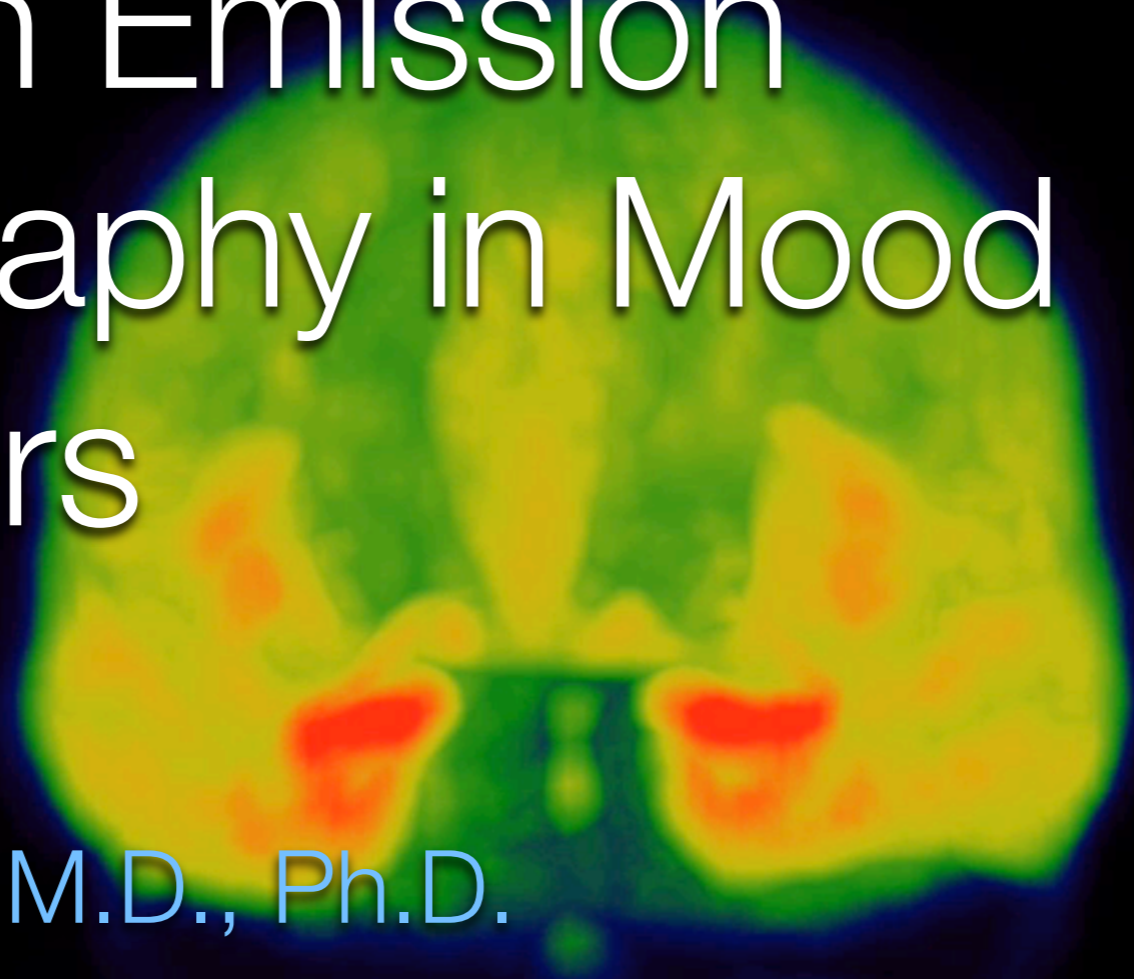




Positron Emission Tomography in Mood Disorders



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Director of PET Research

Stony Brook **Medicine**



DSM-IV-TR Criteria for Major Depressive Episode (MDE)

≥ 5 Symptoms in the same 2-week period

Sleep:	Insomnia or hypersomnia	Concentration:	Diminished ability to think or make decisions
Interest:	Depressed mood,* loss of interest or pleasure*	Appetite:	Weight loss or weight gain
Guilt:	Feelings of worthlessness	Psychomotor:	Psychomotor retardation or agitation
Energy:	Fatigue	Suicide:	Preoccupation with death

* Must include 1 of these

DSM-IV-TR. 2000.

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DSM-IV-TR. 2000.

2 patients may share only 1 symptom

1099 ways to meet criteria

Biomarkers

- Moderators: Identify on whom and under what circumstances treatments have different effects
- Mediators: Why and how treatments have effects
- Clinical need for ‘response endophenotypes’
- Research need for biomarker-stratified design

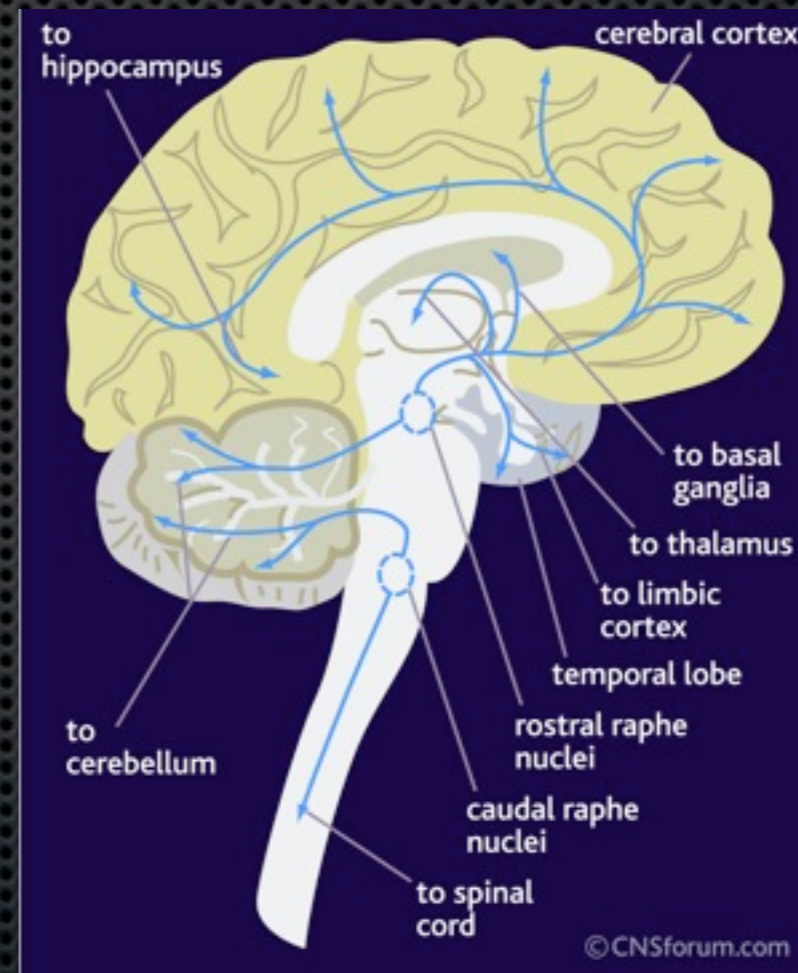
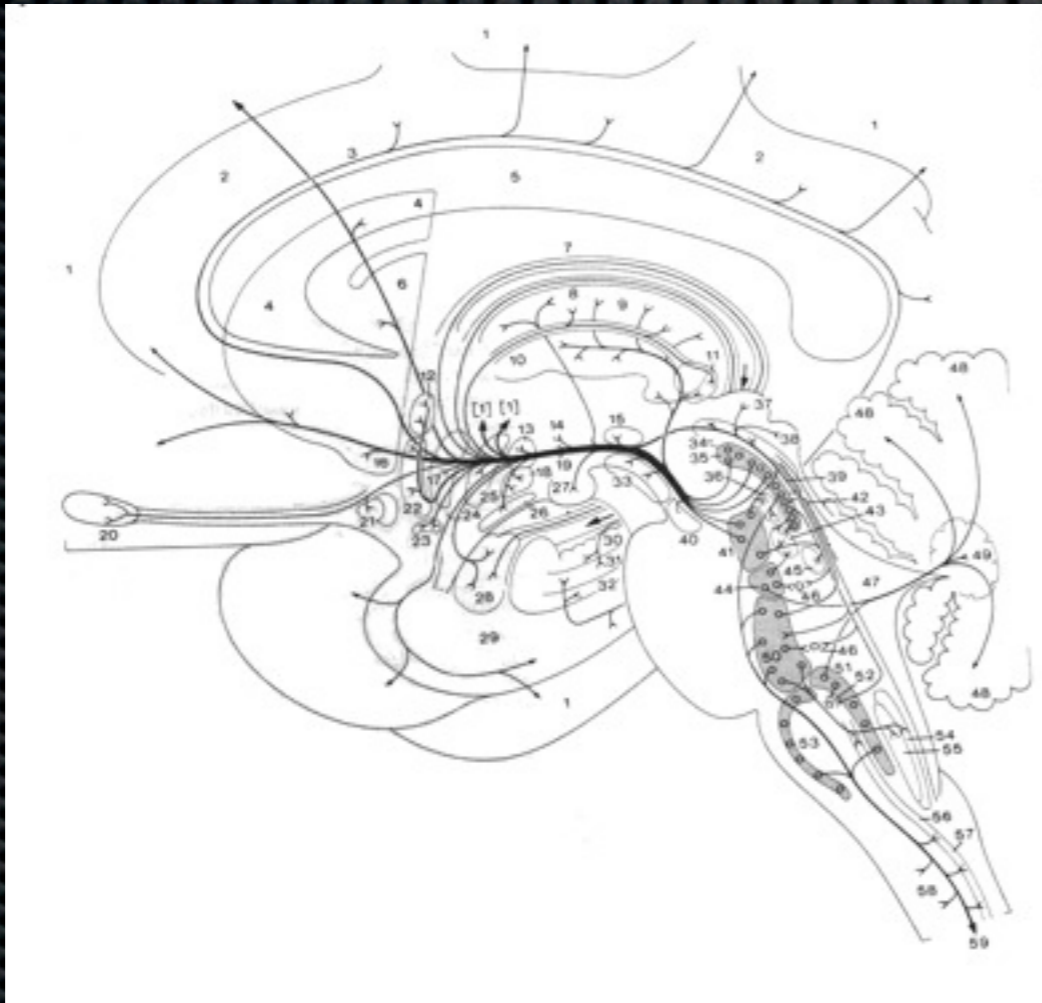
Impact of Depression

- ✦ 6-7% 12-month; **15-17% lifetime prevalence**
- ✦ Episodes can last **years**
- ✦ 50% **recurrence** after one episode, 70% after two, 90% after three
- ✦ **Morbidity** comparable to angina and advanced CAD
- ✦ By 2020 MDD will be the second most common cause of **disability** worldwide. Number 1 for those under 45. (WHO)
- ✦ High **mortality** from:
 - ✦ 15% will commit **suicide**
 - ✦ Risk of **death** (all causes) greater in MDD (1.58 to 2.07)
- ✦ Total annual **cost** – \$48 billion/unipolar (\$29 billion/bipolar)
 - ✦ 55% due to lost productivity: days lost per year 27.2/unipolar (65.5/bipolar)

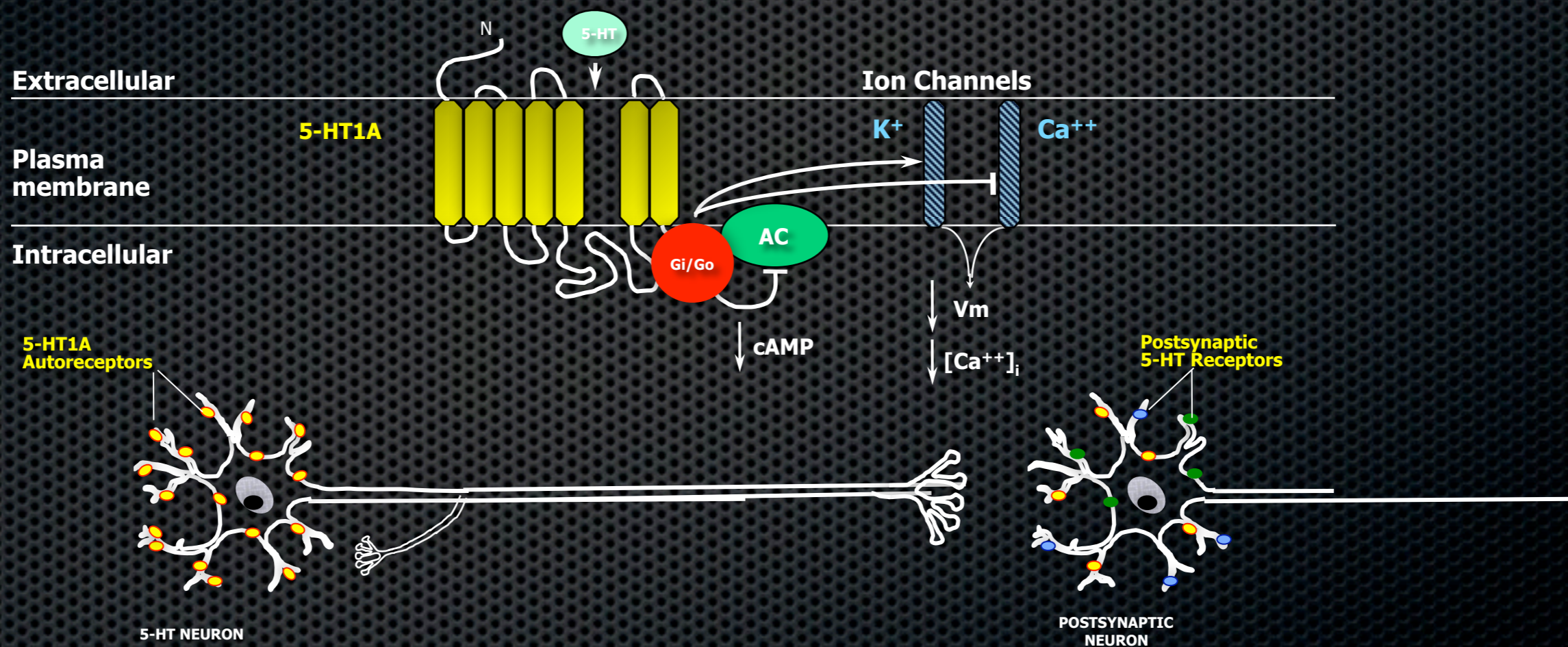
Why Study Depression?

- 50-60% response rate
- 20%-35% remission rate
- No tools to allow selection of pharmacological treatments based on the likelihood of response in individuals
- Reduce stigma/barriers to treatment

The Serotonin System



5-HT_{1A} Receptor



Higher Serotonin 1A in Depression

- Old Controls (n=42)
- New Controls (n=9)
- NRM 1 (n=8)
- NRM 2 (n=22)
- NRM (n=15)

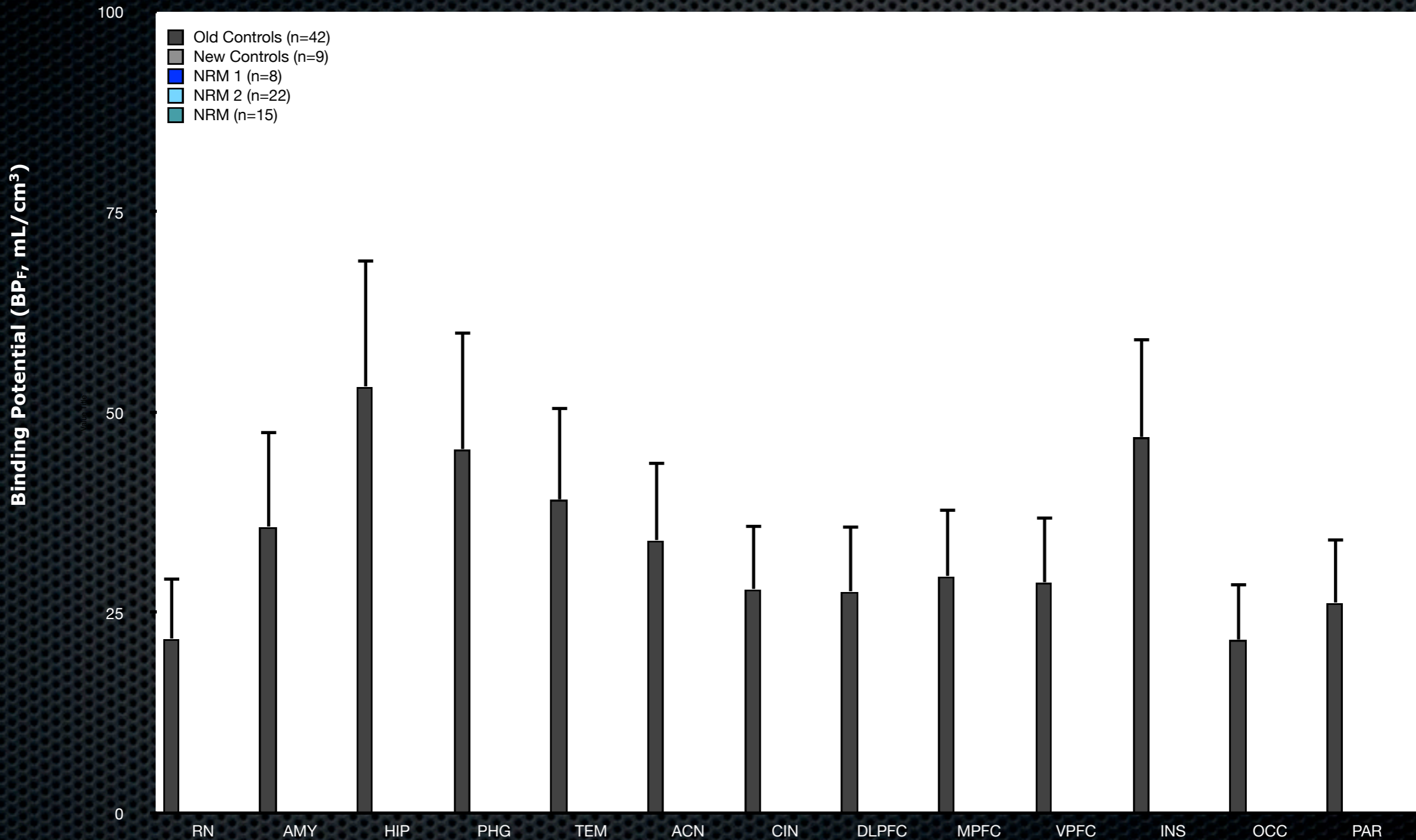
Binding Potential (BP_F, mL/cm³)

Higher Serotonin 1A in Depression



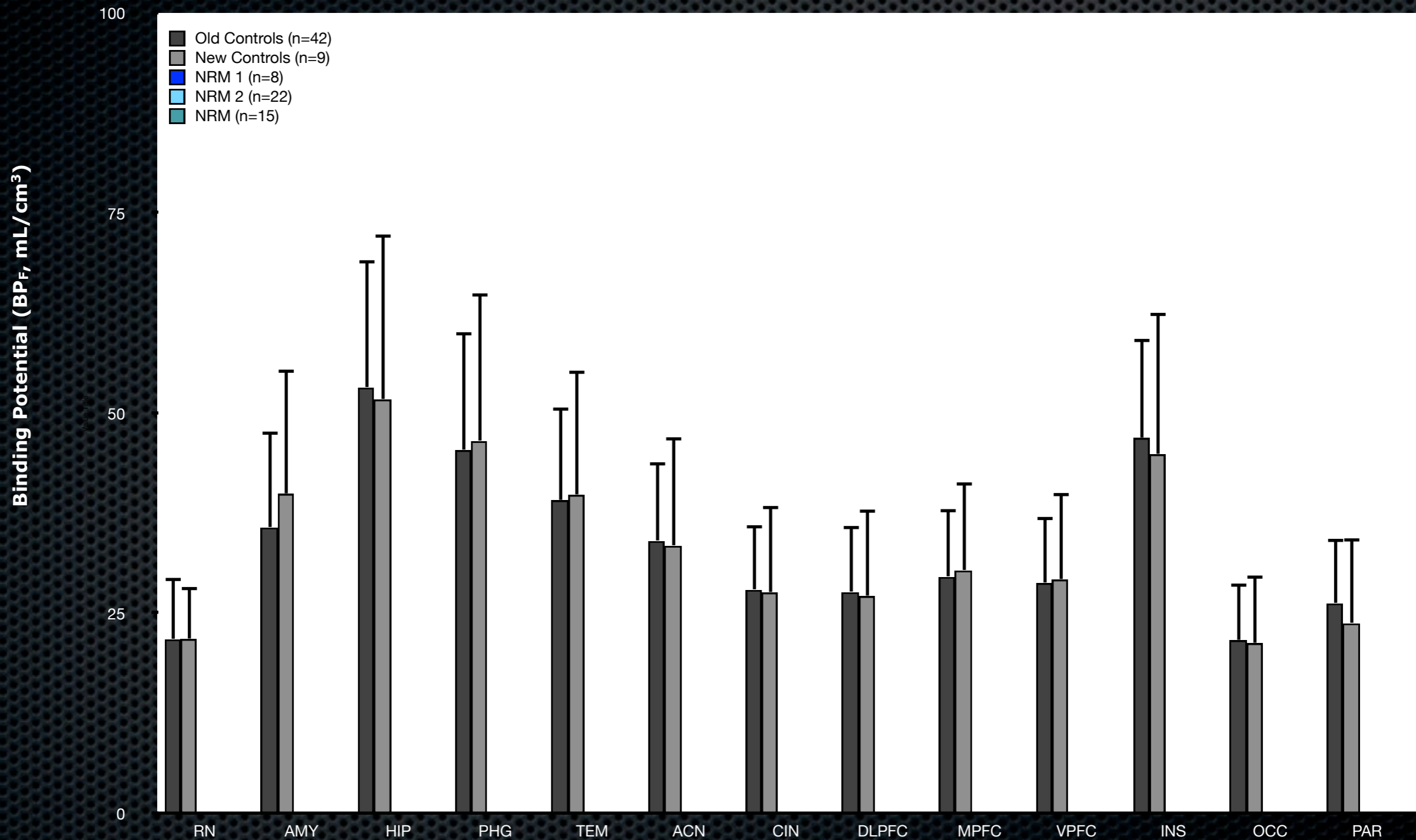
Parsey 2006, Parsey 2010, Miller, in press

Higher Serotonin 1A in Depression



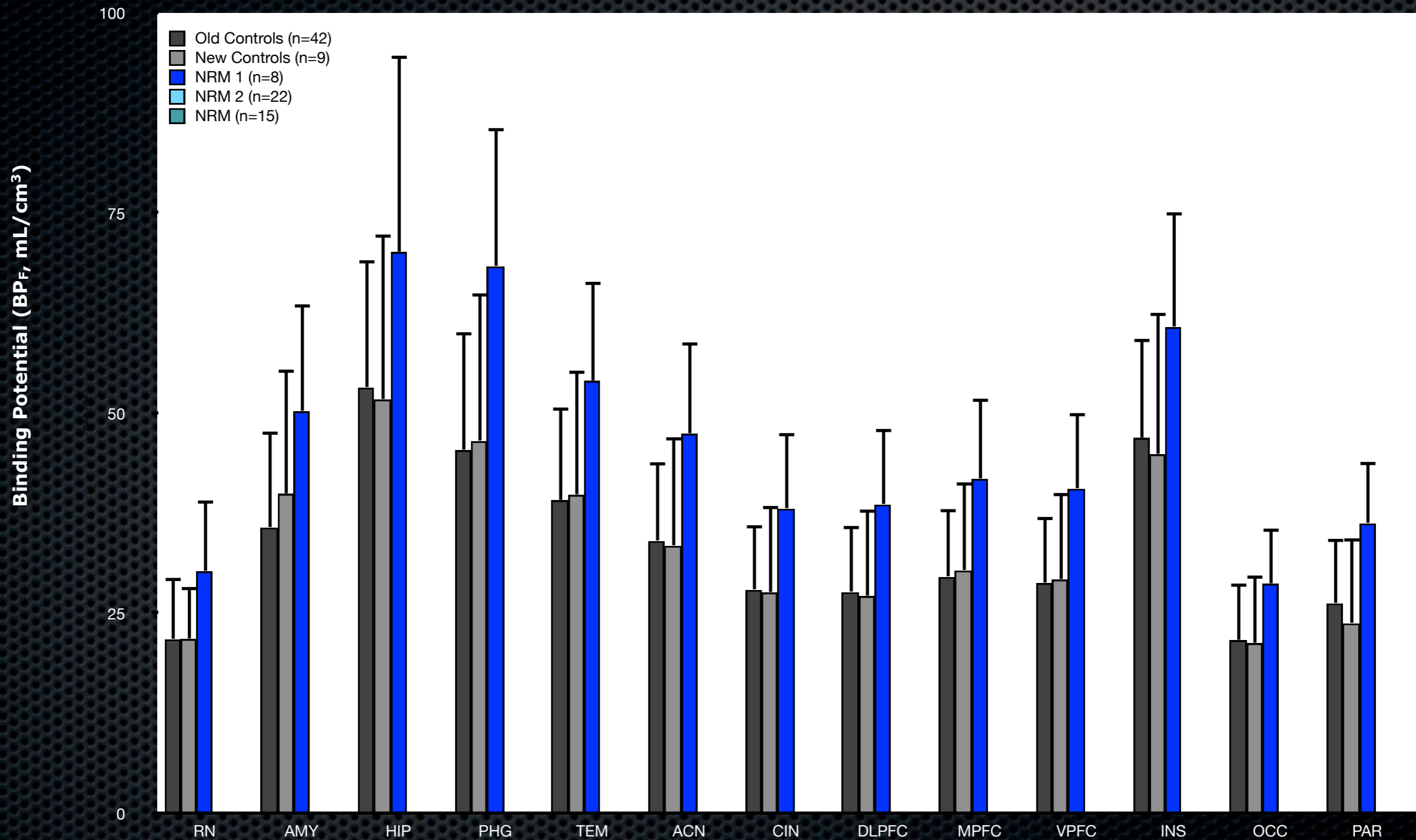
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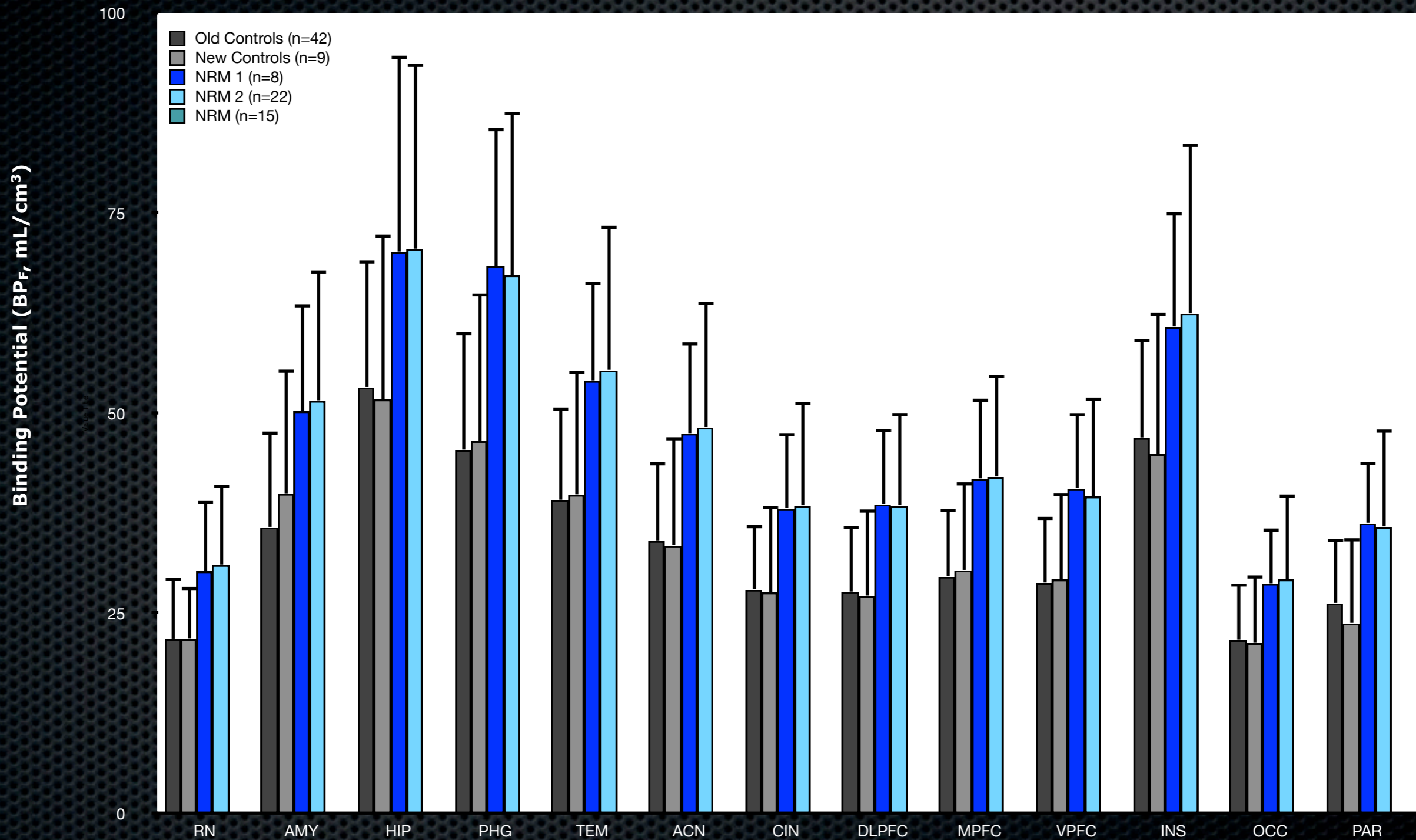
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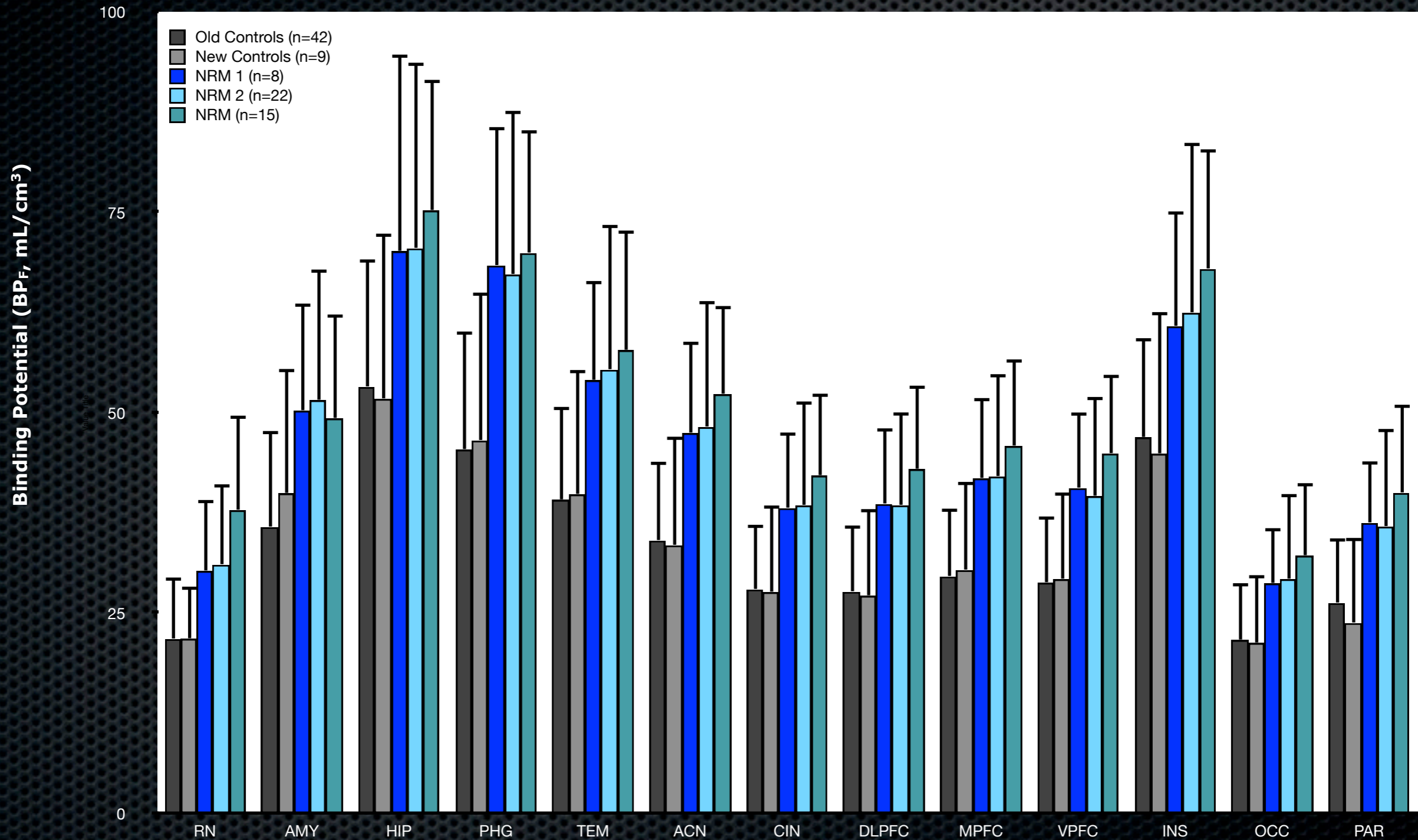
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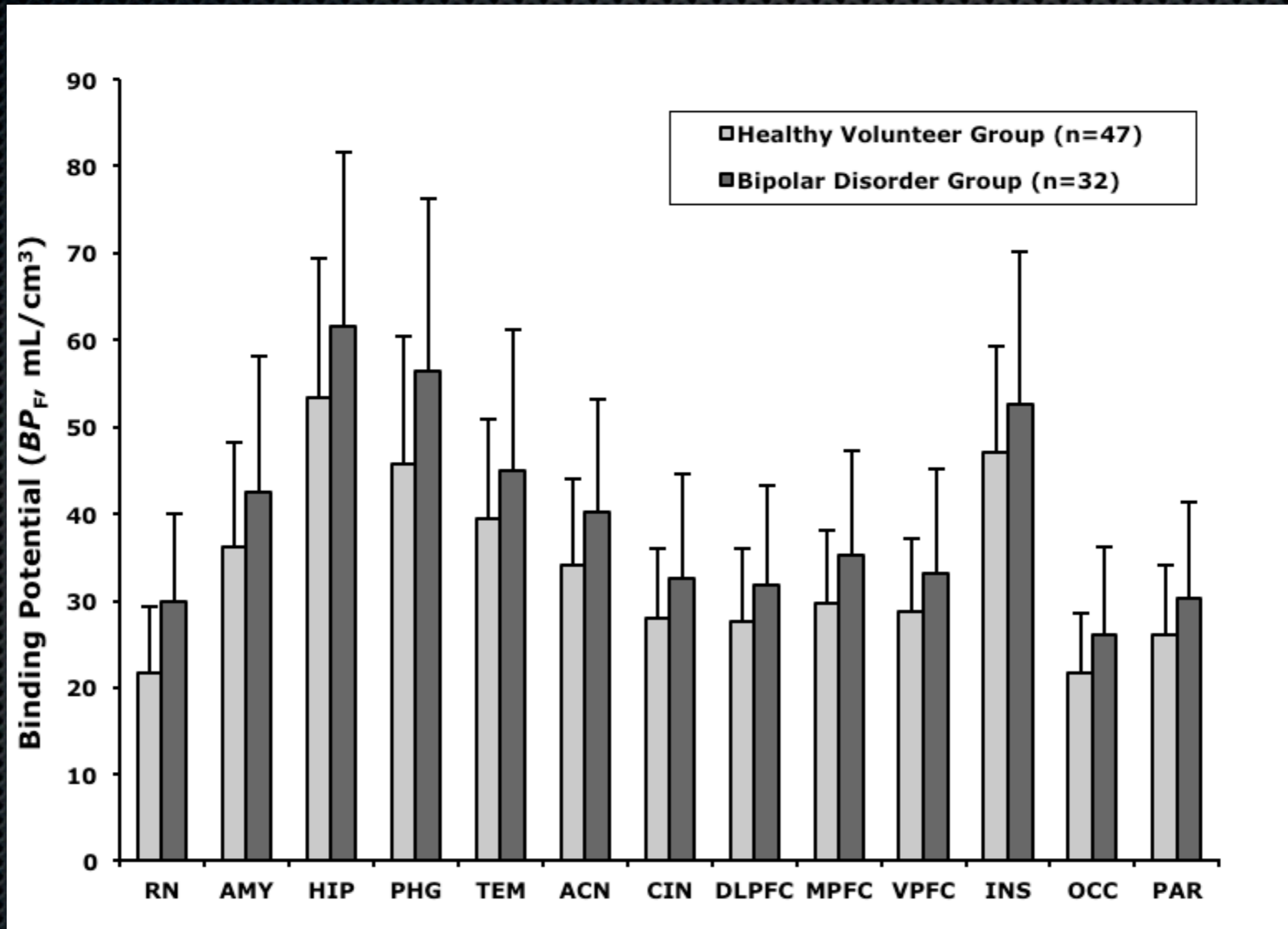
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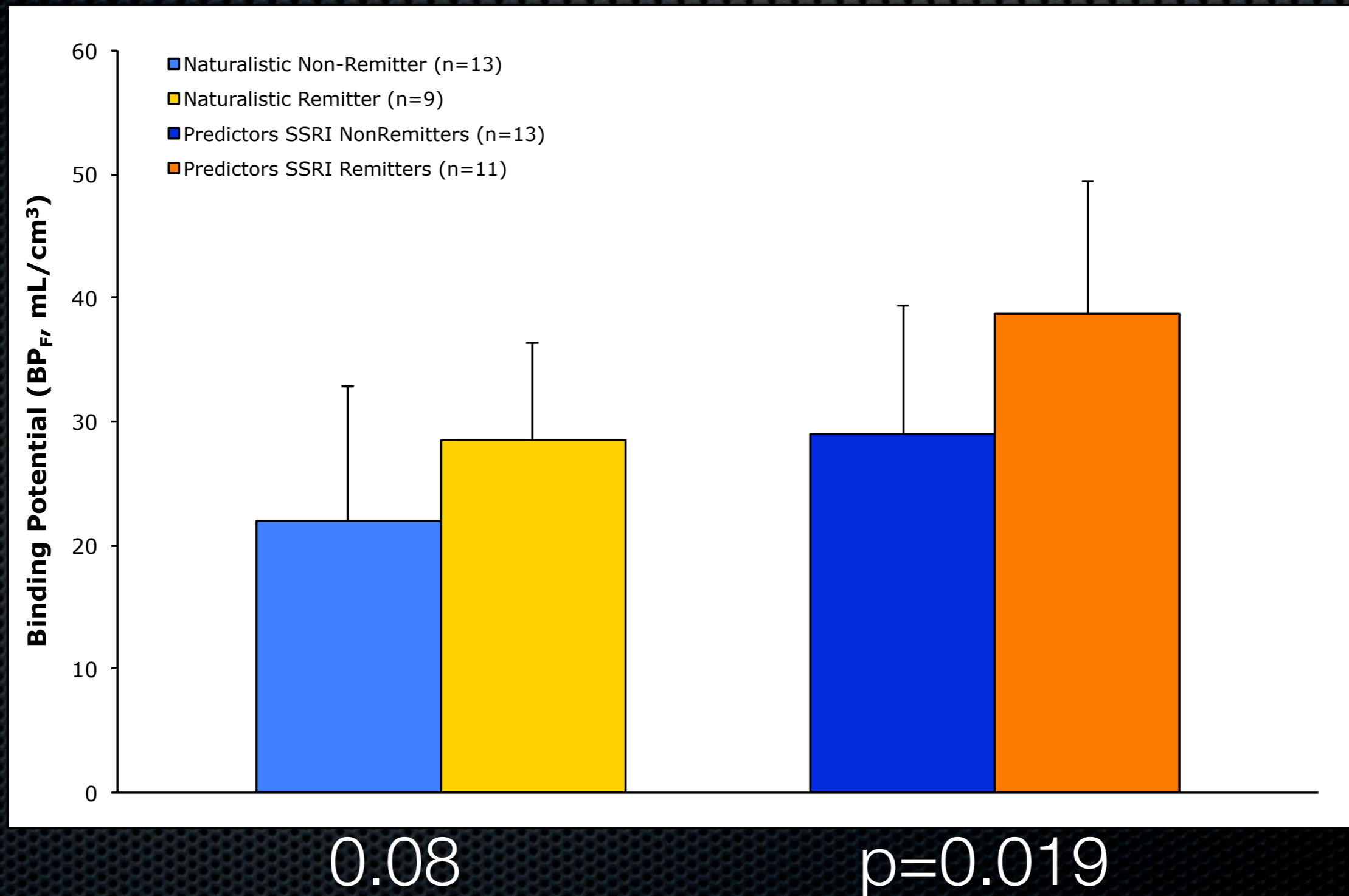


Parsey 2006, Parsey 2010, Miller, in press

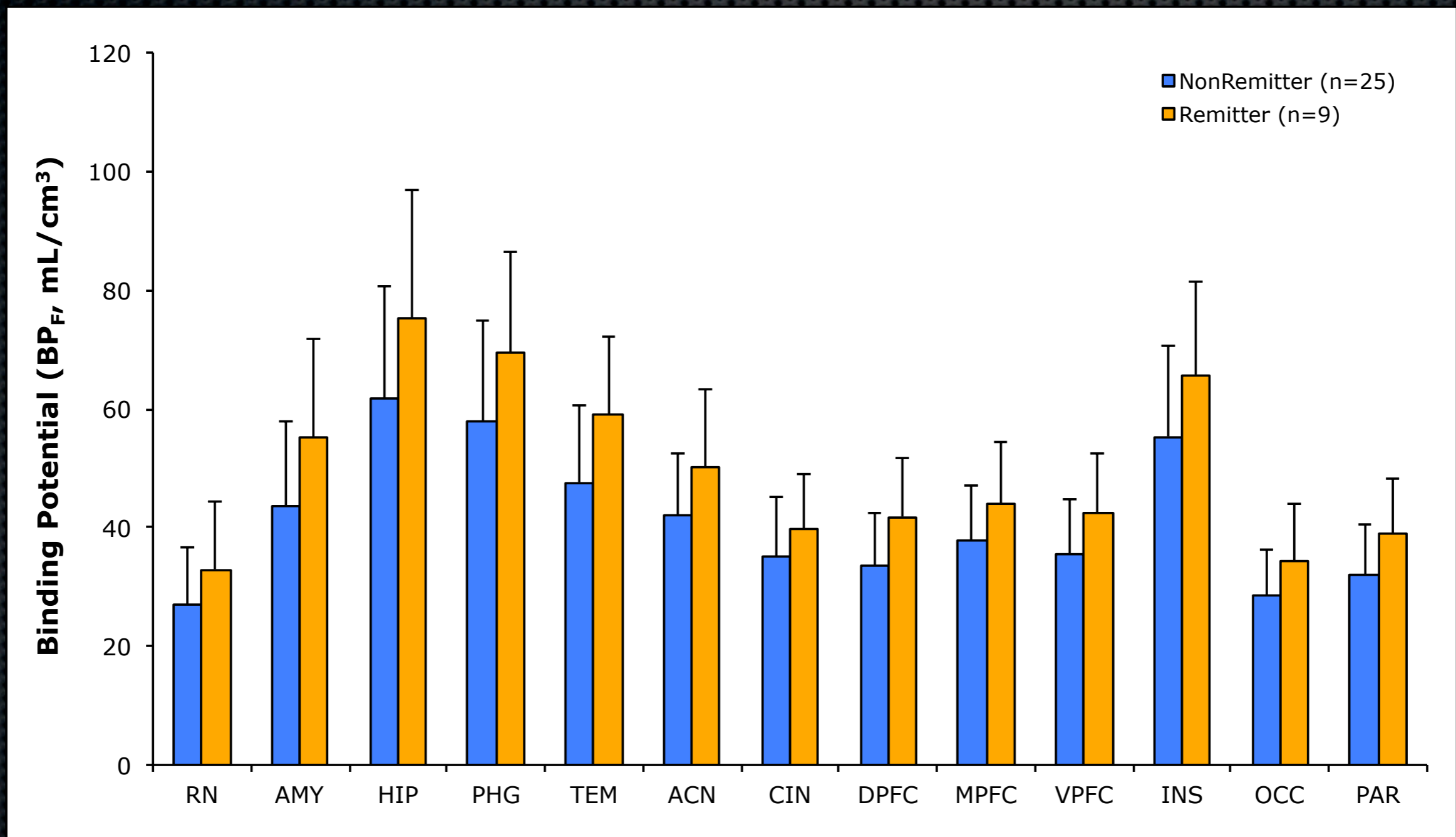
Higher 5-HT_{1A} in Bipolar Depression



Raphe 5-HT_{1A} Binding Potential Predicts Response in MDD



5-HT_{1A} Predicts Response in Bipolar Disorder

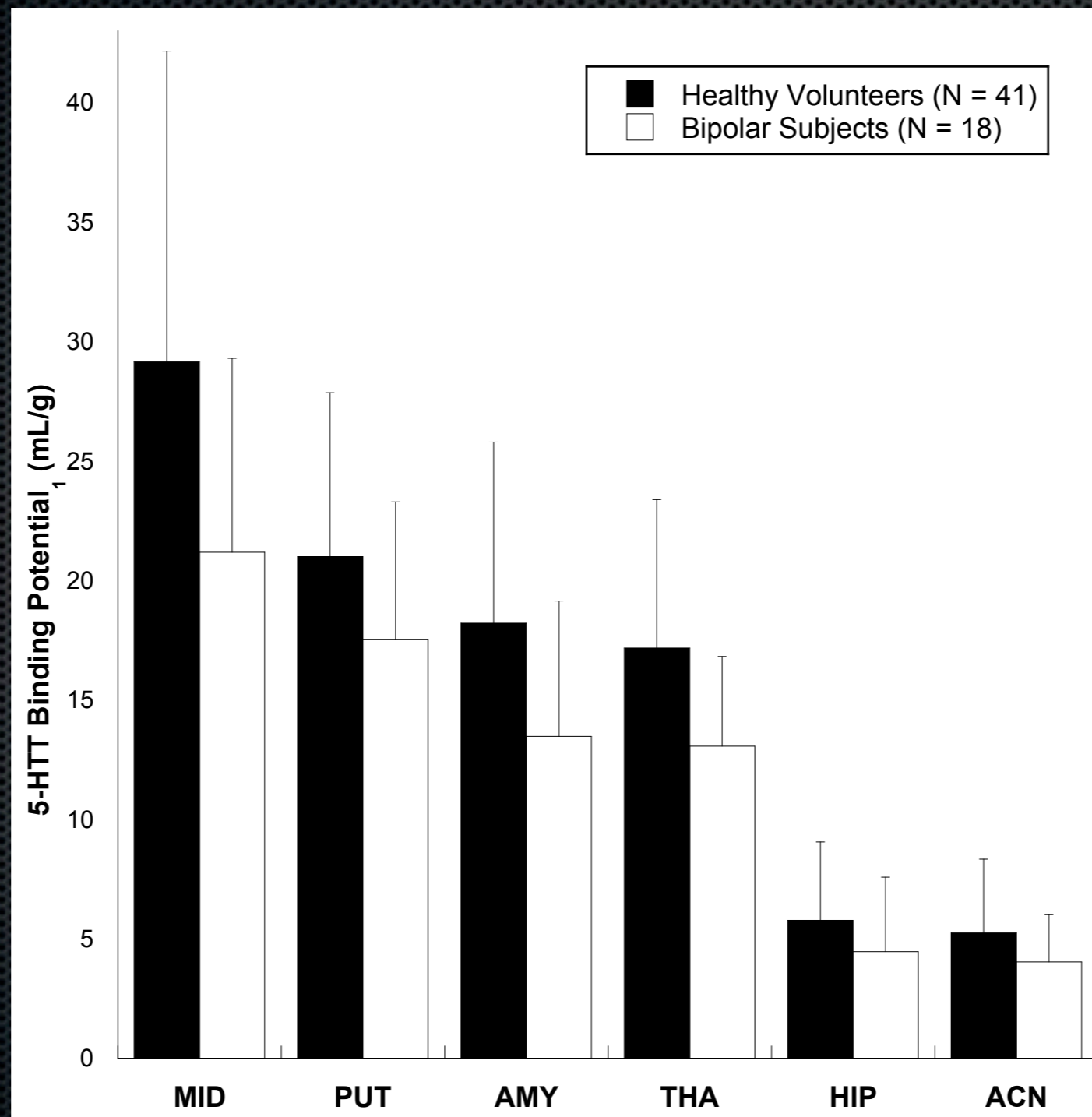


Lan, in press

Serotonin Transporter

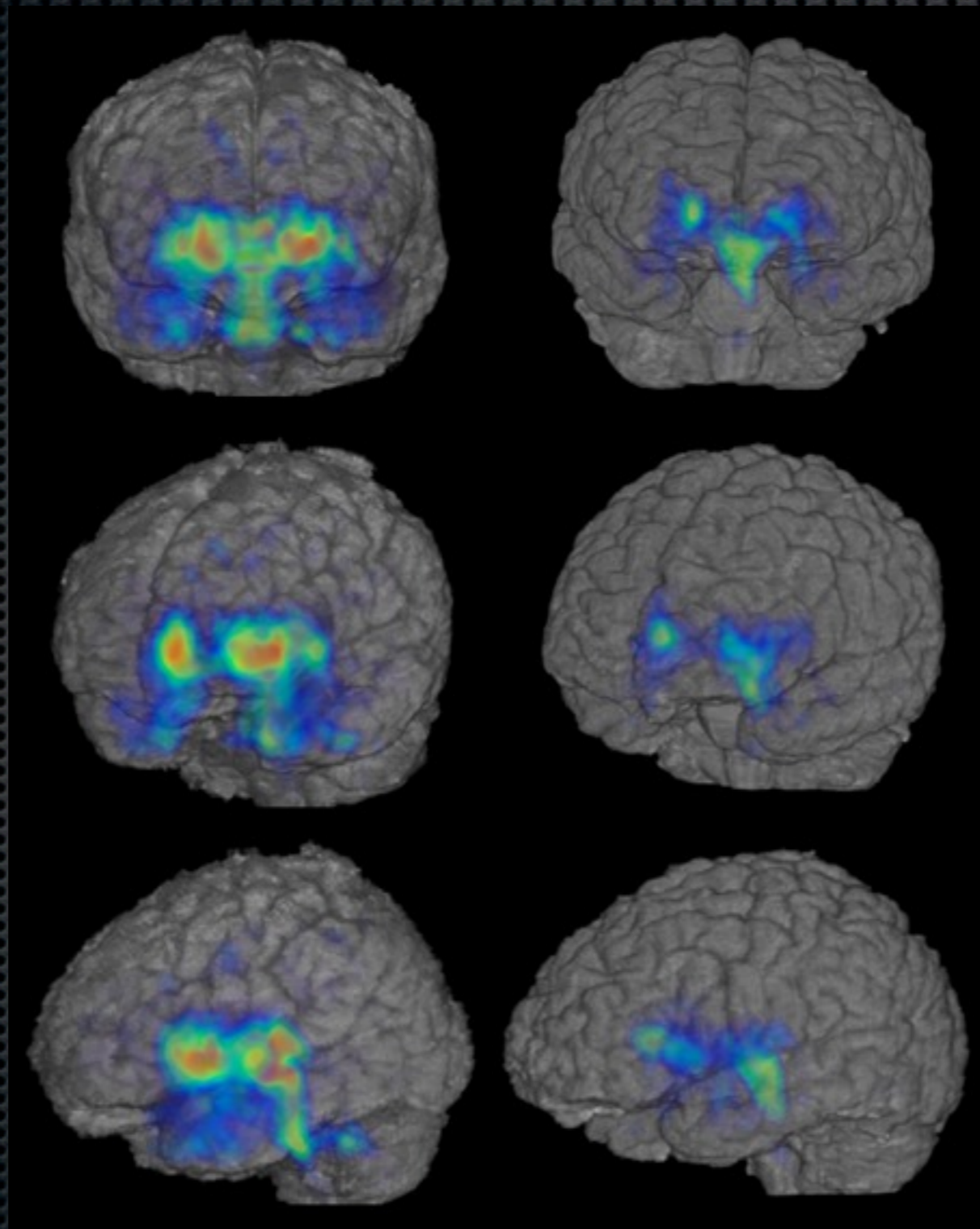
- 5-HTT terminates action of 5-HT
- 5-HTT target of most antidepressants
- Measure of serotonergic neurons (Soucy et al. 1995)
- 5-HTT also regulated by:
 - Gene expression
 - Intra-synaptic serotonin levels
- 5-HTT abnormalities in MDD (Malison et al 1998; Mann et al 2000)

Lower [C-11]MCN 5652 BP_P in Midbrain and Amygdala in MDD



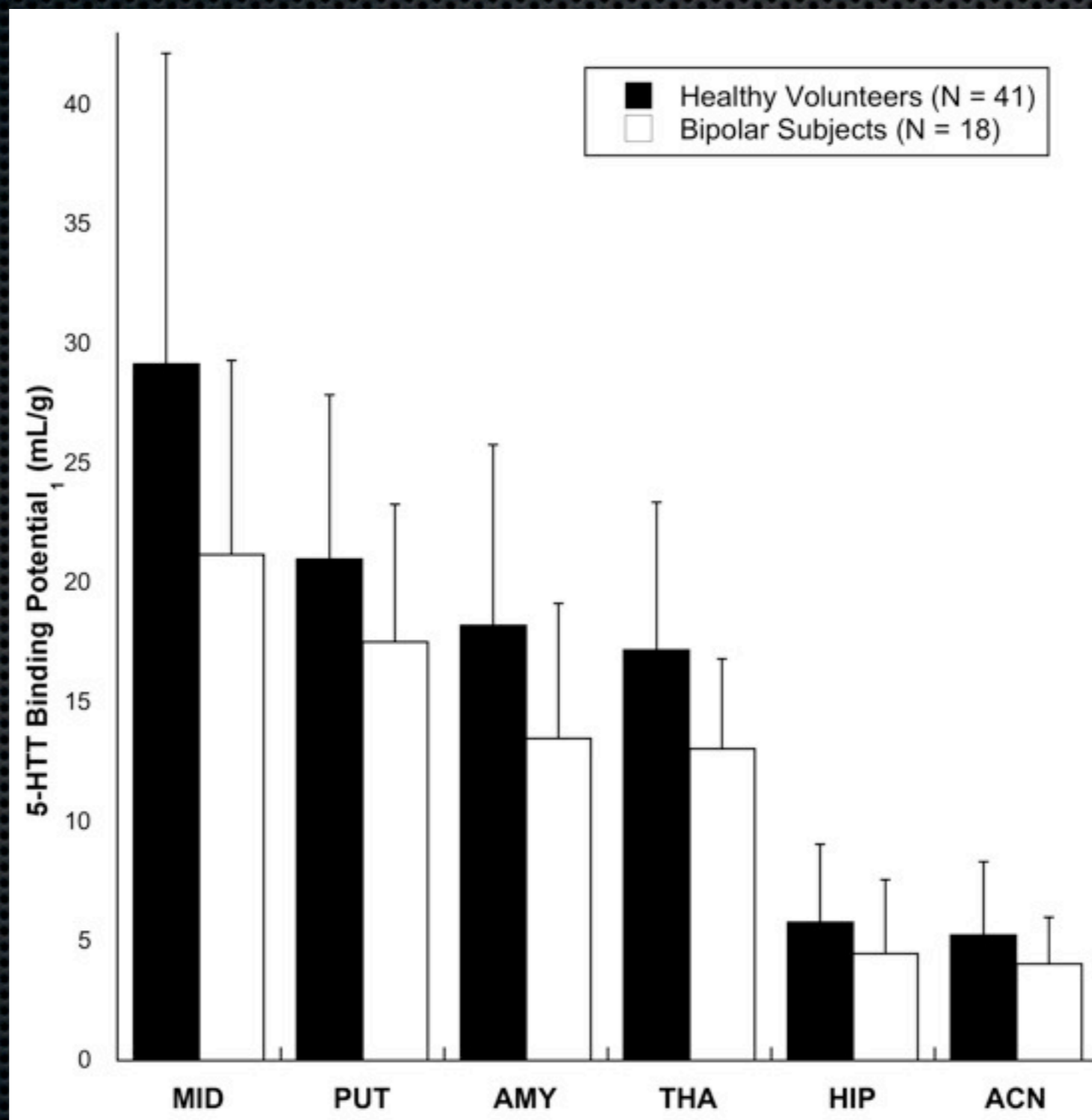
Parsey 2006

Lower [C-11]MCN 5652 BP_p in MDD



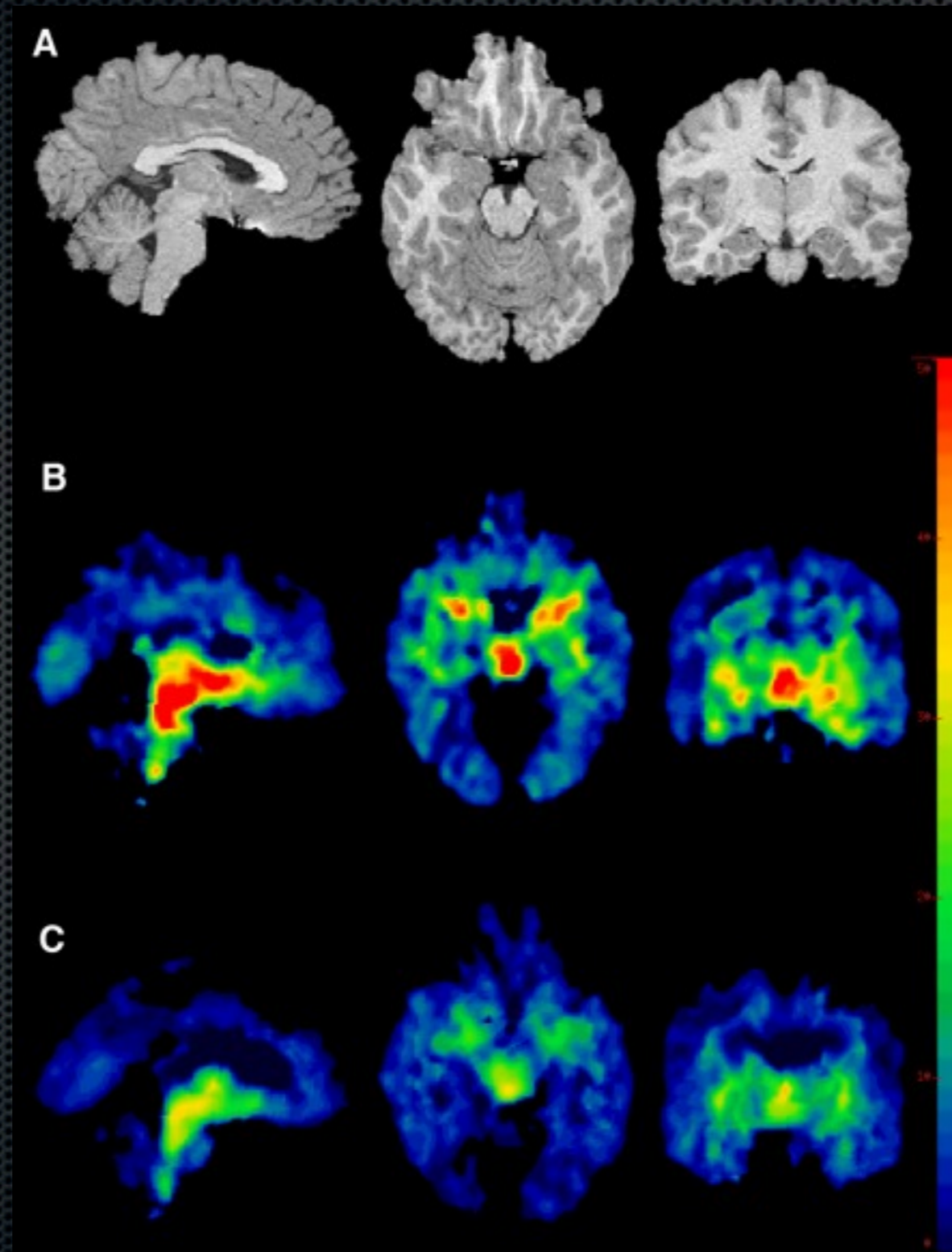
Parsey 2006

Lower [C-11]MCN 5652 BP_p in BPD



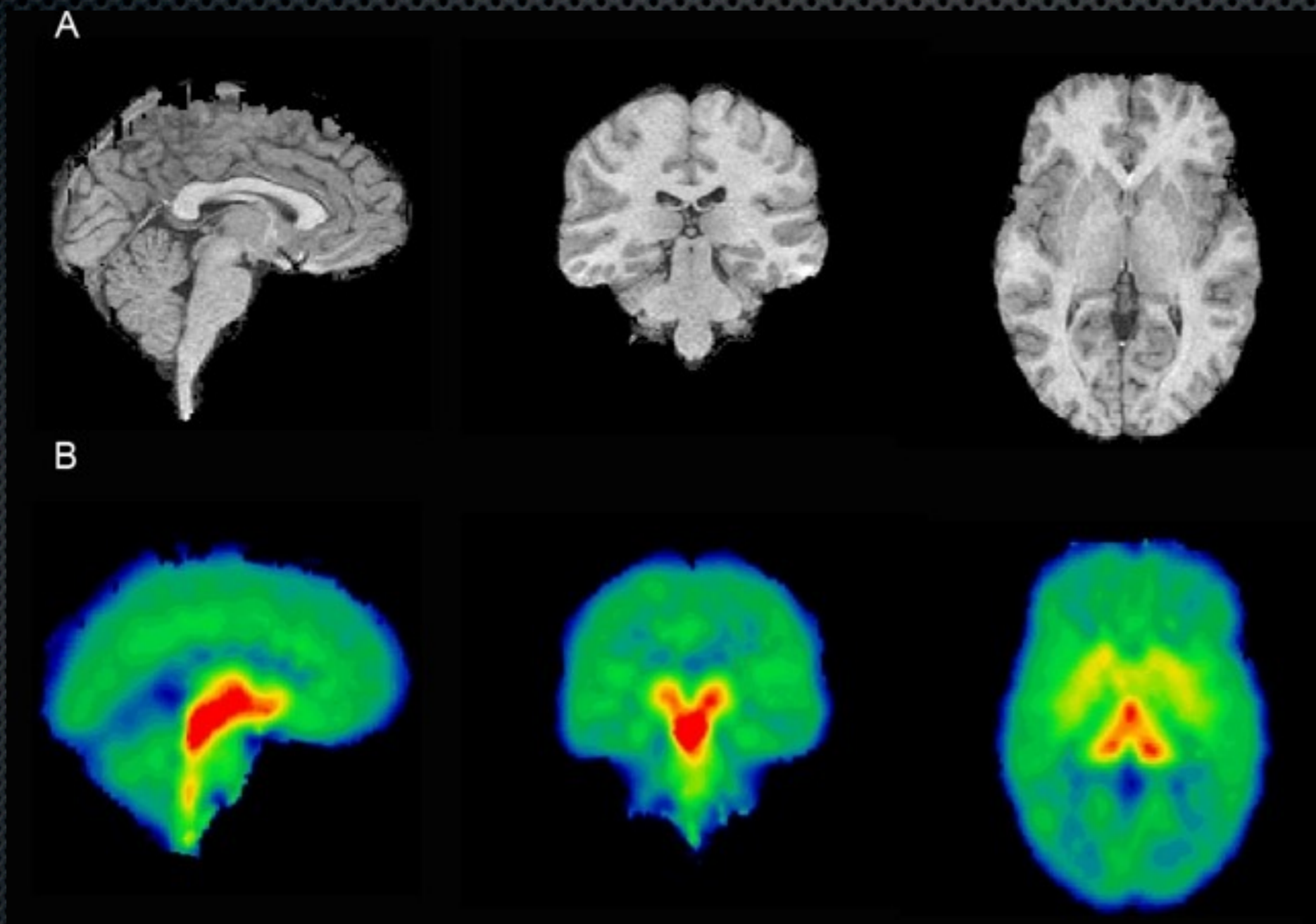
Oquendo
2007

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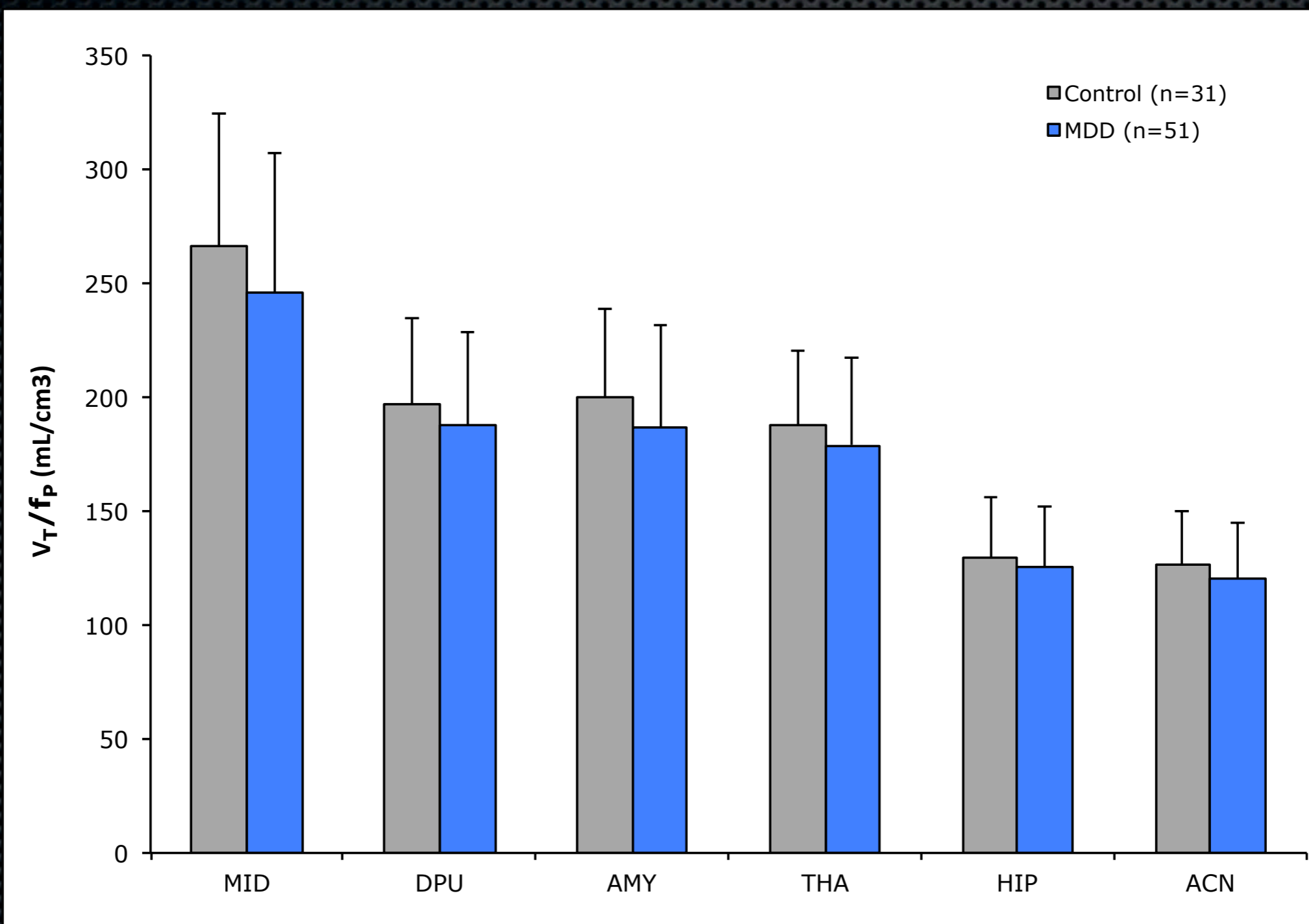
Oquendo
2007

Measuring 5-HTT with [C-11]DASB

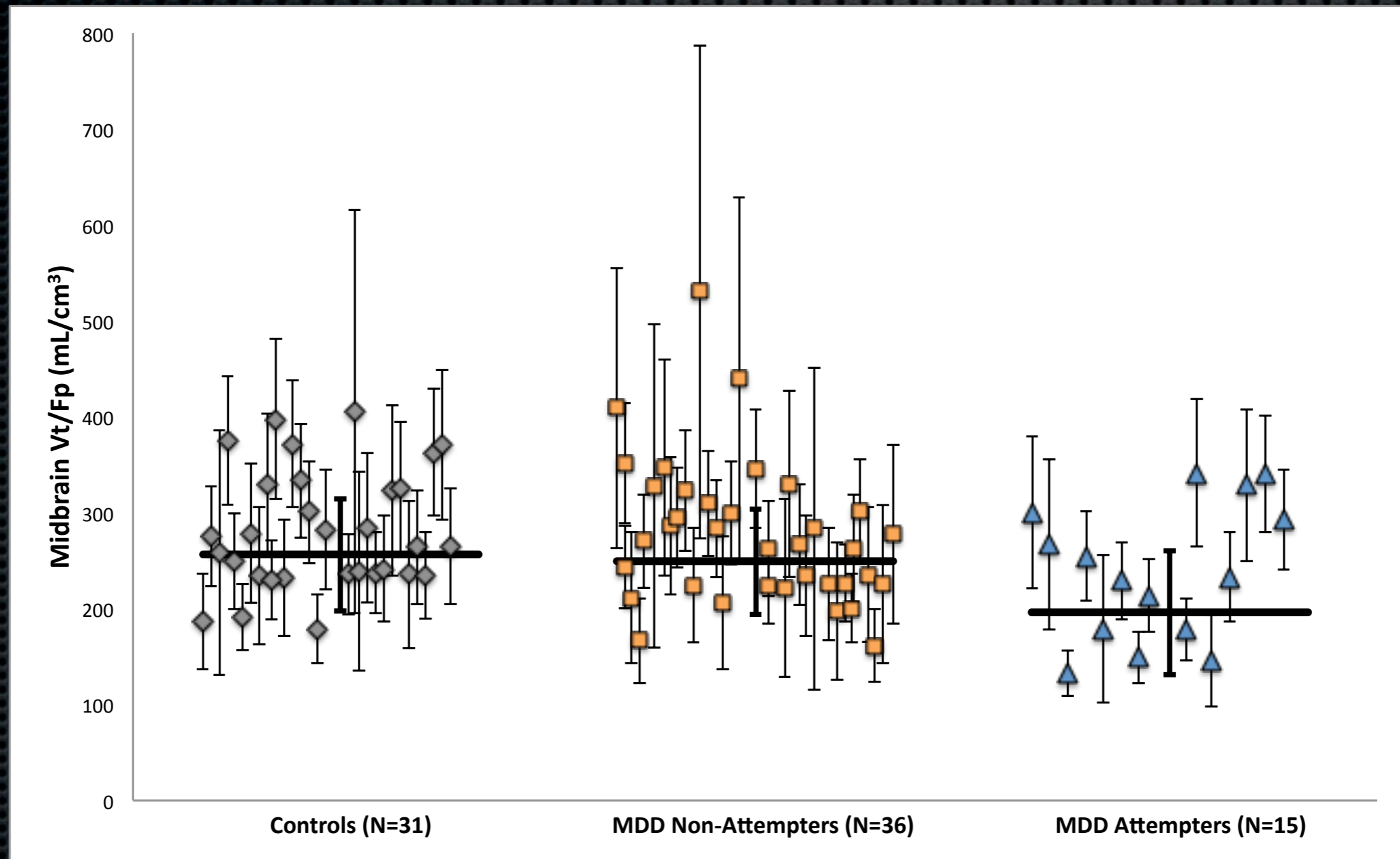


Ogden 2006

[C-11]DASB in MDD



Serotonin Transporter and Suicidality



Suicide Attempters have low 5-HTT in midbrain

(Attempters vs. Non-Attempters: $p=0.031$; Attempters vs. Controls: $p=0.0093$)

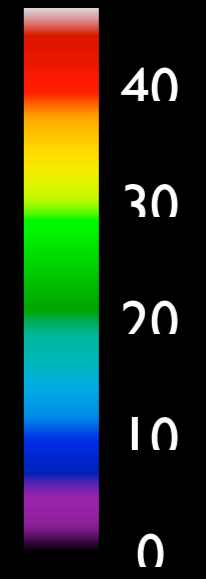
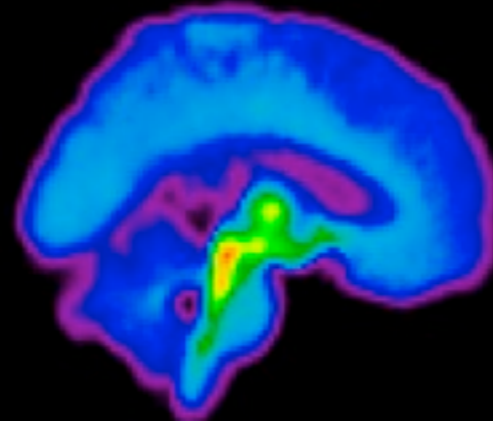
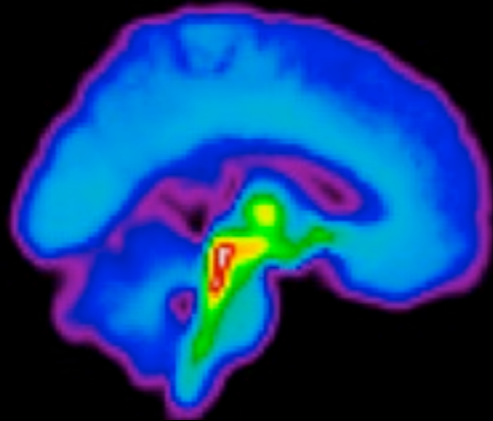
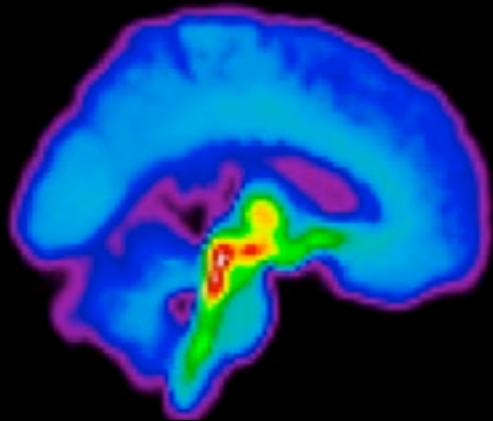
Miller 2013

Controls

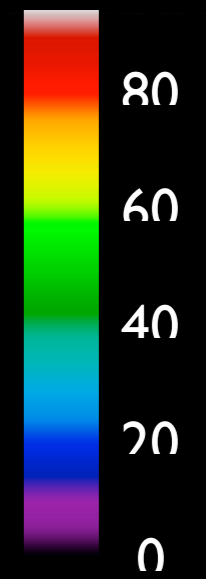
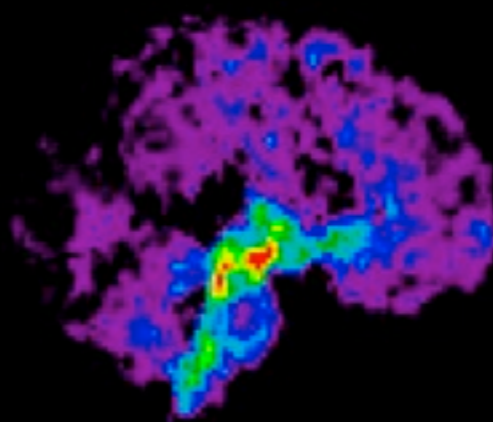
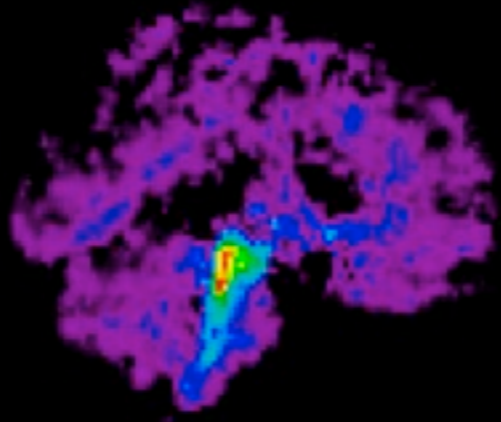
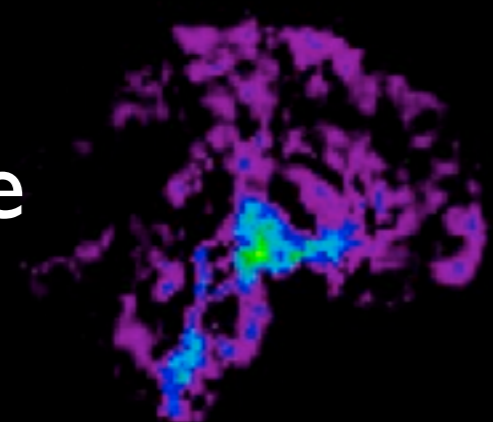
NonAttempters

Attempters

Mean
Images



Difference
Images

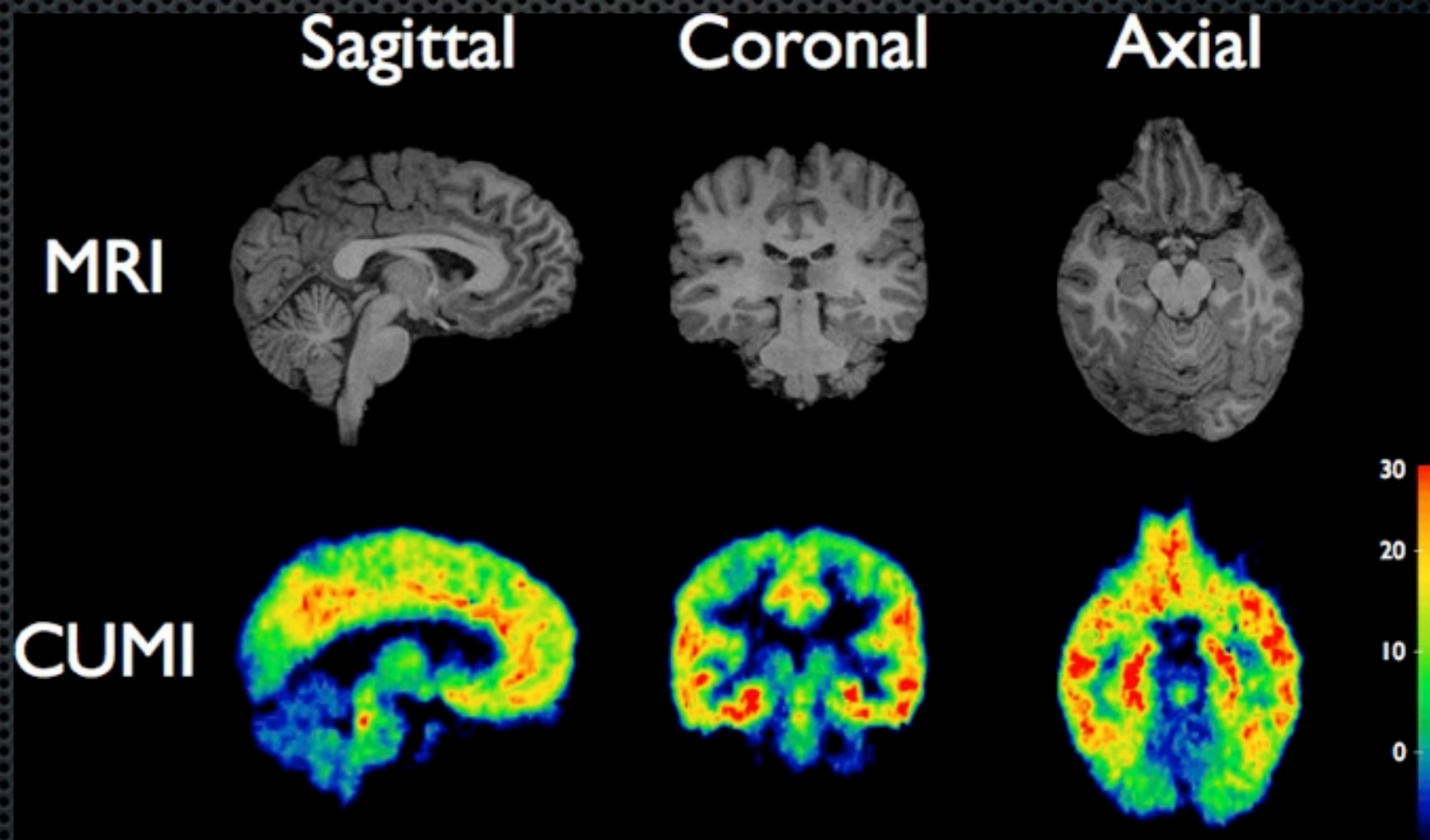
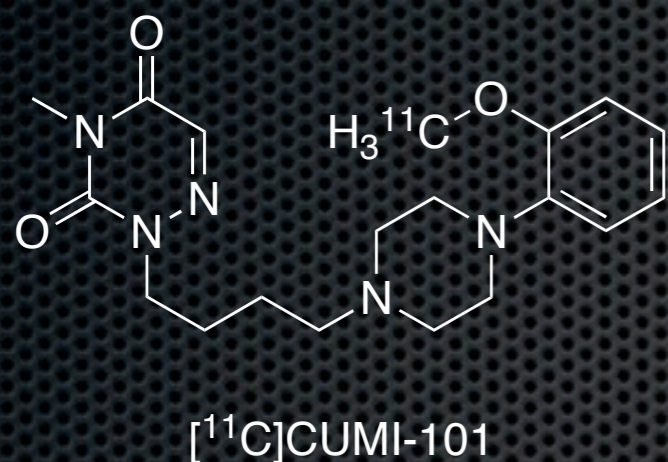


Controls -
NonAttempters

NonAttempters -
Attempters

Controls -
Attempters

5-HT_{1A} Agonist PET Radiotracer [C-11]CUMI101



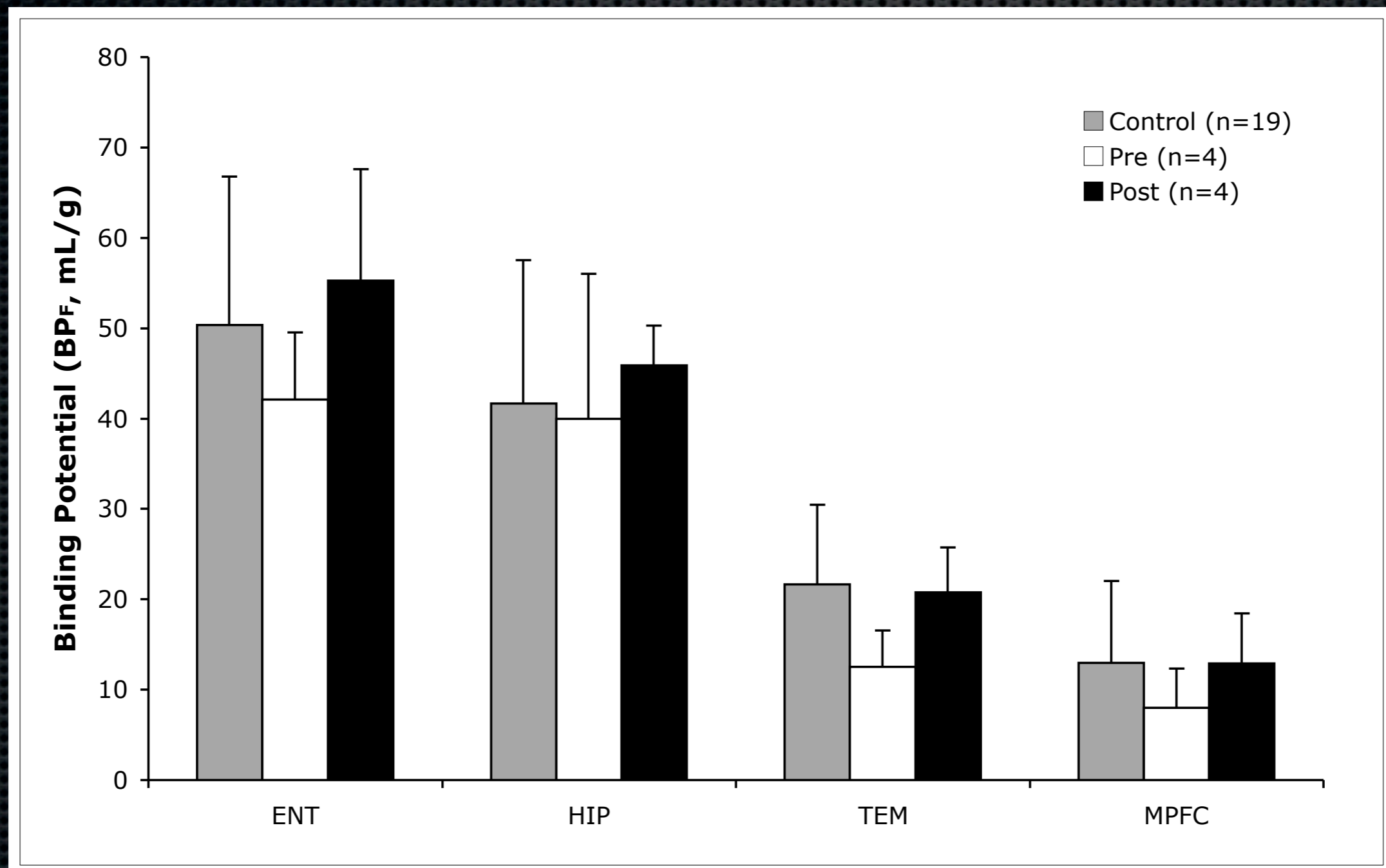
Pathophysiology and treatment of bipolar disorder as assessed by in vivo imaging

- PI: Ramin Parsey, MD, PhD

Specific Aims

- Quantify serotonin transporter (5-HTT) binding potential (BP_F) in vivo in bipolar disorder patients (BPD) during a major depressive episode (MDE).
- Assess the effect of lithium treatment of BPD on 5-HTT BP_F
 - lithium will increase the low 5-HTT BP_F in BPD patients in the temporal, frontal, and entorhinal cortices towards 'normal' levels.
 - clinical improvement of depression as measured by Hamilton Depression Rating Scale (HDRS) scores will be positively correlated to the change in BP_F .
 - reductions in suicidal ideation as measured by Beck Scale for Suicidal Ideation (SSI) will be positively correlated with the change in BP_F .

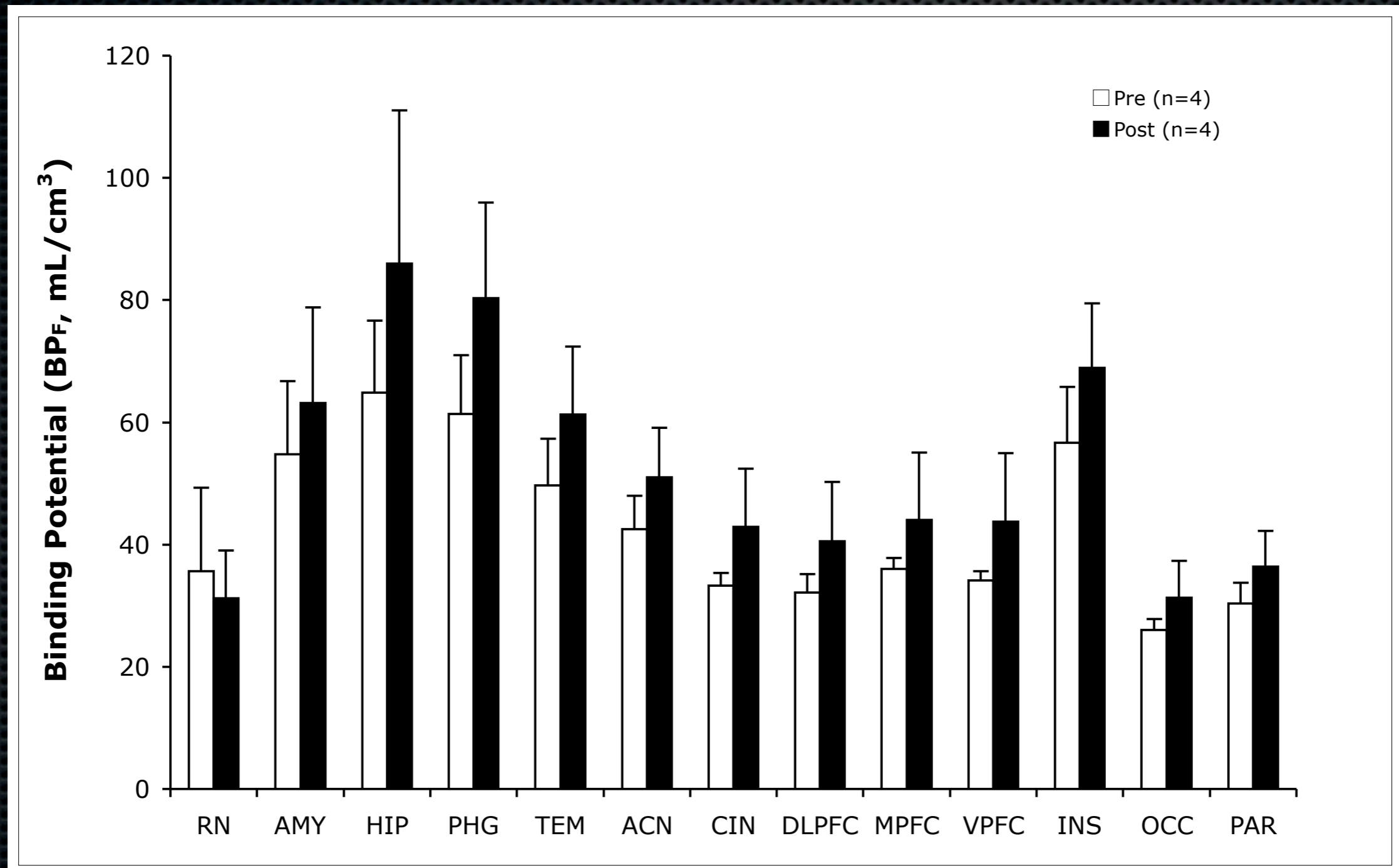
[C-11]DASB before and after lithium



Specific Aims

- Assess the effect of lithium treatment of BPD on 5-HT_{1A} BP_F.
 - lithium will increase postsynaptic 5-HT_{1A} BP_F and decrease presynaptic 5-HT_{1A} BP_F.
 - clinical improvement of depression as measured by HDRS scores will be positively correlated to the change in presynaptic BP_F and negatively correlated to postsynaptic BP_F
 - similar correlations will be observed with reductions in suicidal ideation as measured by SSI scores.

[C-11]WAY100635 before and after lithium



Exploratory Aims

- Assess the effect of lithium treatment of **unipolar** depression on 5-HTT BP_F. We will perform baseline and post treatment [11C]DASB scans in 10 unipolar depressed subjects. We will determine if the effects of lithium treatment are specific to bipolar depression.
- Examine effects of **lamotrigine** on [11C]WAY 100635 and [11C]DASB BP_F. Subjects who have baseline scans but cannot tolerate or do not respond to lithium will be switched to lamotrigine and scanned after 6-8 weeks. We will be able to determine if the lithium effects are specific to lithium or all mood stabilizers.
- Determine if pretreatment 5-HT_{1A} or 5-HTT BP_F **predicts response** to mood stabilizers. We have shown that lower (more normal) 5-HT_{1A} binding predicts response to antidepressants.³⁵ We will explore whether baseline 5-HT_{1A} or 5-HTT BP_F predicts response to lithium or lamotrigine.

METHODS

- Baseline Scans:
 - 1 pre-treatment, unmedicated MRI scan session using both structural and functional pulse sequences.
 - 2 pre-treatment, unmedicated PET scans using different radiotracers:
 - [11C]DASB to assess 5-HTT binding.
 - [11C]CUMI-101 to assess 5-HT1A binding.
- Treatment:
 - Baseline scans are followed by treatment with either lithium or lamotrigine, as clinically indicated.
 - Clinical response is assessed 6 weeks after reaching the therapeutic dose of medication using the 17-item Hamilton Depression Rating Scale.
 - Response defined as 50% decrease from baseline HDRS score.

METHODS

- Post-treatment Scans

- Patients who have a 50% or greater reduction in their HDRS score have post-treatment, medicated [^{11}C]DASB and [^{11}C]CUMI-101 scans.

- Patients who do not have a 50% reduction in their HDRS score are switched to the other medication under study (lithium or lamotrigine) and are reassessed 6 weeks after reaching the therapeutic dose.

- Control Group

- Age and sex matched control participants undergo 1 MRI scan session and 2 PET scans ([^{11}C]DASB and [^{11}C]CUMI-101) for comparison.

PARTICIPANTS

- N = 78 (38 patients, 38 healthy controls) proposed
 - To date: 5 patients and 6 healthy controls enrolled.
 - PET Scans: 18 scans (12 scan sessions) completed to date; 202 additional scans (101 scan sessions) anticipated.

Collaboration

- [C-11] CUMI
- [C-11] DASB
- [C-11] Raclopride
- [F-18] Fallypride