Pharmacological Treatment of Stuttering

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Disclosure

- No medication is FDA approved for stuttering
- Psyadon has provided medication but no financial support for the study discussed. The study was supportive through philanthropic donations to UC Riverside
- UC Riverside has a grant from Teva to support Deutetrabenazine in the Treatment of Stuttering

Stuttering Treatment

- *"During the past 25 years, consumption of prescription and OTC drugs for every conceivable problem has mushroomed, becoming part of the daily life and culture of the Western world. In light of this, the search of people who stutter for a relief, if not complete cure, by means of drugs, is understandable."*
  - *Yairi & Seery, 2011, p. 265*

Stuttering's Many Similarities With Tourette's Syndrome

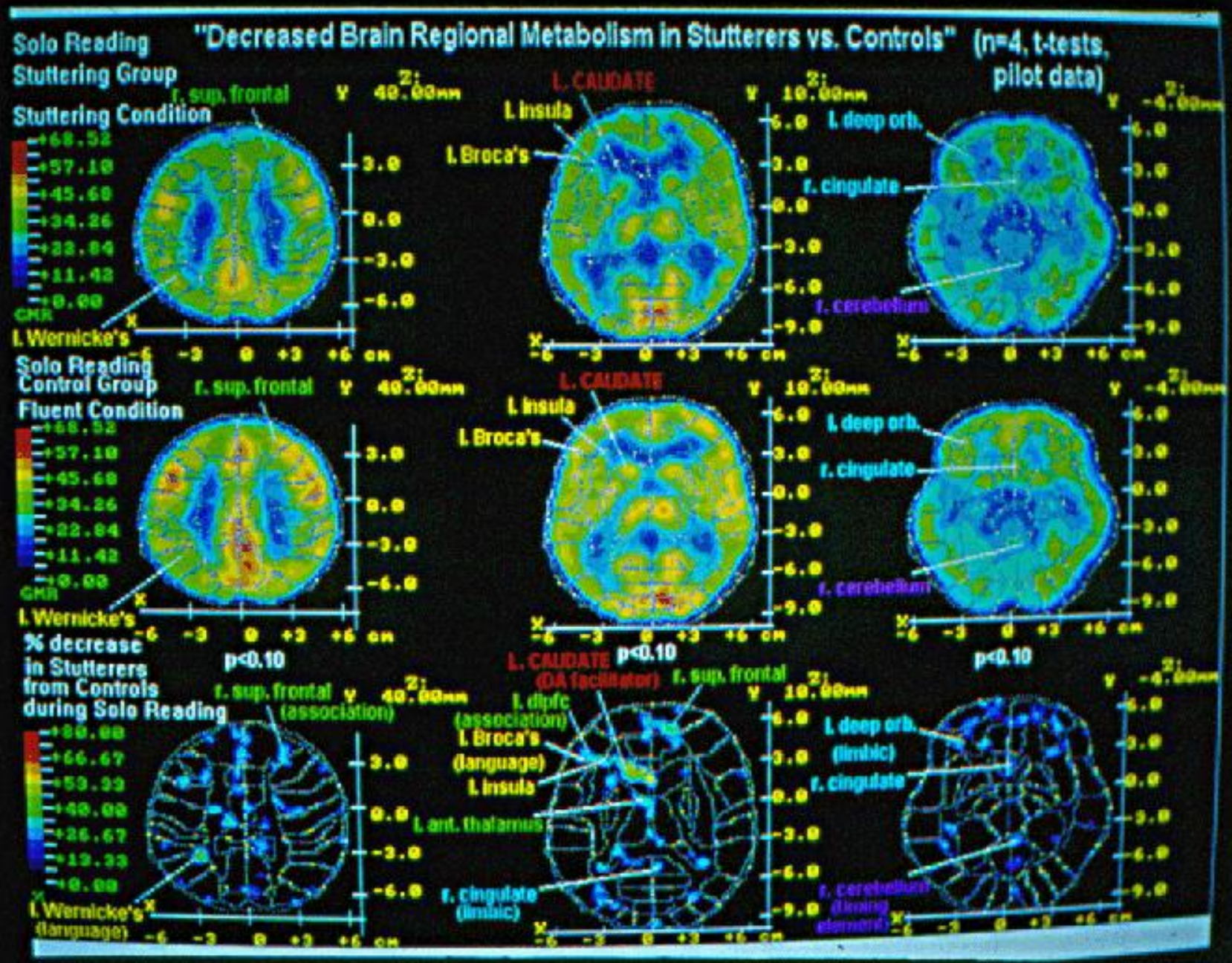
- Both associated with tic motions
- Both follow a waxing and waning course
- Made worse under anxiety or stress
- 4:1 male to female ratio
- Begins in childhood
- Symptoms worsened by dopamine agonists and improved with dopamine antagonists
- Related to abnormalities in the basal ganglia
- Genetic linkage postulated[1]

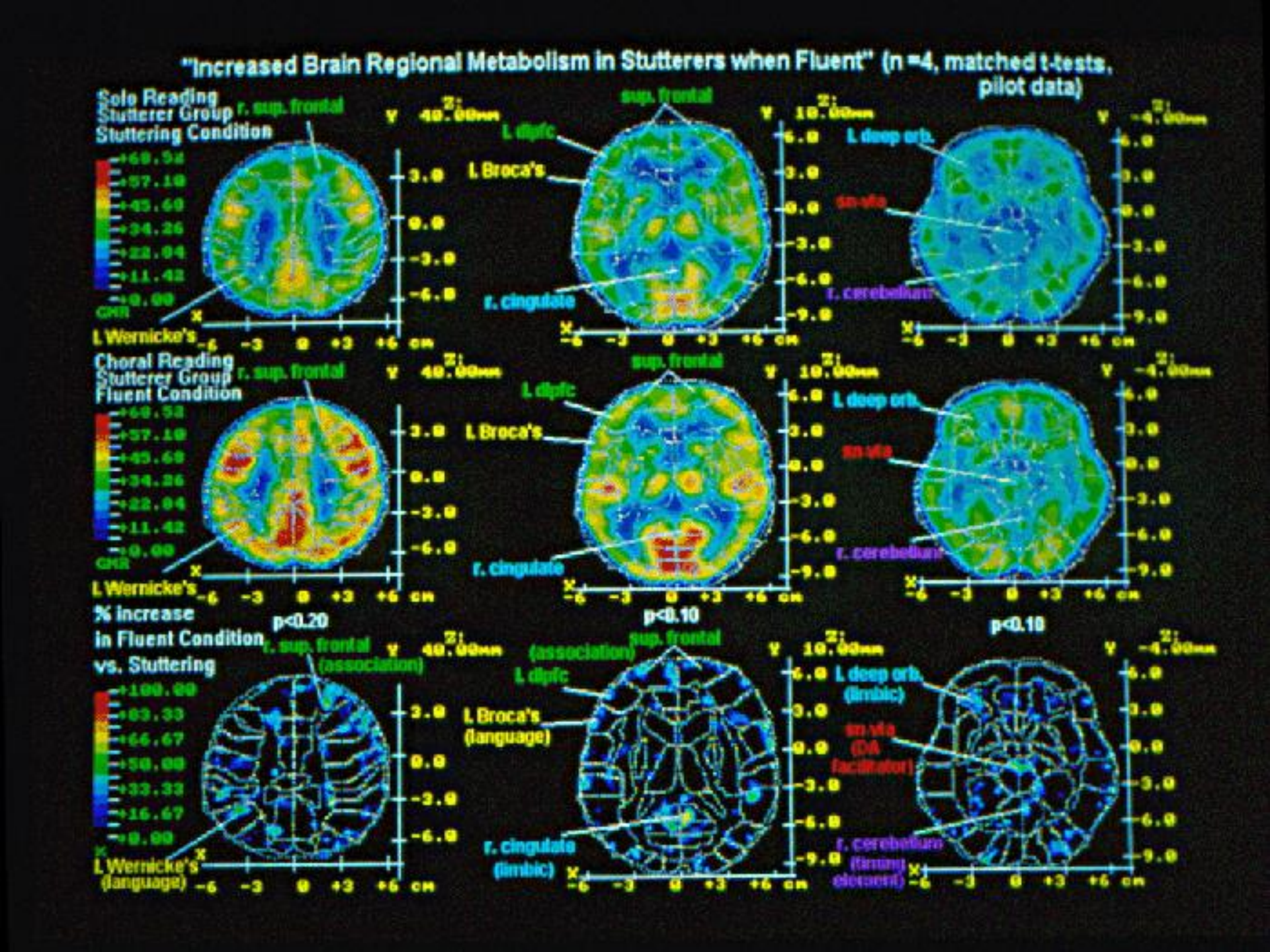
1. Comings DE. *J Am Acad Child Adolesc Psychiatry.* 1995;34(4):401-402.

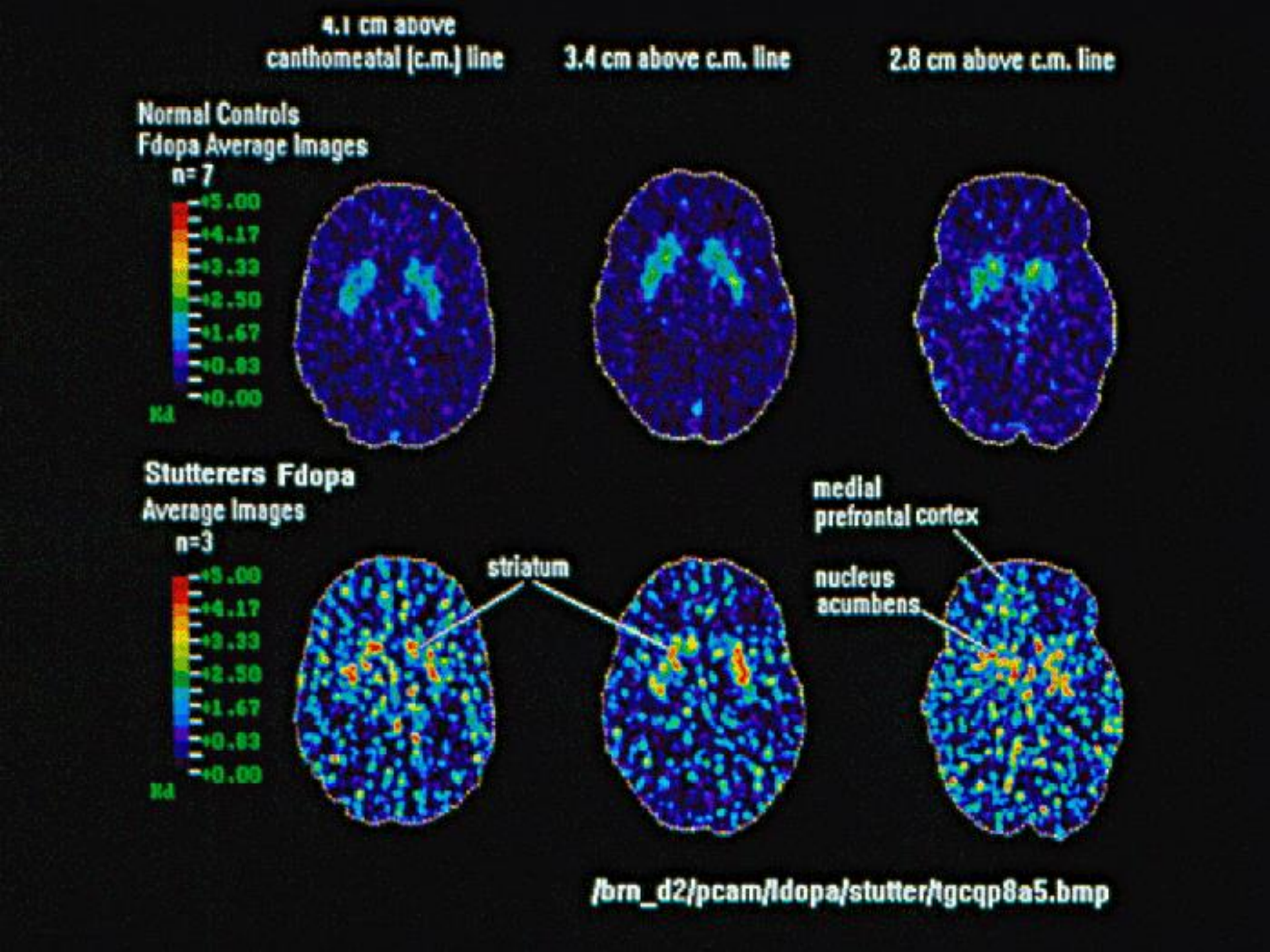
FDG Brain Imaging Studies of Stuttering

- Wu, Maguire, Riley, et al. utilized FDG to measure glucose metabolism in stuttering
  - Stuttering associated with abnormal low activity of speech cortical areas (Broca's and Wernicke's) and striatum
  - During induced fluency, cortical speech areas increase to normal or high normal areas, but striatum remains low

Wu JC, et al. *Neuroreport.* 1997;8(3):767-770.


"Decreased Brain Regional Metabolism in Stutterers vs. Controls" (n=4, t-tests, pilot data)
Solo Reading
Stuttering Group
Stuttering Condition
r. sup. frontal
L. CAUDATE
l. Insula
l. Broca's
l. deep orb.
r. cingulate
r. cerebellum
l. Wernicke's
Solo Reading
Control Group
Fluent Condition
r. sup. frontal
L. CAUDATE
l. Insula
l. Broca's
l. deep orb.
r. cingulate
r. cerebellum
l. Wernicke's
p<0.10
p<0.10
p<0.10
% decrease in Stutterers from Controls during Solo Reading
r. sup. frontal (association)
L. CAUDATE (DA facilitator)
r. sup. frontal
l. dlpfc (association)
l. Broca's (language)
l. insula
l. deep orb. (limbic)
r. cingulate
l. ant. thalamus
r. cingulate (limbic)
r. cerebellum (timing element)
l. Wernicke's (language)


"Increased Brain Regional Metabolism in Stutterers when Fluent" (n =4, matched t-tests, pilot data)
Solo Reading
Stutterer Group
Stuttering Condition
r. sup. frontal
l. dlpfc
l. Broca's
sup. frontal
l. deep orb.
sm vis
r. cingulate
r. cerebellum
l. Wernicke's
Choral Reading
Stutterer Group
Fluent Condition
r. sup. frontal
l. dlpfc
l. Broca's
sup. frontal
l. deep orb.
sm vis
r. cingulate
r. cerebellum
l. Wernicke's
% increase
in Fluent Condition
vs. Stuttering
p<0.20
p<0.10
p<0.10
r. sup. frontal
(association)
l. dlpfc
l. Broca's
(language)
sup. frontal
(association)
l. deep orb.
(limbic)
sm vis
(DA
facilitation)
r. cingulate
(limbic)
r. cerebellum
(final
element)
l. Wernicke's
(language)


4.1 cm above
canthomeatal (c.m.) line
3.4 cm above c.m. line
2.8 cm above c.m. line
Normal Controls
Fdopa Average Images
n= 7
+5.00
+4.17
+3.33
+2.50
+1.67
+0.83
+0.00
Bq
Stutterers Fdopa
Average Images
n=3
+5.00
+4.17
+3.33
+2.50
+1.67
+0.83
+0.00
Bq
striatum
medial
prefrontal cortex
nucleus
acumbens
/brn_d2/pcam/fdopa/stutter/tgcqp8a5.bmp

Dopamine Target for Stuttering Pharmacotherapy

- Empirical Data suggests dopamine antagonists may be beneficial (Brady 1991 Am J. Psych) [1]
- Striatal hypometabolism=elevated dopamine[2]
- Dopamine antagonists increase striatal metabolism[2]
- Dopamine antagonists improve stuttering[2]
- Dopamine activity elevated in persons who stutter[2]
- Dopamine agonists worsen stuttering[3]

1.Brady, JP. *Am J Psych* 1991
2 Maguire GA. *Lancet-Neurology*. 1(7) November 2002.
3. Burd L, Kerbeshian J. *J Clin Psychopharmacol.* 1991;11(1):72-73.

Haloperidol

- First-Generation Dopamine Antagonist
- Associated with improved fluency
- However, poor long-term compliance secondary to disabling side effects (e.g., dysphoria,
sexual dysfunction, extrapyramidal symptoms, tardive dyskinesia)

Rosenberger PG, et al. *Am J Psychiatry.* 1976;133:331-334.

Pimozide/Paroxetine Study

- Positive clinical response in those on pimozide (dopamine antagonist)
- Paroxetine (serotonin reuptake inhibitor) exhibited no clinical response
- However, Pimozide associated with limiting side-effects such as EPS, TD, dysphoria, prolactin elevation and cardiac conduction concerns

Stager S, et al. A double-blind trial of pimozide and paroxetine for stuttering. In: Hulstijn W, et al., eds. *Speech Production: Motor Control, Brain Research, and Fluency Disorders*; 1997:379-382.

Second Generation Antipsychotics Studied in Stuttering

- Risperidone, Olanzapine, Asenapine, Lurasidone, Aripiprazole

- These agents have a lower risk of motor system side-effects (e.g. tardive dyskinesia) and are generally better tolerated than first generation agents

Risperidone Study

- n=16
- Double-blind, placebo-controlled
- 6-week duration
- Investigator Initiated Trial

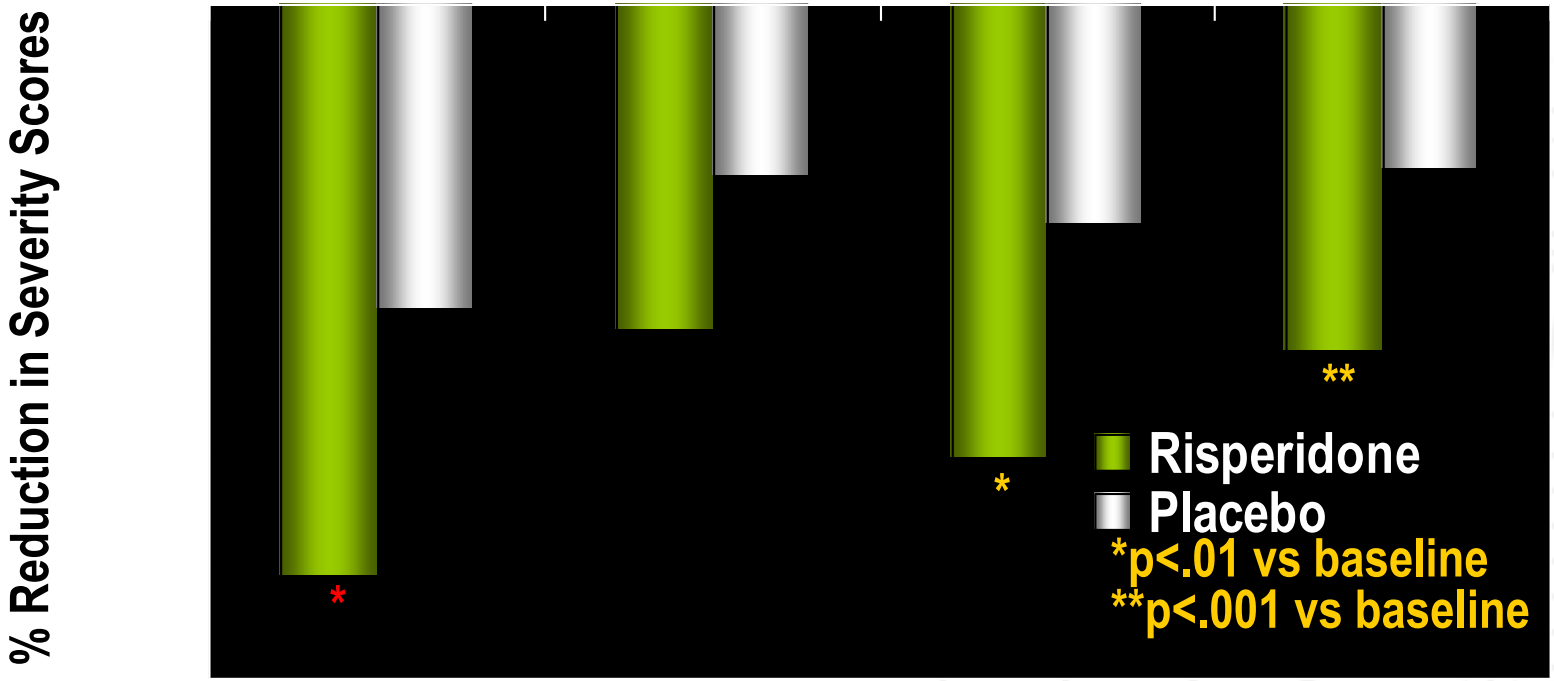
Maguire GA, et al. *J Clin Psychopharmacol.* 2000;20(4):479-482.

Risperidone Study (cont.)

- Ages 20-74 (mean 40.75)
- 12 males/4 females
- Dose 0.5-2.0 mg
- Ratings (% SS, duration, % TS, SSI-3)

Maguire GA, et al. *J Clin Psychopharmacol.* 2000;20(4):479-482.

Reductions in Severity Scores at best time-point in Subjects Receiving Risperidone or Placebo

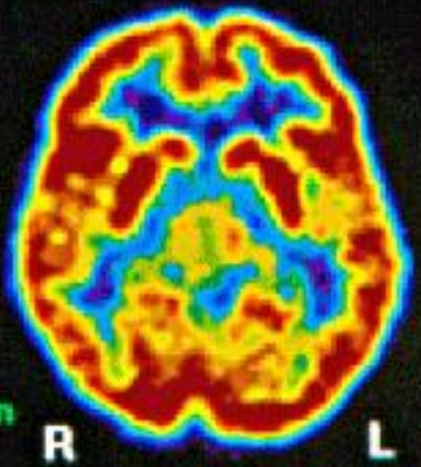


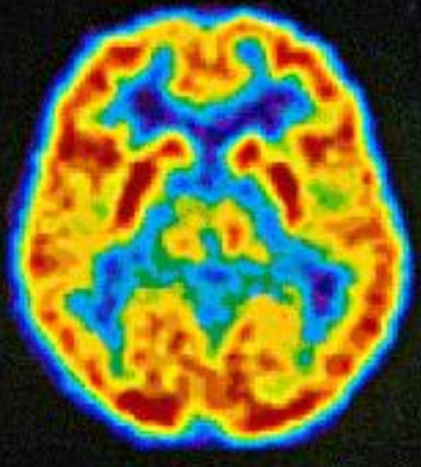
% SS=syllables stuttered; % TS=time stuttering as a % of total time speaking.
SSI-3=Stuttering Severity Instrument, Third Edition (measured overall stuttering severity).
Maguire GA, et al. *J Clin Psychopharmacol.* 2000;20(4):479-482.

ON Risperidone

OFF Risperdone

Stutterer Average Image

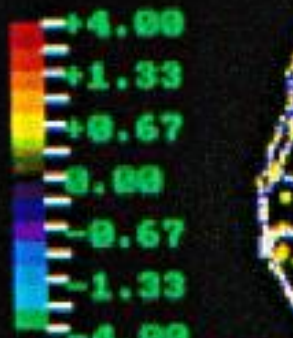


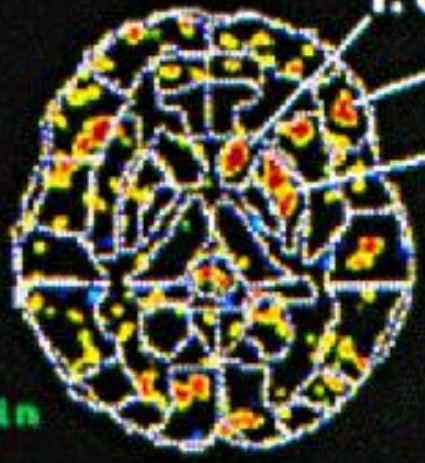


Subtraction: ON-OFF

Changes w/ Risperidone:

1. Caudate Increase
2. Broca's area (speech production) increase
3. Putamen increase





PET Imaging of the Effects of Risperidone in Stuttering

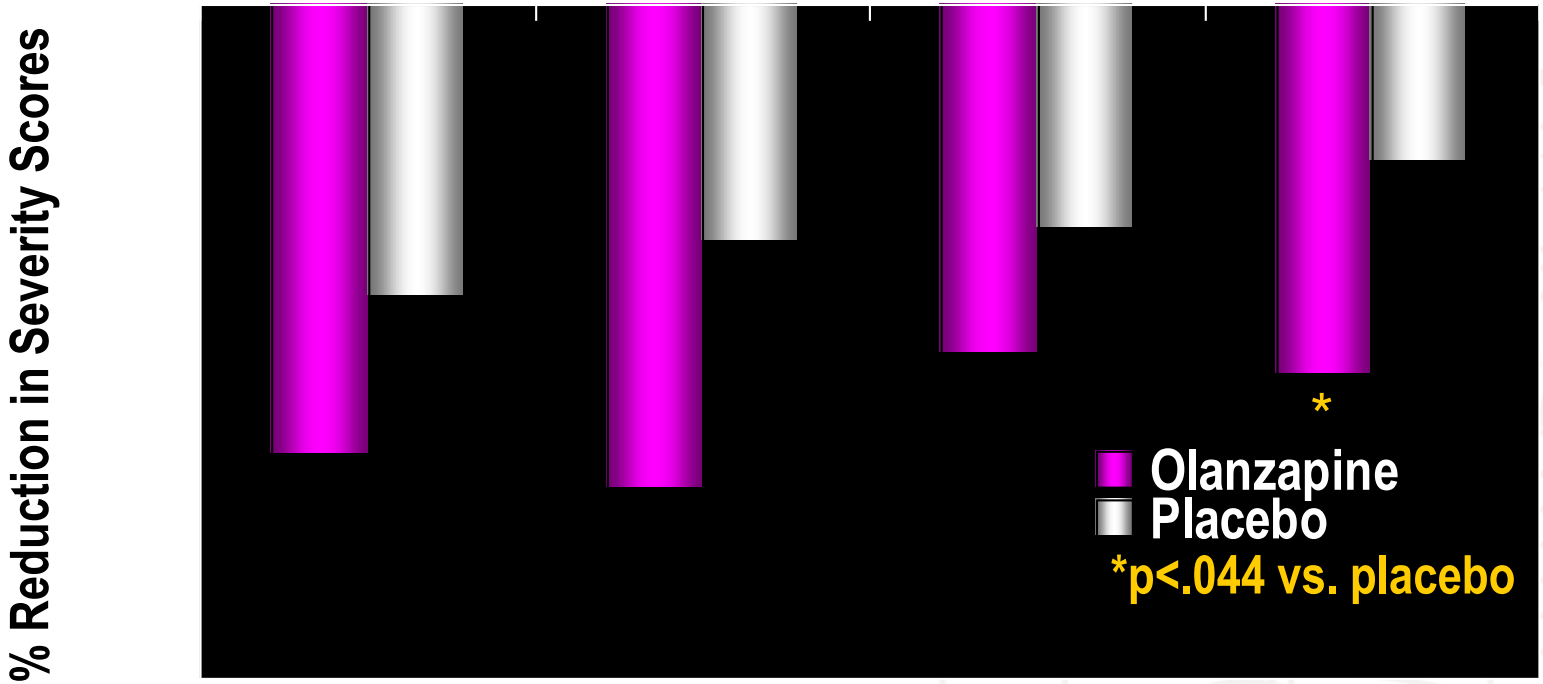
- Risperidone is associated with increased activity in the striatum and cortical speech areas

Olanzapine vs Placebo: 3-Month Study

- 24 adult patients who stutter (ages 18-55)
- Investigator Initiated Trail
- Multicenter, 3-month, double-blind, placebo-controlled trial
- Dose range 2.5→5 mg (starting dose 2.5 mg)

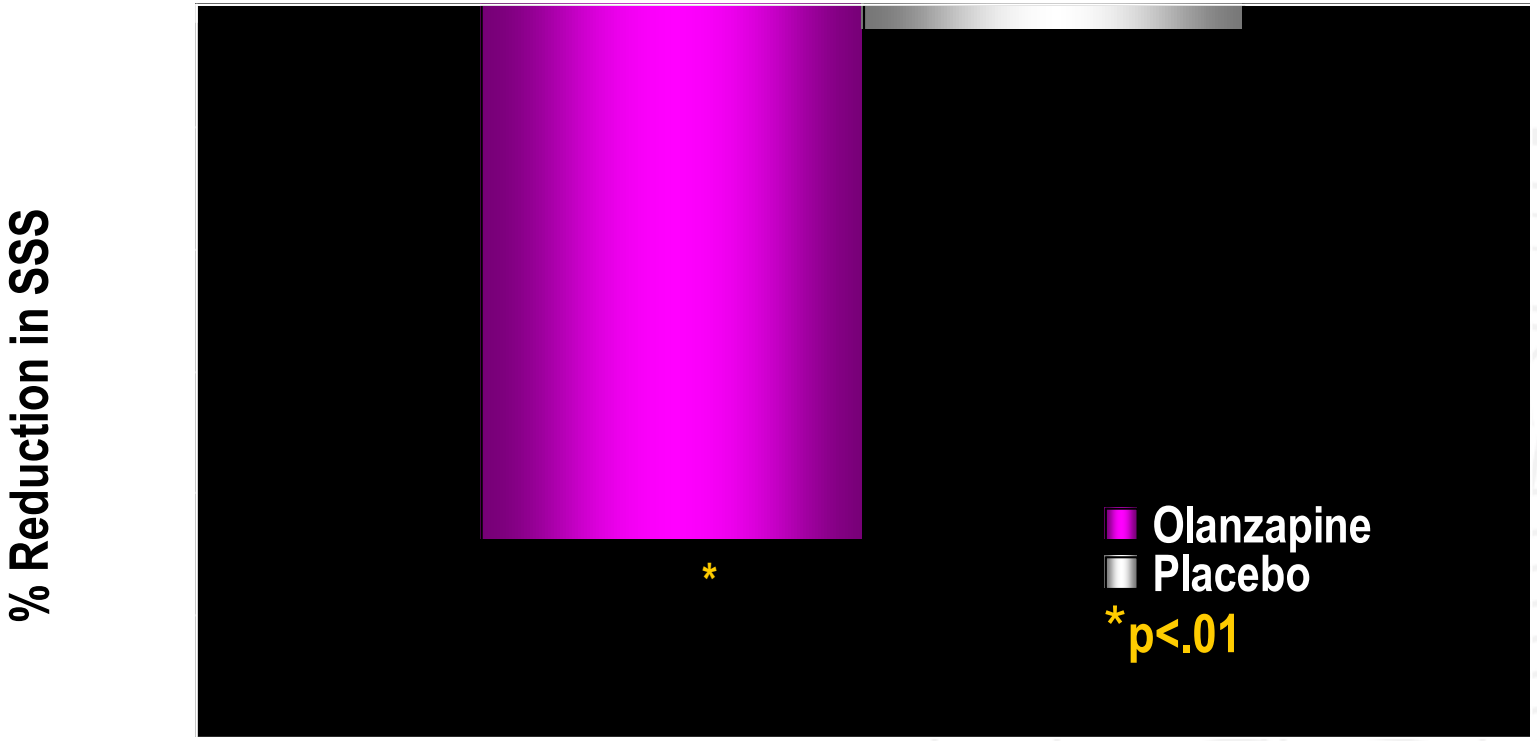
Maguire GA, et al. Annals of Clinical Psychiatry

Reductions in Severity Scores on the SSI-3 Measures in Subjects Receiving Olanzapine or Placebo



% SS=syllables stuttered; % TS=time stuttering as a % of total time speaking.
SSI-3=Stuttering Severity Instrument, Third Edition (measured overall stuttering severity).
Maguire GA, et al. Annals of Clinical Psychiatry

Reduction in Subjective Stuttering Scale in Subjects Receiving Olanzapine



SSS=Subjective Stuttering Scale
Maguire GA, et al. Annals of Clinical Psychiatry

Results

- Olanzapine more effective than placebo in reducing stuttering on all 3 ratings (SSI-3, CGI, and SSS)
- Weight gain seen—average 4 kg

Maguire GA, et al. Annals of Clinical Psychiatry

Asenapine

- Less association with significant weight gain or glucose/lipid increases compared to olanzapine
- Sublingual administration
- Associated with bitter taste but flavored available in US
- Published data supporting utility in Stuttering (Am. J Psychiatry—June 2011)

Aripiprazole

- Partial dopamine agonist
- Akathisia can limit utility in stuttering
- Published report examining safety and effectiveness in adult stuttering (15 mg per day) and published for use in adolescents as well
- FDA approved for Tourette's in children and adults. Generic available so perhaps cost effective

Tran NL, Maguire GA. Journal of Clinical Psychopharmacology

Lurasidone

- Non-randomized, open-label study of lurasidone in patients with stuttering (N = 7)
  - Patients self-reported stuttering severity, locus of control, and avoidance using the Subjective Screening of Stuttering (SSS) scale and were assessed with the Clinical Global Impression (CGI) Scale.

Charoensook, J, Maguire GA. Ann Clinical Psychiatry 2017 Aug;29(3):191-194.

Lurasidone

- This open-label study of lurasidone in patients with stuttering showed improvement in subjective symptoms, in CGI scores, and on the SSS scale.
- Advantages of lower risk of metabolic side effects including weight gain, lipid elevations, sedation
- Approved in children/adolescents for other conditions

Charoensook, J, Maguire GA. Ann Clinical Psychiatry 2017 Aug;29(3):191-194.

Pagoclone

- Pagoclone, is a selective GABA-A partial agonist
- The Largest Pharmacologic Trial of Stuttering Ever Conducted was Completed. Funded by Industry
- Based on an unclear mechanism for stuttering treatment—GABA agonism.
- Strong Placebo Response. Likely under-dosed. Funding ceased when company sold and economic downturn occurred. No further development

J. Clin Psychopharm (2010)

Pharmacologic Treatment

- Every trial with dopamine 2 antagonists have shown efficacy in stuttering
  - olanzapine, risperidone, haloperidol, lurasidone. Olanzapine study with replicated results
- Ecopipam has been studied in a limited pilot trial of stuttering
  - Promise as an efficacious and tolerable medication to treat stuttering.

Ecopipam

- Ecopipam
  - Investigational
  - non-FDA approved medication for any indication
- Selective dopamine D1 receptor antagonist
  - Little affinity for D2 receptors.

Ecopipam

- No reports of parkinsonian-like extrapyramidal symptoms typically seen with D2 antagonists. No reported weight gain—in fact, weight loss

- Dopamine receptor antagonists are effective in improving stuttering
  - Investigation of use of ecopipam for stuttering

Trial of Ecopipam

- Open-label single-case experimental design of ecopipam in adults who stutter. Funded by Philanthropy
  - Primary purpose
    - Investigate the efficacy of ecopipam on adults who present with moderate to very severe developmental stuttering
  - Secondary purpose
    - determine tolerability of this investigational, non-FDA approved medication

Methods

- Design
  - Single center, open-label study
  - A–B treatment efficacy design
    - Treatment condition (B) is a tolerated 8th week dose of ecopipam.
      - Eight weeks transpired between A and B, including 5 visits to the study center.
      - No withdrawal condition was planned
      - Participant self-reports about medication withdrawal were collected.

Methods

- Scales
  - *Stuttering Severity Instrument* (SSI-4; Riley, 2009),
  - *Clinical Global Impression–Severity scale* (CGI-S)
  - *Clinical Global Impression – Improvement scale* (CGI-I)
  - *Subjective Screening of Stuttering* (SSS; Riley, Riley & Maguire, 2004)
  - *Overall Assessment of the Speaker's Experience of Stuttering* (OASES; Yaruss & Quesal, 2010).

Figure 1- Ratings OASES

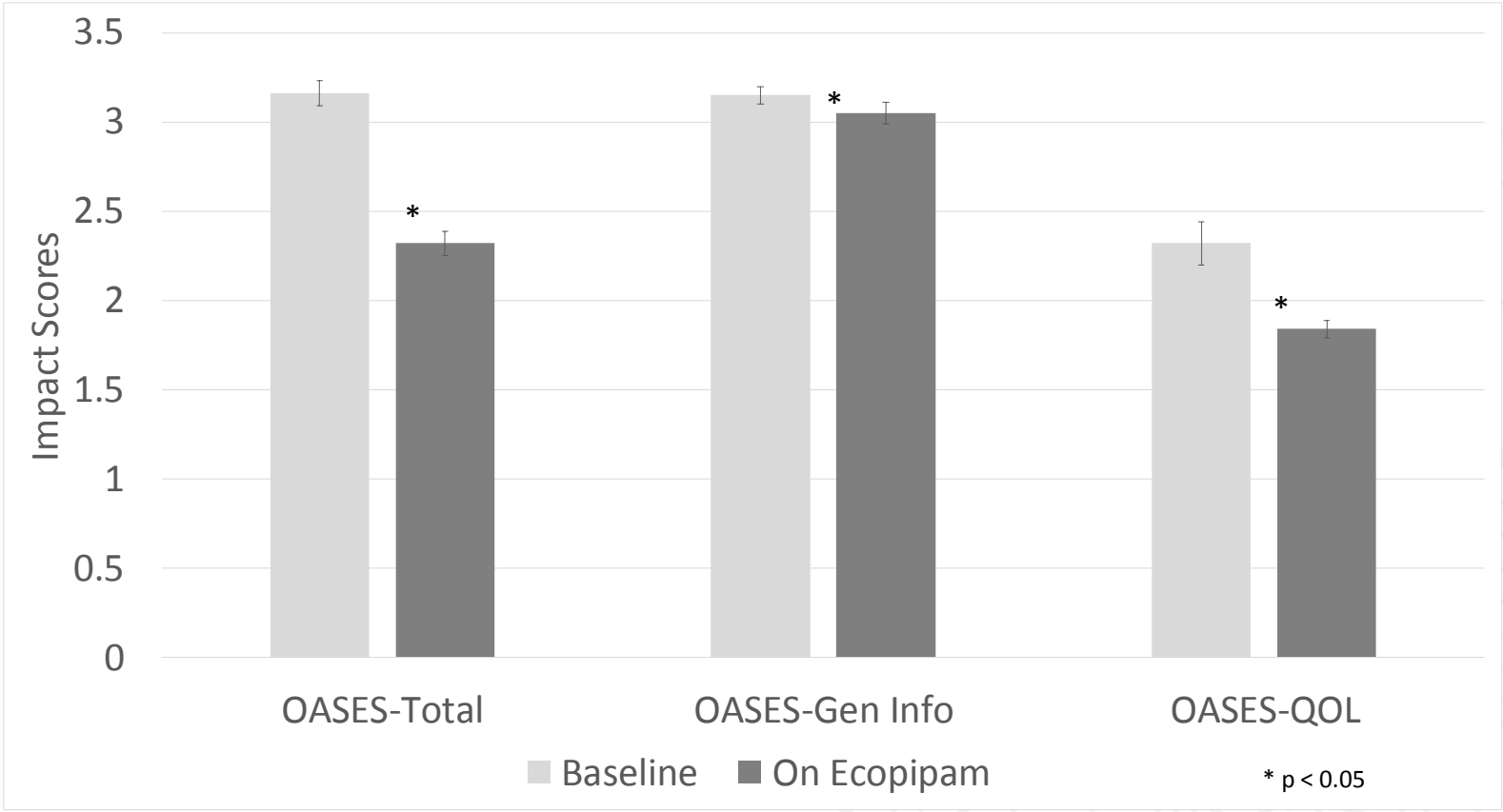
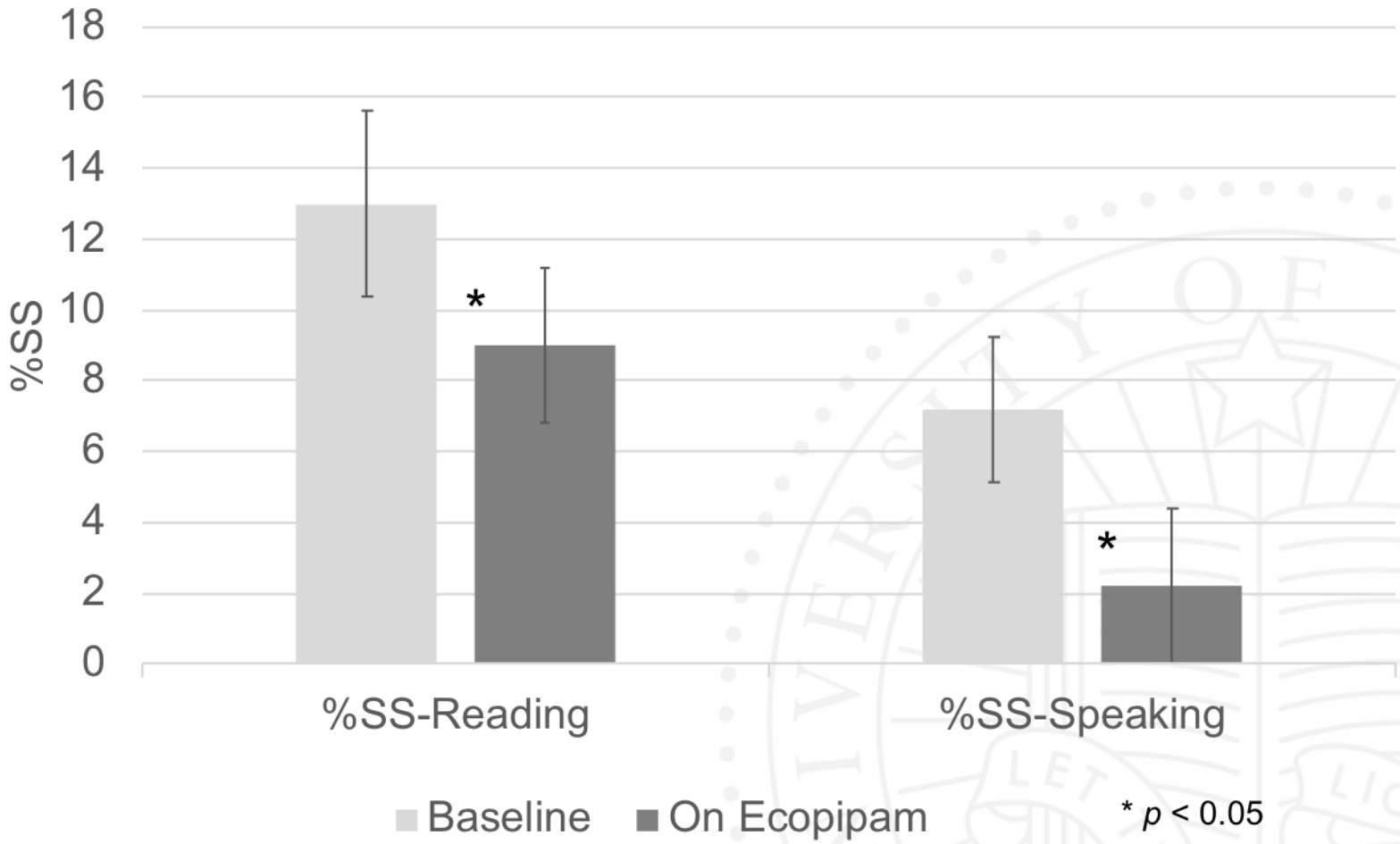


Figure 2 - % Syllabus Stuttered



Results

- Ecopipam (B condition)
  - Fluency improved, reduced %syllables stuttered in both reading and spontaneous speaking
  - Reading completion was faster
  - Stutter duration of the three longest stutters was shortest in the Ecopipam (B condition)
  - Attitudes improved
    - OASES
    - SSS

Discussion

- The findings support the need for a double-blind and randomized control clinical trial to examine the efficacy of ecopipam in the treatment of stuttering.

VMAT-2 Inhibitors

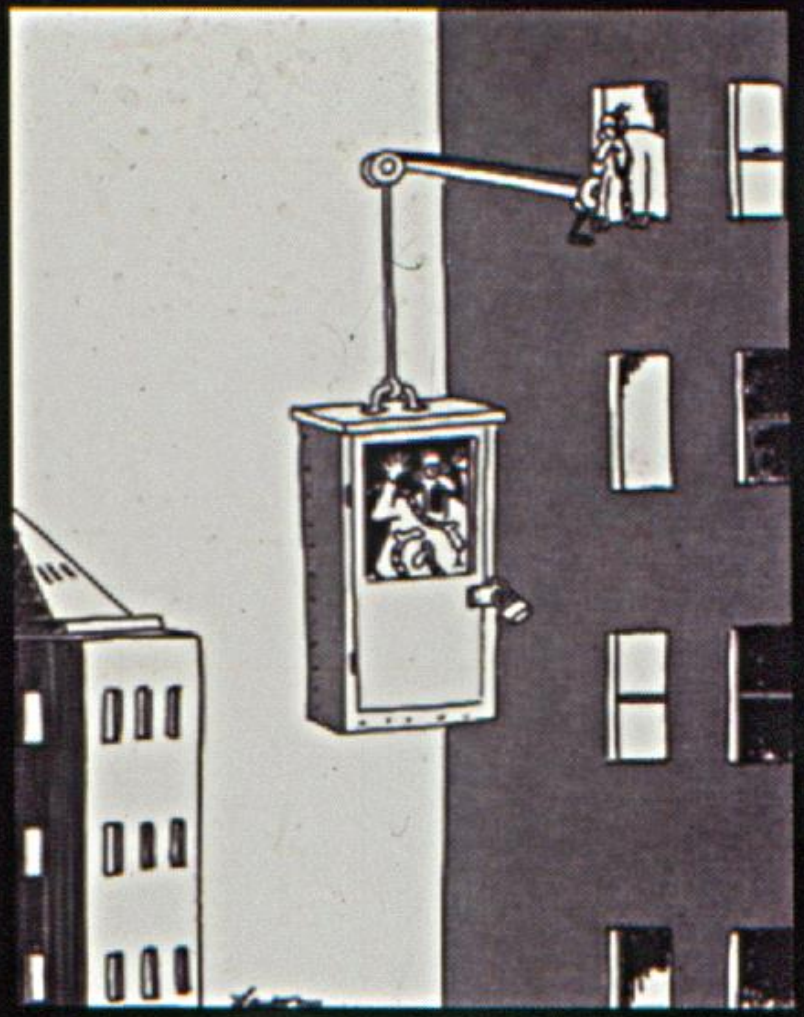
- Decrease synthesis of dopamine
- Two new forms available—valbenazine and deutetrabenazine
- May have potential of leading to depression but newer forms appear to have lower risk
- Efficacy shown in Tourette's, Tardive Dyskinesia, abnormal movements associated with Huntington's

Deep Brain Stimulation (DBS)

- Approved for Treatment of Parkinson's, Essential Tremor
- Cases in the literature of treatment of acquired stuttering
- First case published (Maguire et al, Am J. Psych) of treatment of developmental stuttering with DBS
- DBS case replicated in France
- Patent filed by Medtronic for DBS treatment of stuttering
- Key is identifying the target area

Future Directions in Stuttering Medical Research

- TMS
- TCDS
- How do we accurately assess changes in stuttering severity? Global scales consistent with treatment effect but what about more quantitative measures?
- Biologic Treatments with Speech Therapy?
- Pharmacogenomic Personalized Therapy?



"Professor Gallagher and his controversial technique of simultaneously confronting the fear of heights, snakes, and the dark." *Gary Larson*

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