summary of results

• Non-Remitted:
– poorer verbal memory
– smaller hippocampus tail & parahippocampal cortex
– abnormal activity in posterior cingulate

• Posterior memory-related neural network differences between remitted & non-remitted FES patients

• Markers identified may be related to either positive or negative symptoms or both

Conclusions & Future Directions

• A better understanding of clinical outcome and of schizophrenia

• Highlight specific areas for future clinical research – developing newer, target-specific treatments

• Negative (and positive) symptoms should be explored in further detail to determine specificity of markers related to remission

Thank you

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– Dr. Philippe-Olivier Harvey

- Dr. Martin Lepage

All of the clients and especially those who have kindly given their time to take part in our research.

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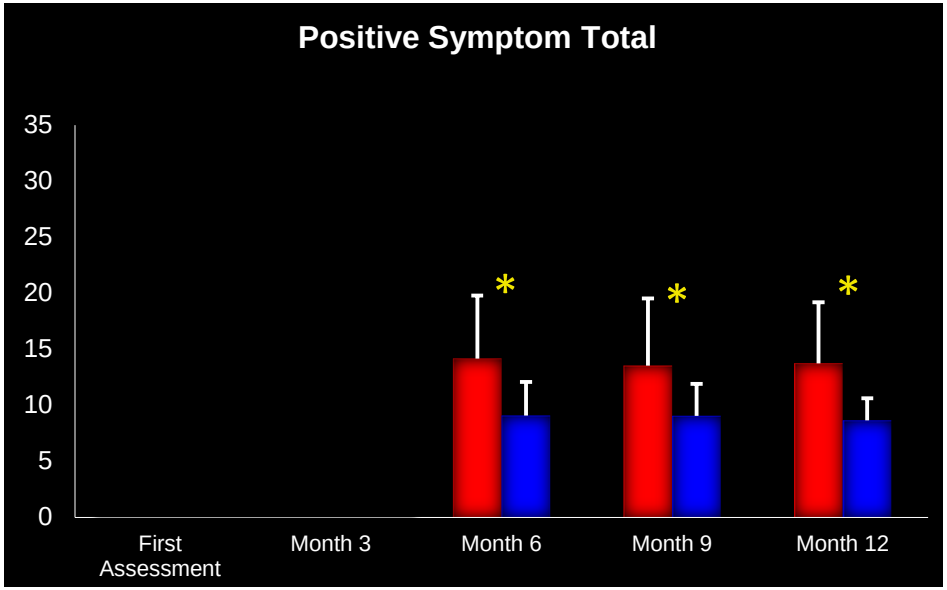
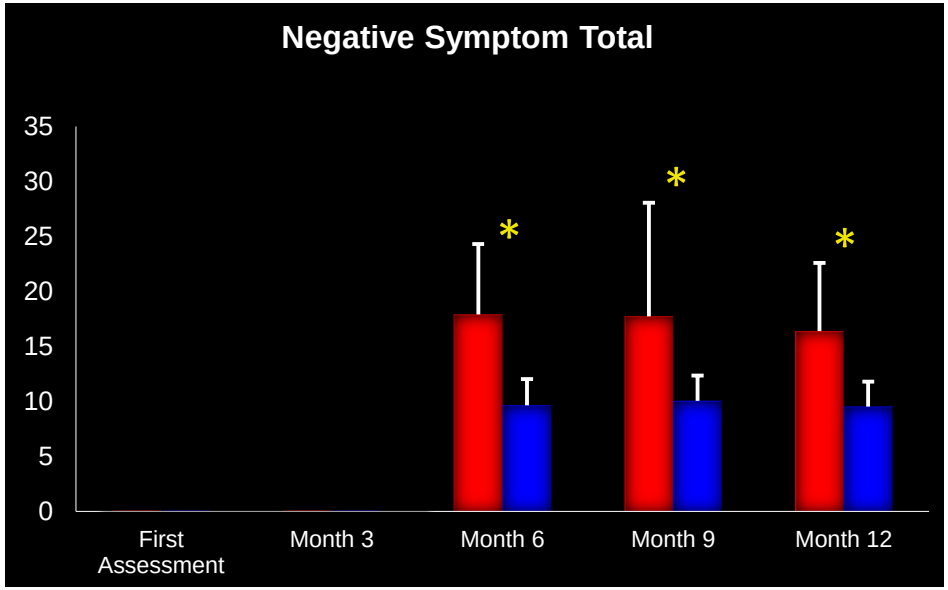
Symptomatic profiles





* p<0.01 * p<0.001

Non-Remitted (n=83)
Remitted (n=25)

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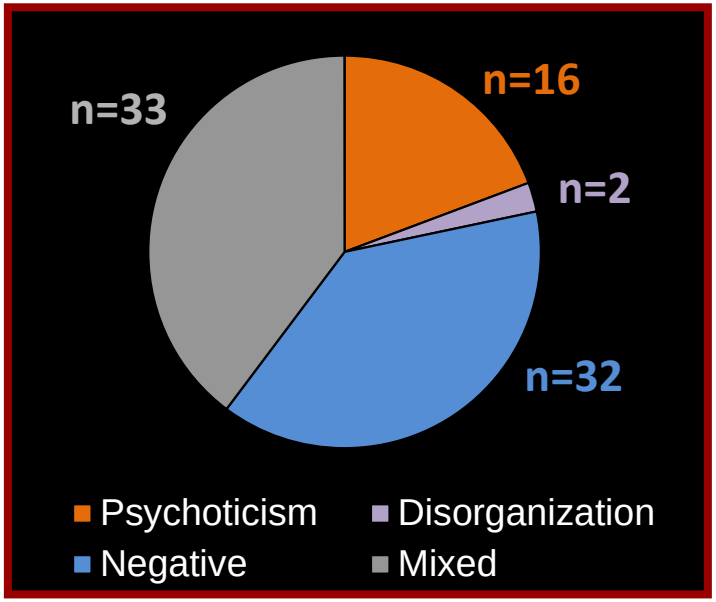
Negative symptoms in remission

Non-Remitted

n=83, 77%



Correlation:

Parahippocampal Cortex and Social Withdrawal

Right, -0.351, *p*=0.008
Left, -0.297, *p*=0.026

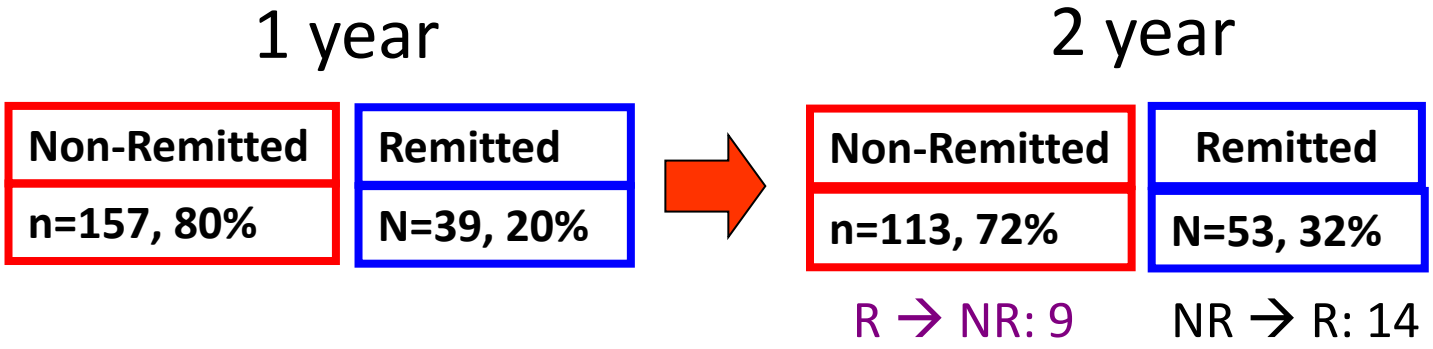
Individual symptoms for not achieving remission:

1 – delusions; 3 – hallucinations

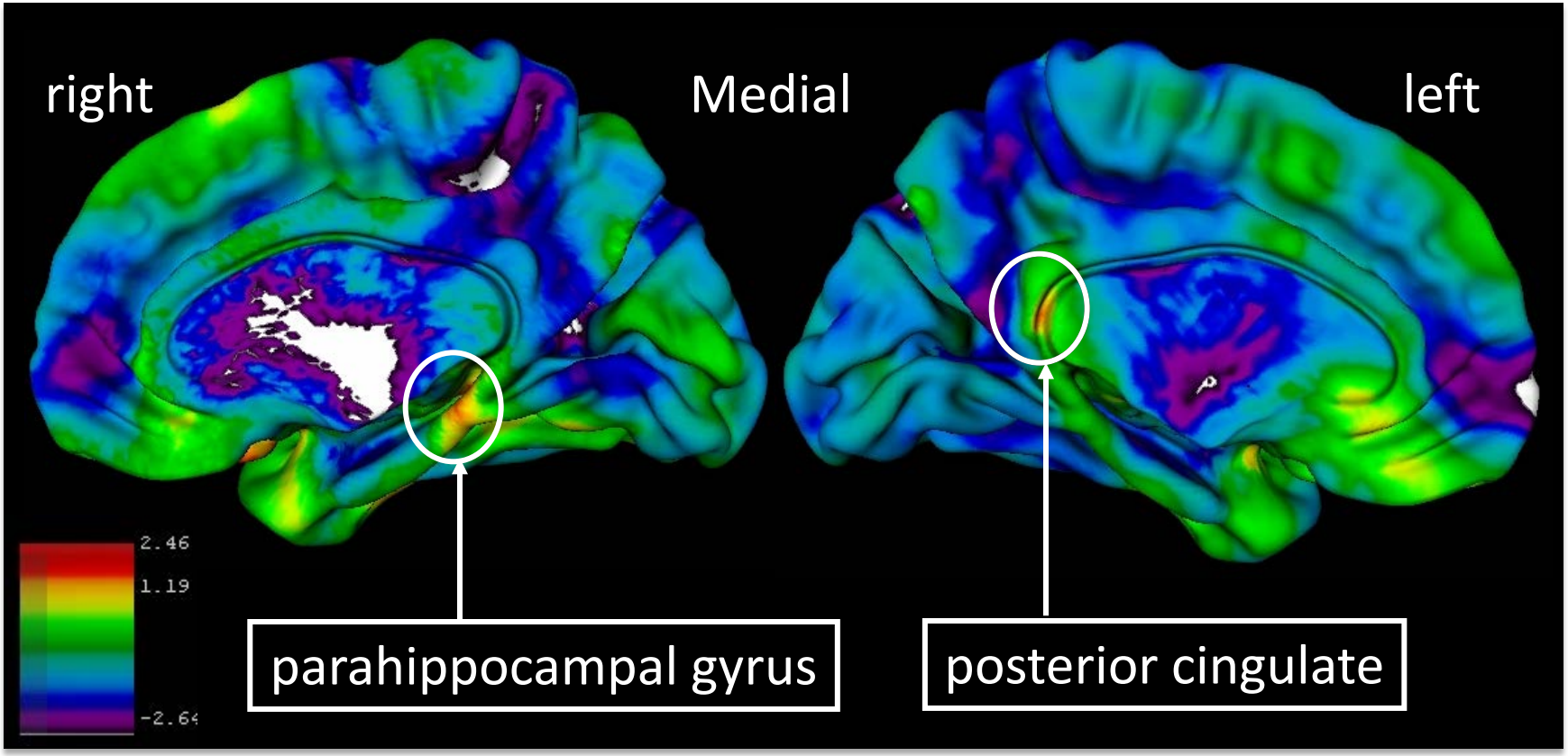
2 – conceptual disorganization

7 – blunted affect; 12 – social withdrawal; 2 – lack of spontaneity

Remitted vs. Non-Remitted



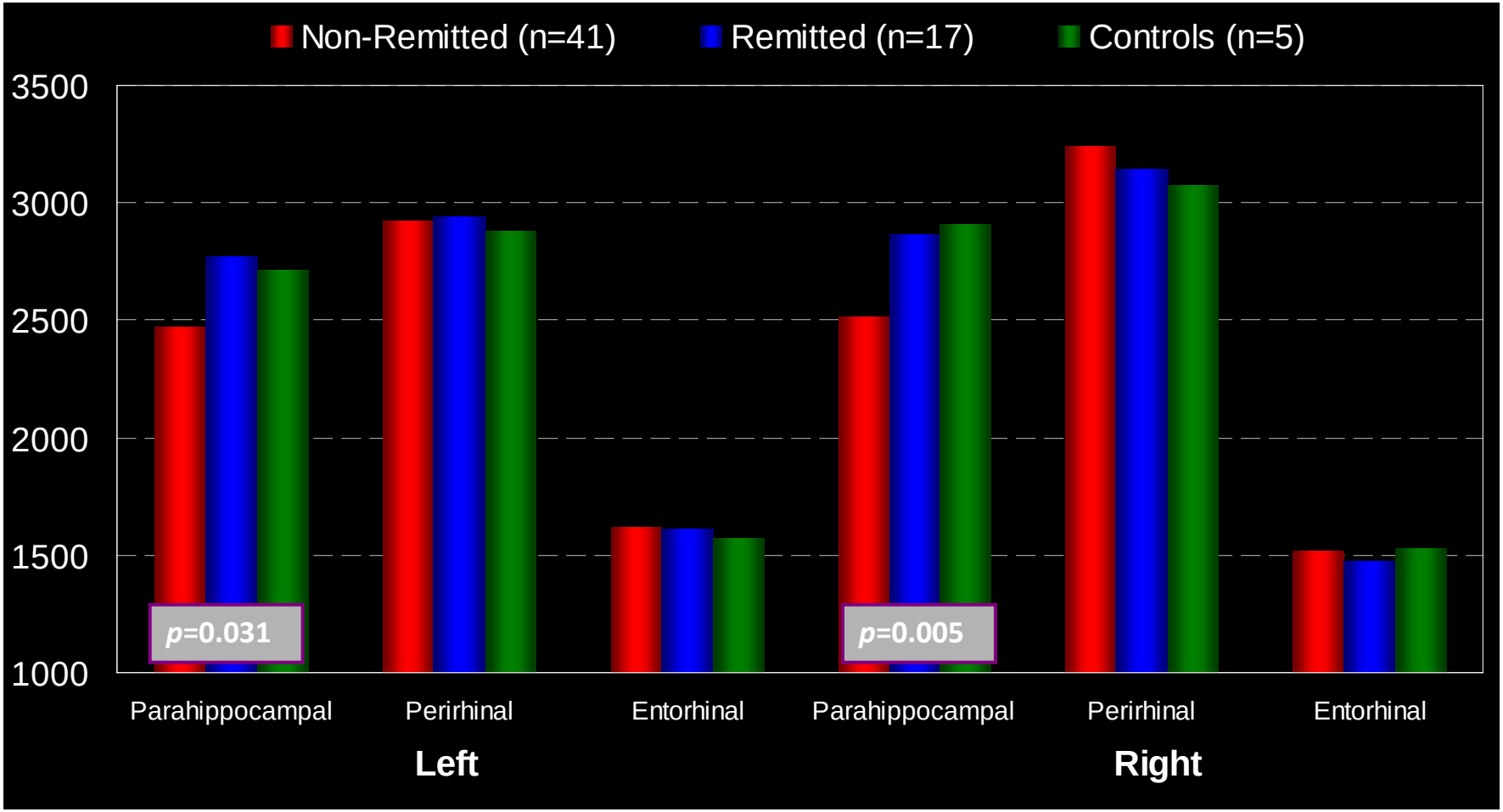
Cortical Thickness



Red = areas with less thickness in non-remitted ($p<0.01$, corrected)

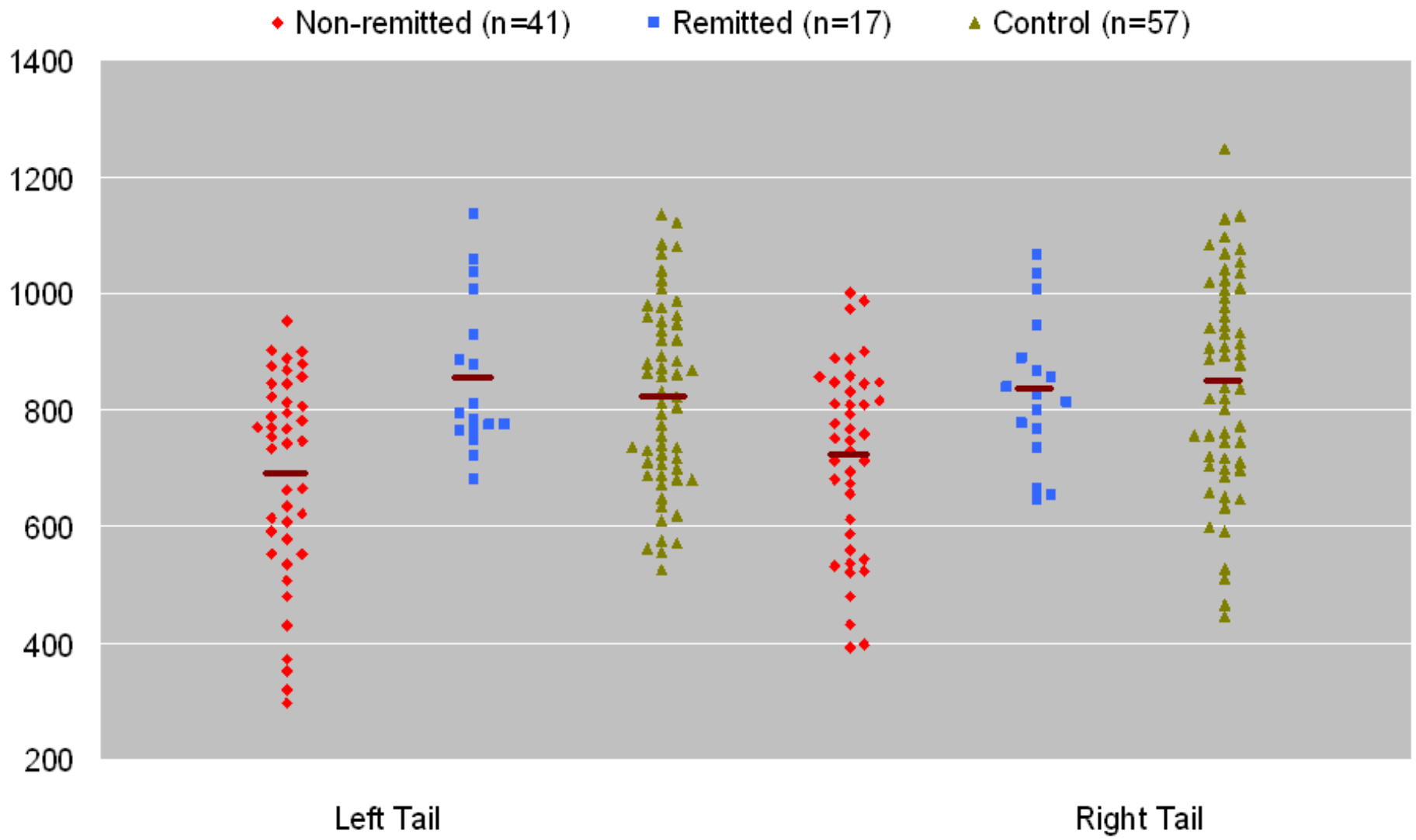
56 FES: 39 non-remitted & 17 remitted

Parahippocampal Gyrus

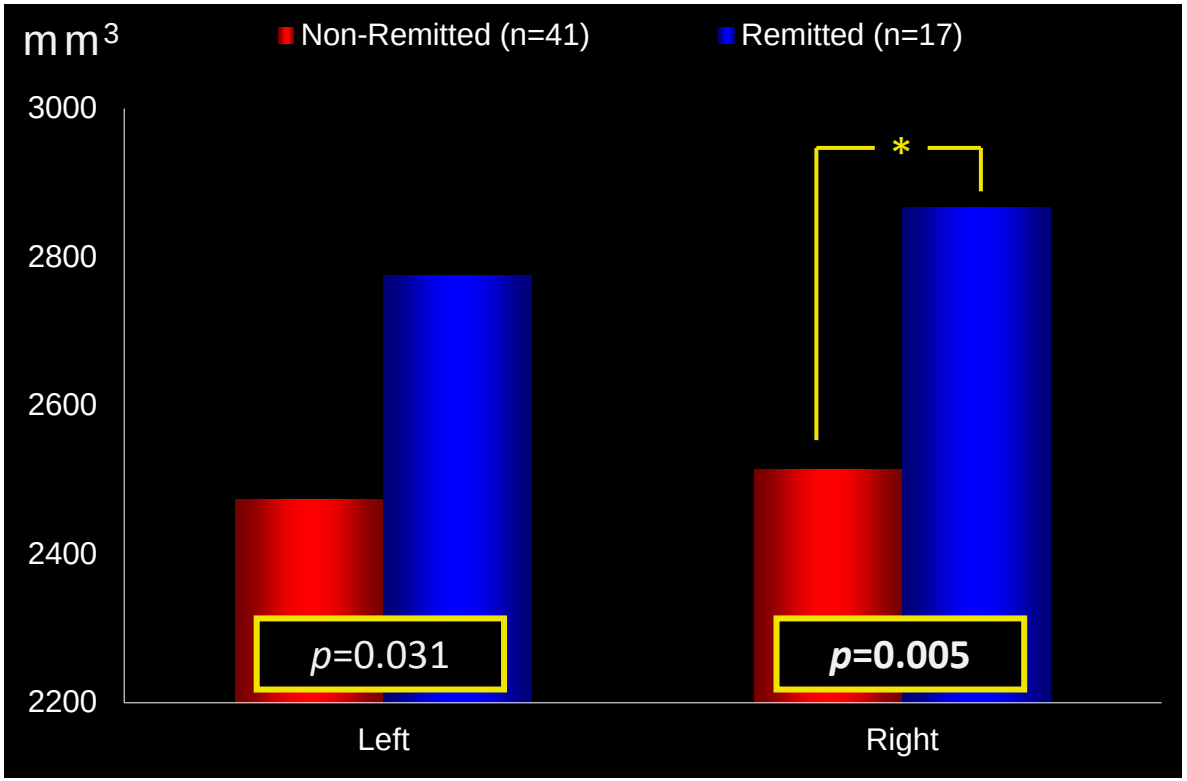


Comparison between non-remitted and remitted patients only.
No significant [group x region x side] interaction: F=0.36, df=2,54, *p*=0.70

Hippocampus Tail



Parahippocampal Cortex



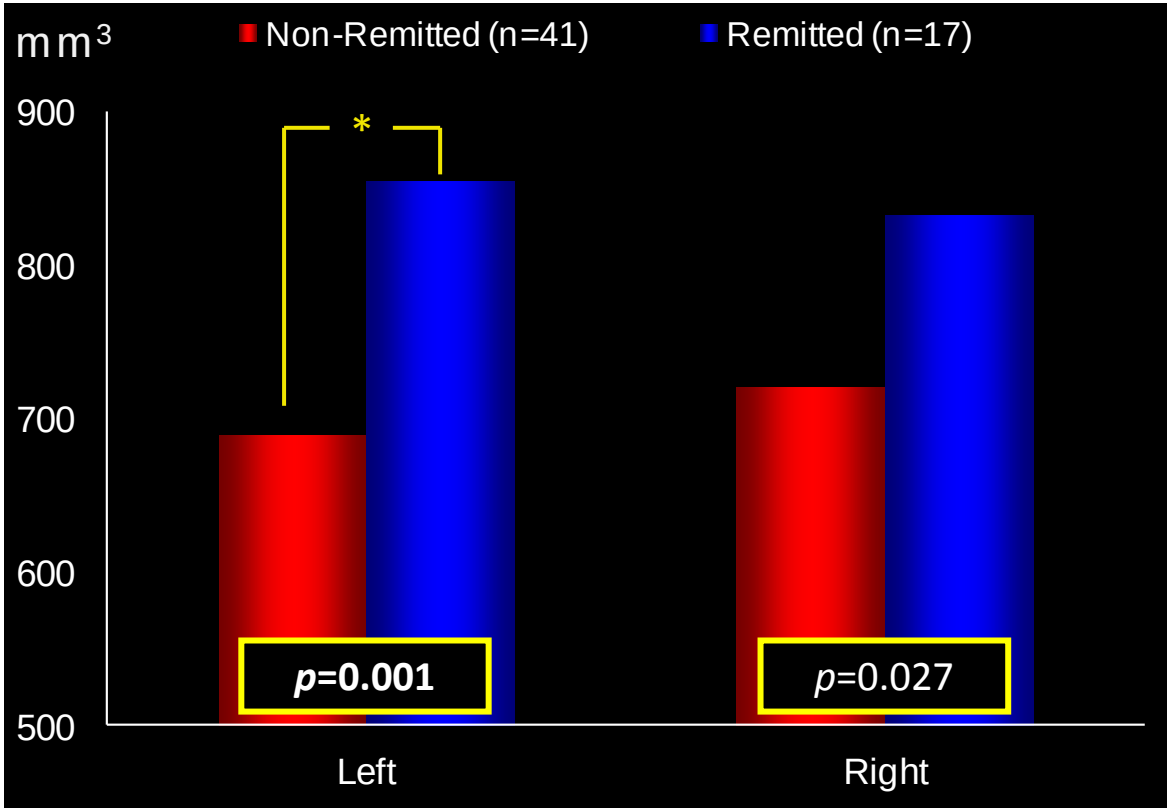
Correlation:

Social Withdrawal
Right, -0.351, *p*=0.008
Left, -0.297, *p*=0.026

No significant differences in entorhinal or perirhinal cortices

(adapted from Bodnar et al, 2012, *Psychiatry Res*)

Hippocampus Tail

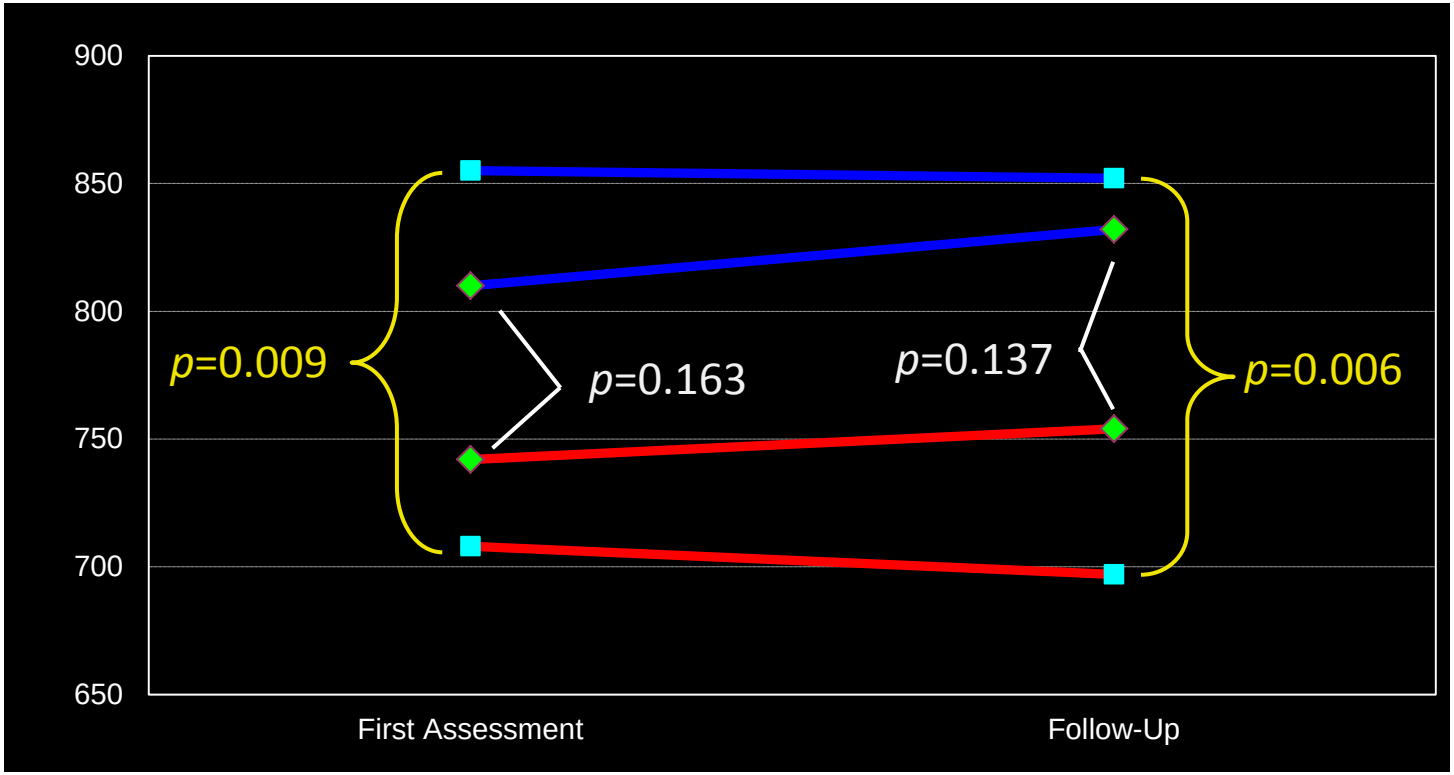


(adapted from Bodnar et al, 2010, *Schizophr Res*)

No significant correlations

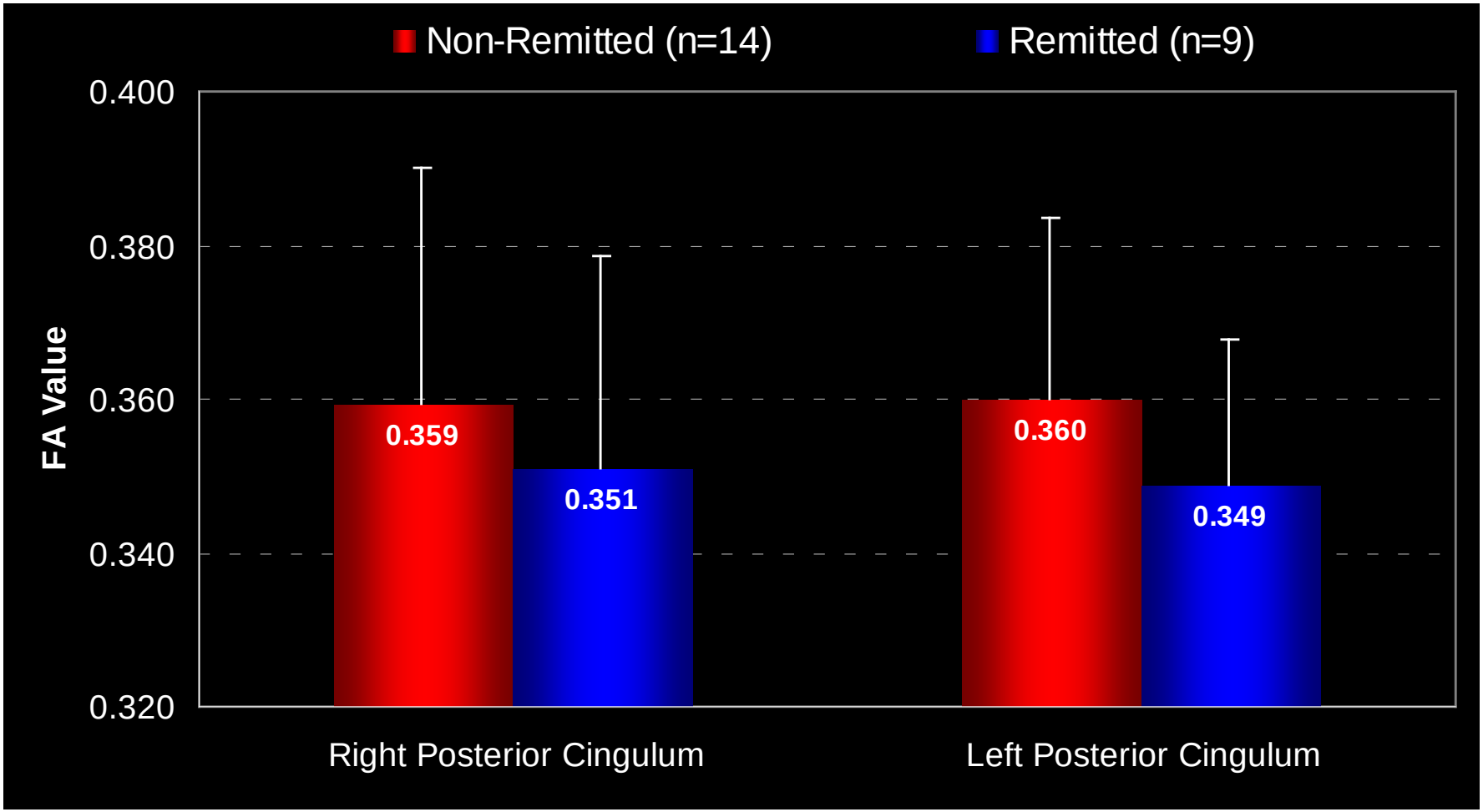
No significant differences in body or head subregions or amygdala

Hippocampus Tail – 1 year follow-up



Left
Right
Non-Remitted (n=26)
Remitted (n=12)

DTI: posterior cingulum bundle



posterior cingulum bundle: hippocampus to cingulate

Defining remission

• Consensus definition of remission in schizophrenia published in 2005 (Andreasen et al, *Am J Psychiatry,* 2005, 162:441-449).

•Measured with PANSS, SAPS & SANS, or BPRS & SANS.

• Easily implemented in clinical trials and clinical practice.

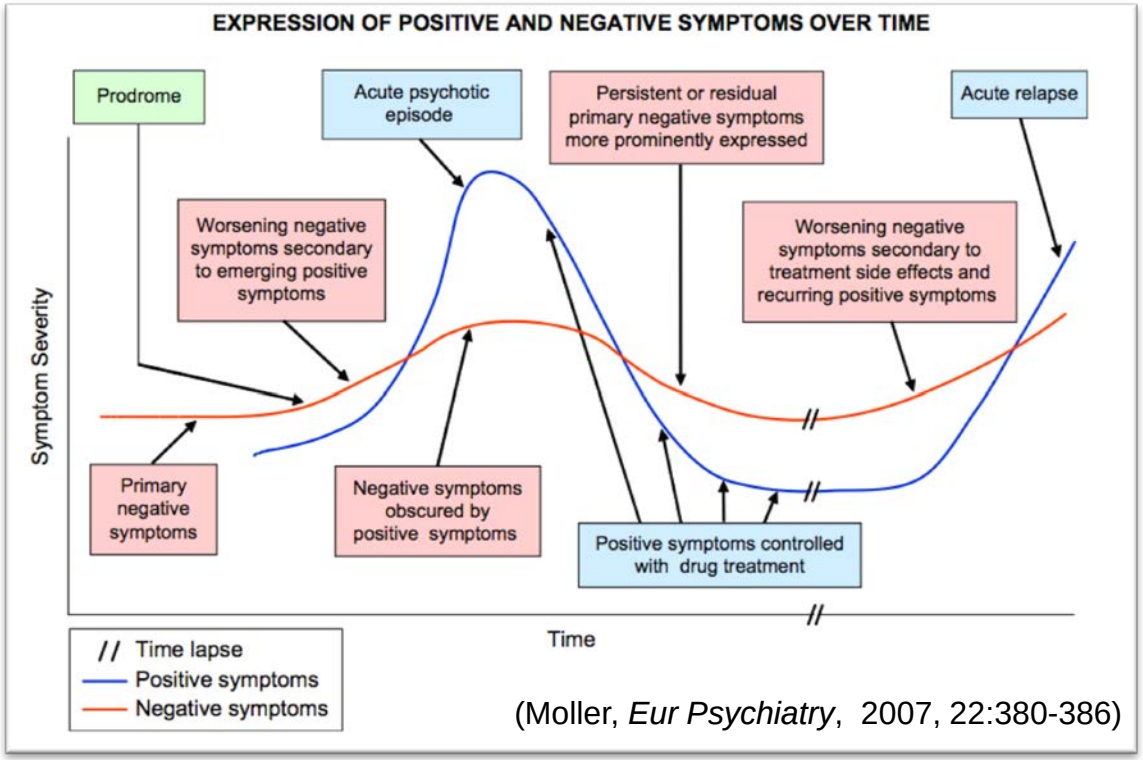
• Can easily and directly compare studies of outcome and across cultures.

Table 1. Proposed remission criteria and relationship to diagnostic criteria

Diagnostic criteria	Remission criteria
DSM-IV (at least 2 are present)	PANSS items (score 3 or less on all items)
Delusions	P1. Delusions
	G9. Unusual thought content
Hallucinations	P3. Hallucinatory behaviour
Disorganized speech	P2. Conceptual disorganization
Grossly disorganized or catatonic behaviour	G5. Mannerisms/posturing
Negative symptoms	N1. Blunted affect
	N4. Passive/apathetic social withdrawal
	N6. Lack of spontaneity and flow of conversation

(van OS et al, *Acta Psychiatr Scand,* 2006, 113:91-95).

Defining remission



(Moller, *Eur Psychiatry*, 2007, 22:380-386)

- Negative symptoms equally important:
  – higher baseline levels related to a poorer outcome (White et al, *Psychol Med*, 2009, 39: 1447-1456)
  – necessary to properly assess remission (Cassidy et al, *Schizophr Bull*, 2010, 36: 1001-1008).

- 6-month time component as symptoms tend to fluctuate
  – 3-month equally valid (Cassidy et al, *Schizophr Bull*, 2010, 36: 1001-1008).