Repetitive Transcranial Magnetic Stimulation in the Treatment of Tobacco Use Disorder

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Disclosure Information

- Christine E Sheffer, PhD, Professor of Oncology, Department of Health Behavior, Roswell Park Comprehensive Cancer Center
  - No Disclosures

Acknowledgments

- R21 CA178813-01 (PI: Sheffer/Mantovani). Enhancing relapse prevention with rTMS. Goal: To examine the feasibility of adding high frequency transcranial magnetic stimulation to a minimal relapse prevention intervention.

- P20 RR020146–06 (PI: Garcia-Rill). Project included in the Center for Translational Neuroscience. Project title: Changing thought and action with transcranial magnetic stimulation. Goal of project: Examine the influence of high-frequency rTMS on reward-related decision-making and cigarette smoking.

- R01 CA229415 (PI: Sheffer). Enhancing relapse prevention with rTMS: Dose-response parameters for smoking cessation. Goal: To determine a dosing strategy for 20Hz rTMS that will produce the best long-term abstinence outcomes with the fewest undesirable effects.

Learning Objectives

- Increase awareness of the research findings on the efficacy of TMS in addressing craving, withdrawal, abstinence among individuals with tobacco use disorder

- Better understand how the research findings on TMS in the management of tobacco use disorder may be applied in clinical practice

Significance

- Smoking kills ~480,000 individuals in the US annually
  - 30% of cancer deaths, 20% of all deaths in the US are attributable to smoking
  - Most smokers (70-80%) express a desire to quit
  - Over 50% make a quit attempt every year
- About 95% of smokers who make a quit attempt reverse the decision to quit within 12 months[1]
- Remains one of the most profound public health problems in the world

Babb, S., A. Malarcher, et al. (2017). "Quitting Smoking Among Adults - United States, 2000-2015." MMWR. Morbidity and mortality weekly report 65(52): 1457-1464.

Smoking and Substance Use Disorders

- The prevalence of cigarette smoking among individuals in recovery is up to four times greater than the general population[2, 3]

- More than half of individuals who attain sustained remission from other substance use disorders will die of tobacco-related disease[4]

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3. Guydish, J., B. Tajima, et al. (2016). "Use of multiple tobacco products in a national sample of persons enrolled in addiction treatment." Drug and Alcohol Dependence 166: 93-99.

4. Hurt, R. D., K. P. Offord, et al. (1996). "Mortality following inpatient addictions treatment. Role of tobacco use in a community-based cohort." JAMA 275(14): 1097-1103.

Treatment for Tobacco Use Disorder

- Evidence-based treatments for tobacco dependence[5]
  - Nicotine replacement
  - Varenicline
  - Bupropion
  - Cognitive-behavioral treatment
- Personalized treatment plans and combination therapies have the best outcomes
- Most individuals do not use an evidence-based treatment[1]

1. Babb, S., A. Malarcher, et al. (2017). "Quitting Smoking Among Adults - United States, 2000-2015." MMWR. Morbidity and mortality weekly report 65(52): 1457-1464.

5. Fiore, M. C., C. R. Jaén, et al. (2008). Treating tobacco use and dependence: 2008 update. Clinical practice guideline. U. D. o. H. a. H. Services. Rockville, MD, Public Health Service.

rTMS and Tobacco Use Disorder

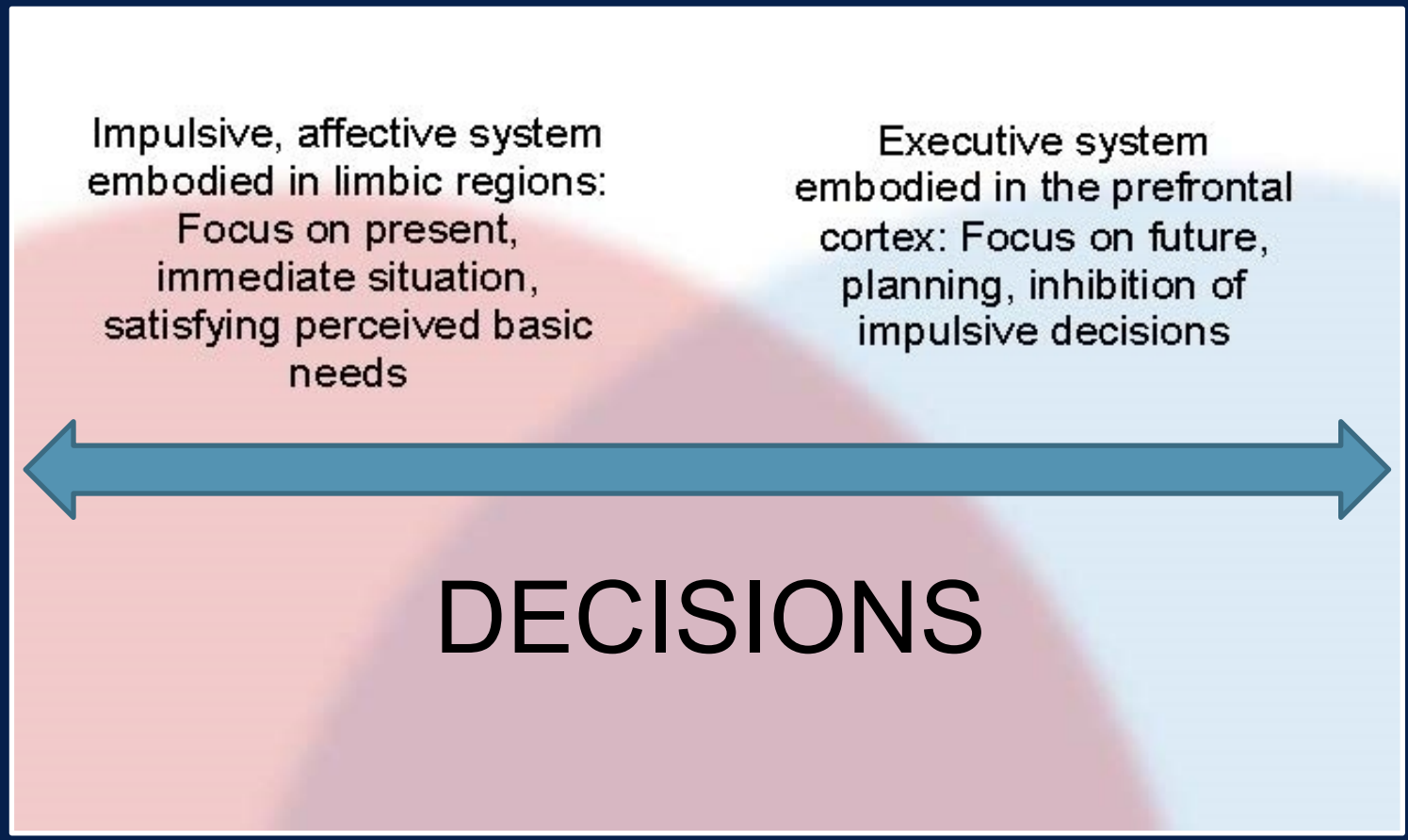
- Tremendous progress since Eichhammer et al. (2003)[6]
- Two dozen studies, several reviews [7,8, 9, 10]
- Results are promising, but mixed
- Not recommend as “efficacious” or “probably efficacious” therapy for Tobacco Use Disorder[11]

Inconsistent Findings

- Inconsistent findings likely associated with methodological variability[12]
  - Stimulation target
  - Targeting method
  - Frequency / power
  - Number of stimulation sessions
  - Motivation to quit among participants
  - Lack of a behavioral treatment component
  - Outcome assessments
    - Craving
    - Abstinence

12. Ekhtiari, H., H. Tavakoli, et al. (2019). "Transcranial electrical and magnetic stimulation (tES and TMS) for addiction medicine: A consensus paper on the present state of the science and the road ahead." Neurosci Biobehav Rev 104: 118-140.

Competing Neurobehavioral Decisions Systems Model



13. Bickel, W. K., M. L. Miller, et al. (2007). "Behavioral and neuroeconomics of drug addiction: competing neural systems and temporal discounting processes." Drug and Alcohol Dependence 90 Suppl 1: S85-91.

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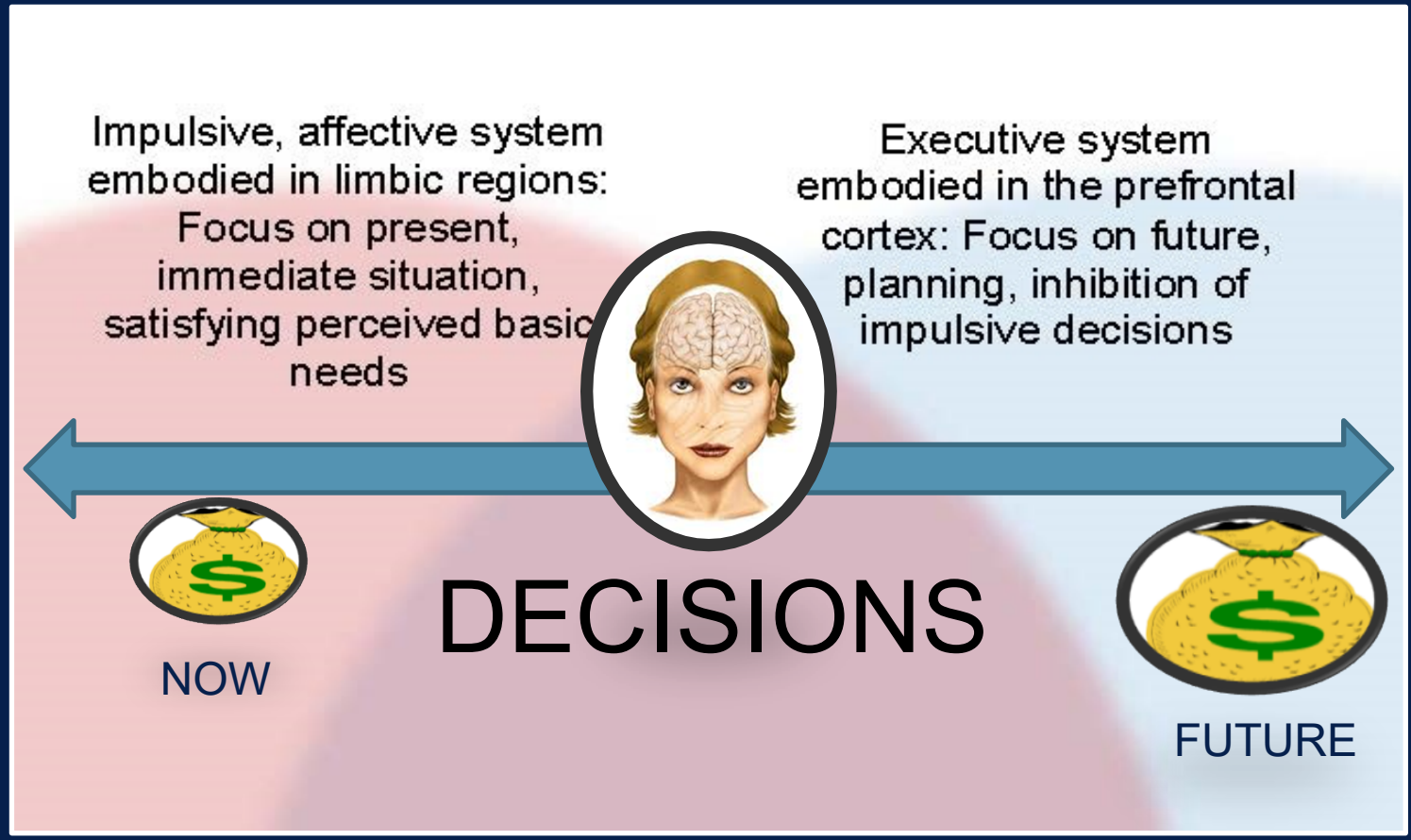

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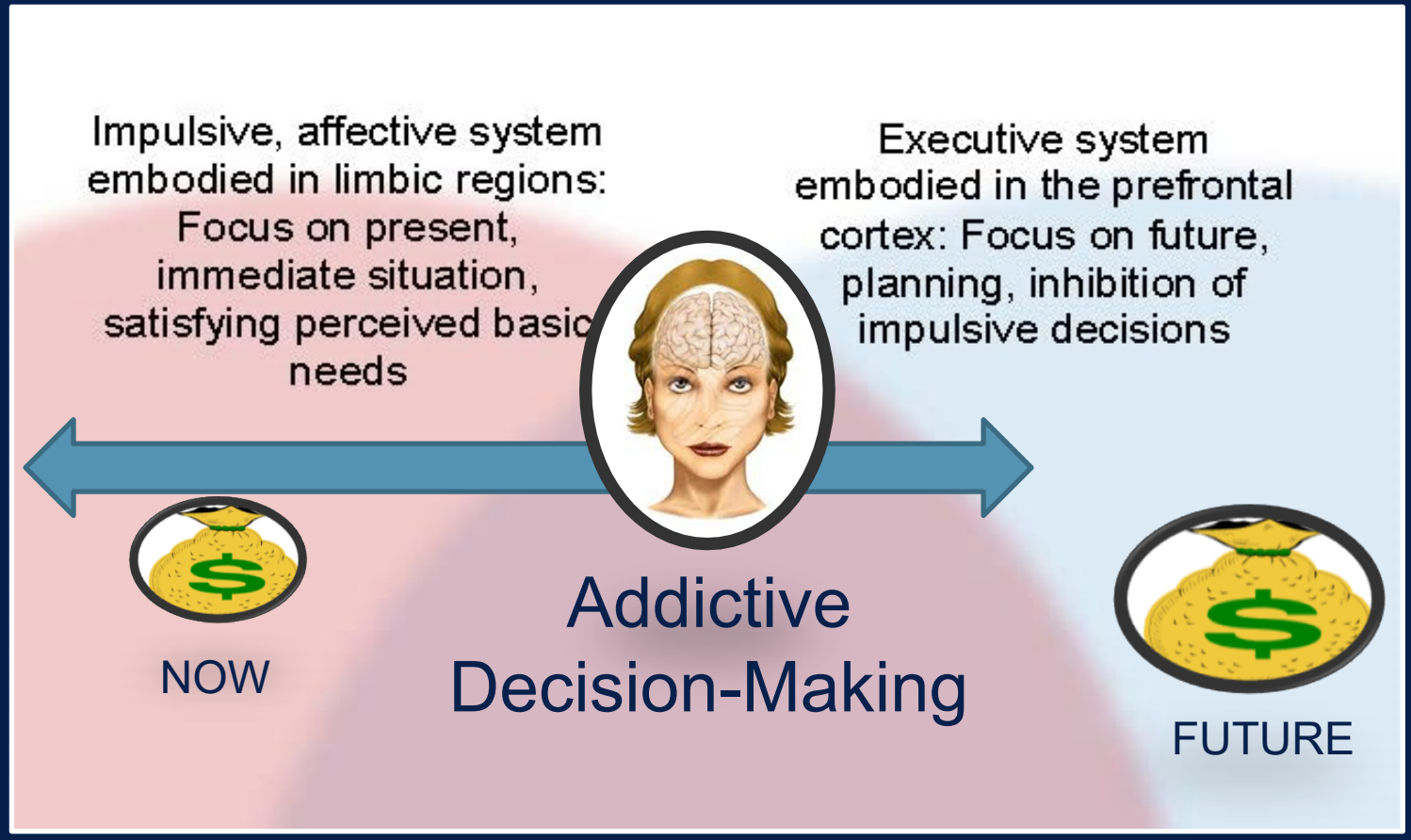

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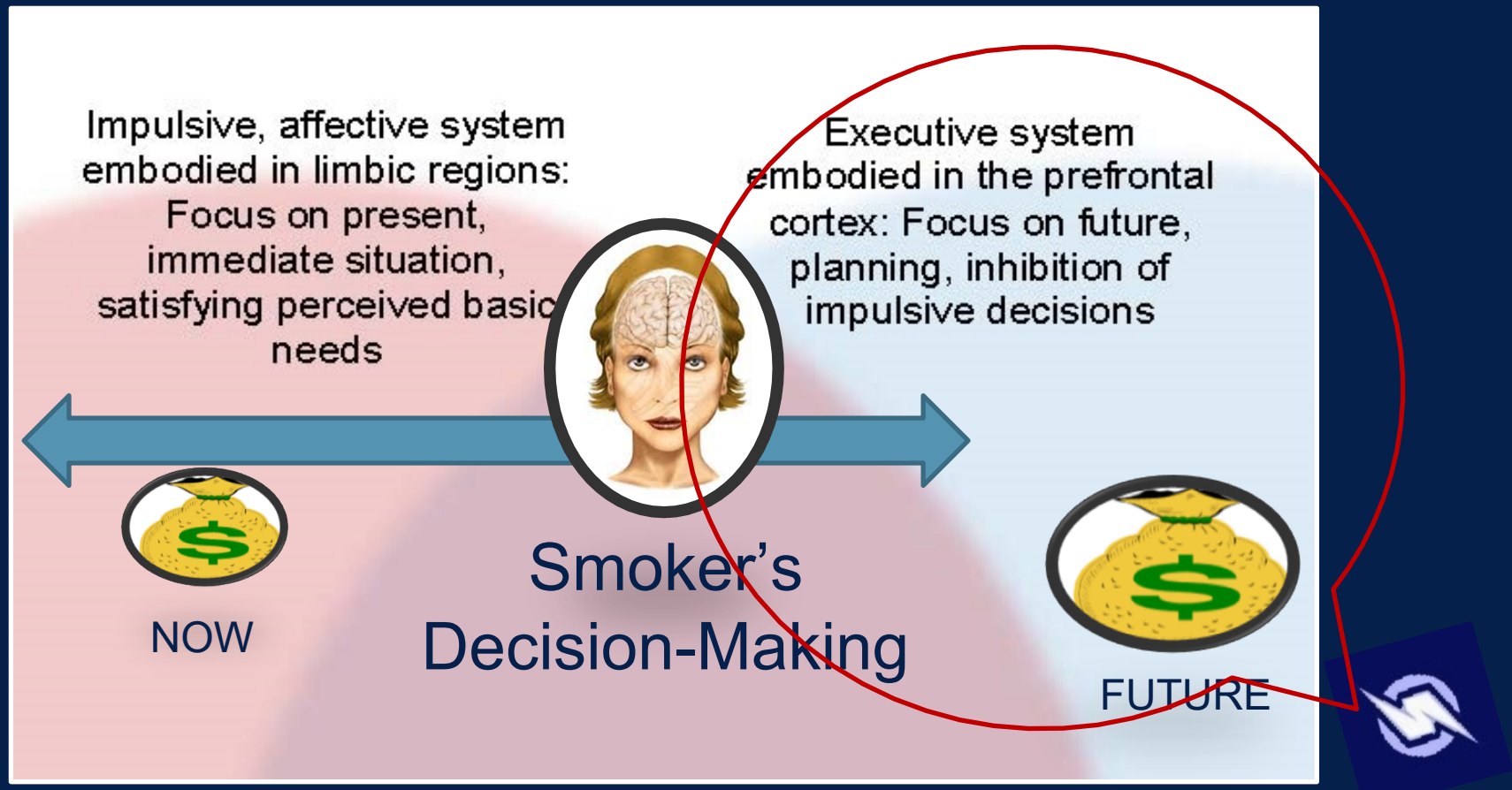

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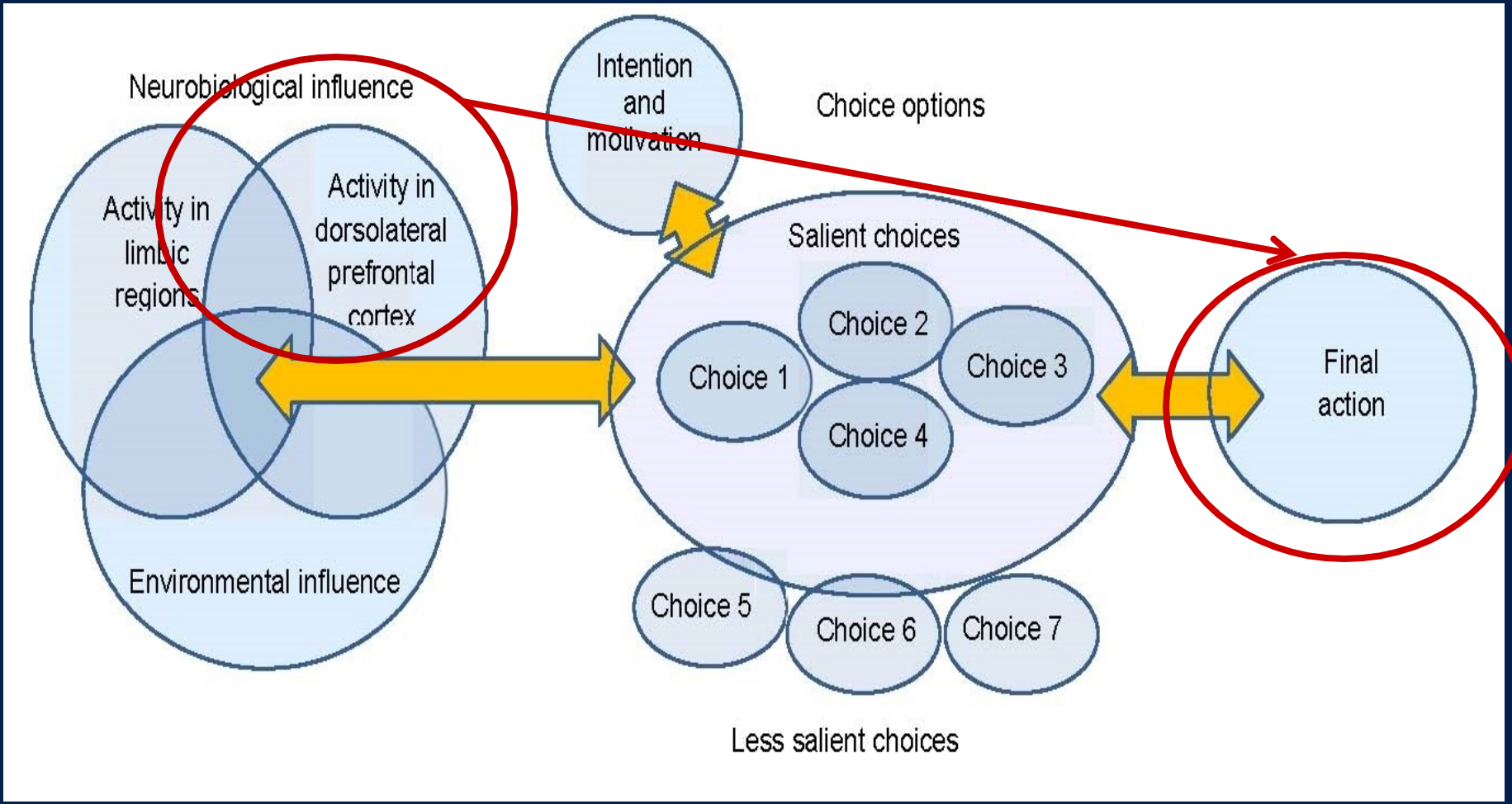
Expanded Model



15. Sheffer, C. E., W. K. Bickel, et al. (2018). "Preventing relapse to smoking with transcranial magnetic stimulation: Feasibility and potential efficacy." Drug and Alcohol Dependence 182: 8-18.

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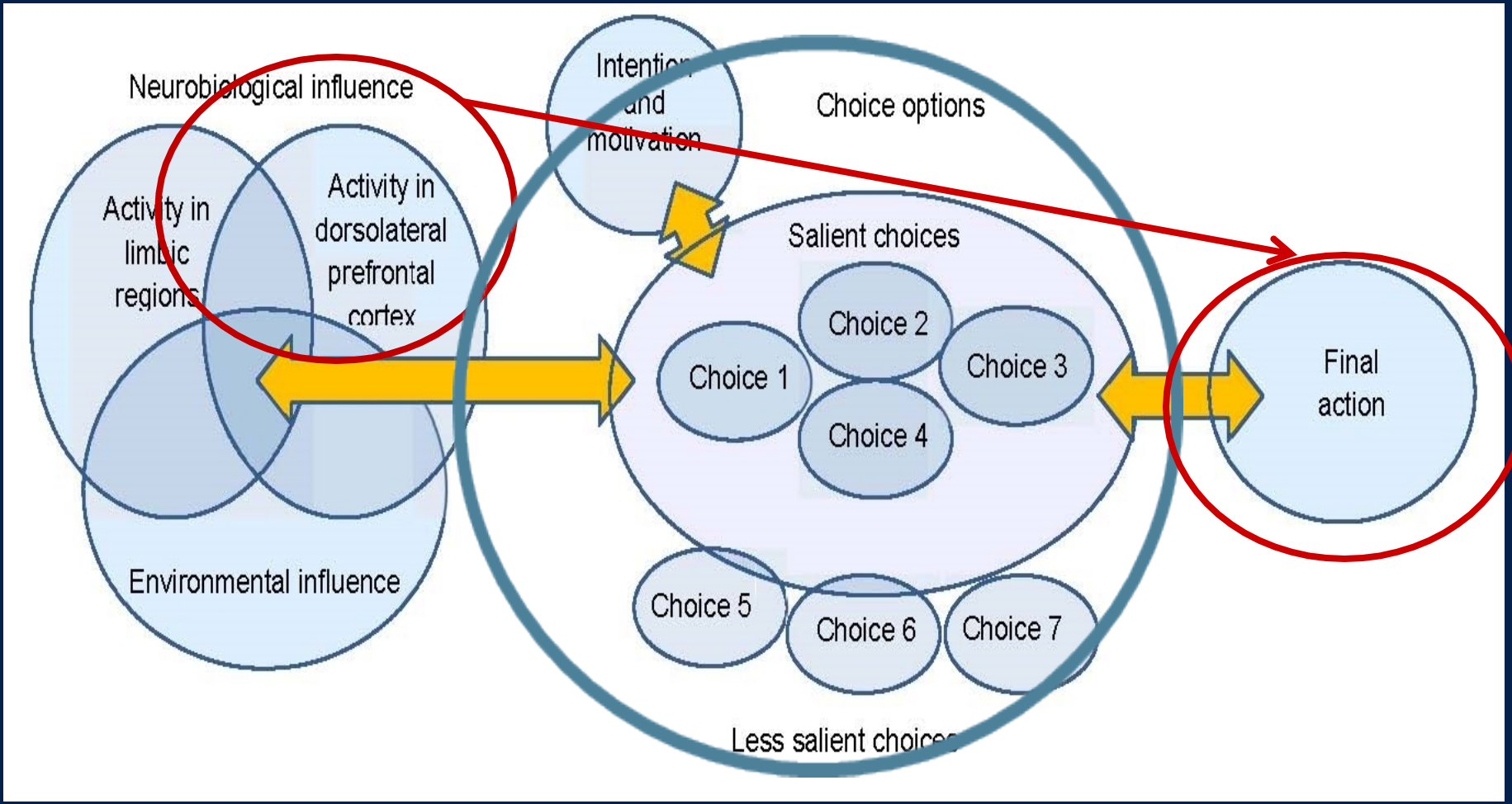

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Feasibility

- Feasibility study[15]
  - TMS Target – Left dorsolateral prefrontal cortex
  - Targeting method - neuro-navigation guided by MRI of the head
  - Frequency – 900 pulses of 20Hz 110% of MT (45 20-pulse trains of 1 second duration with an inter-train interval of 20 seconds)
  - 8 stimulation sessions
  - Combined with a minimal, self-help behavioral treatment component
    - Build on positive effects on learning and memory
  - Highly motivated, assessment consistent with other clinical trials
  - Well-established abstinence outcome measures

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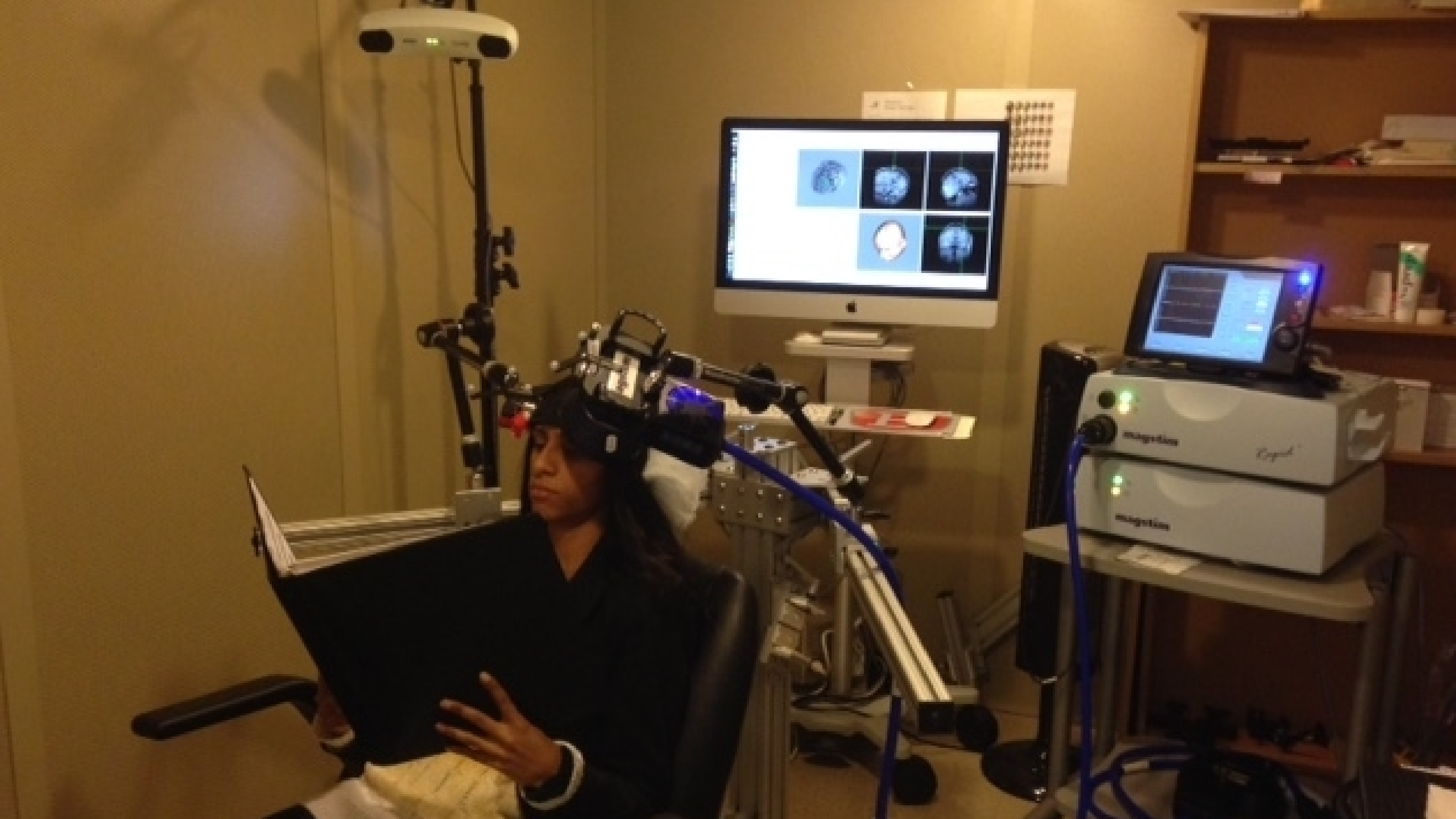
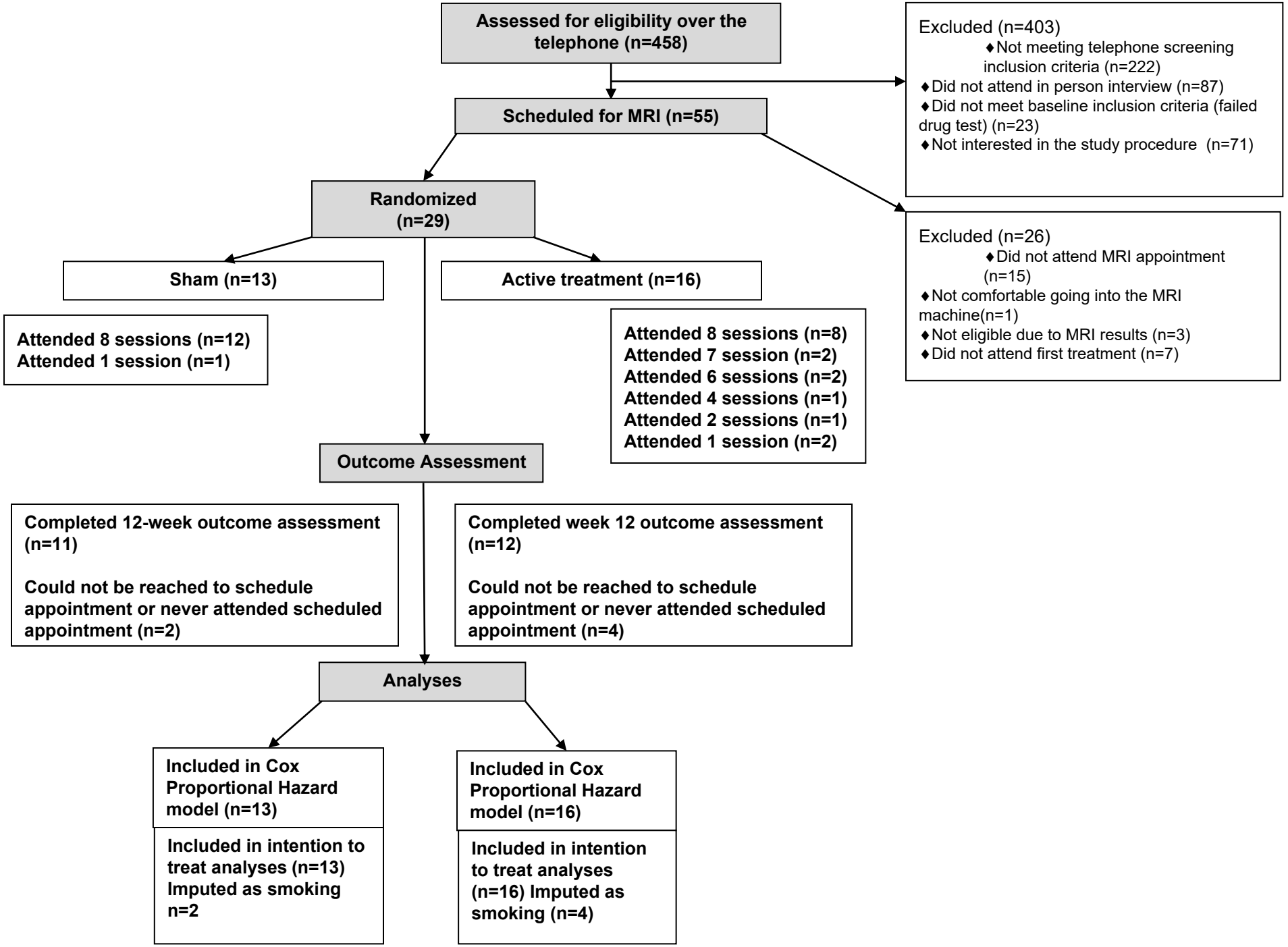



Assessed for eligibility over the telephone (n=458)
Excluded (n=403)
♦Not meeting telephone screening inclusion criteria (n=222)
♦Did not attend in person interview (n=87)
♦Did not meet baseline inclusion criteria (failed drug test) (n=23)
♦Not interested in the study procedure (n=71)
Scheduled for MRI (n=55)
Excluded (n=26)
♦Did not attend MRI appointment (n=15)
♦Not comfortable going into the MRI machine(n=1)
♦Not eligible due to MRI results (n=3)
♦Did not attend first treatment (n=7)
Randomized (n=29)
Sham (n=13)
Active treatment (n=16)
Attended 8 sessions (n=12)
Attended 1 session (n=1)
Attended 8 sessions (n=8)
Attended 7 session (n=2)
Attended 6 sessions (n=2)
Attended 4 sessions (n=1)
Attended 2 sessions (n=1)
Attended 1 session (n=2)
Outcome Assessment
Completed 12-week outcome assessment (n=11)
Could not be reached to schedule appointment or never attended scheduled appointment (n=2)
Completed week 12 outcome assessment (n=12)
Could not be reached to schedule appointment or never attended scheduled appointment (n=4)
Analyses
Included in Cox Proportional Hazard model (n=13)
Included in intention to treat analyses (n=13) Imputed as smoking n=2
Included in Cox Proportional Hazard model (n=16)
Included in intention to treat analyses (n=16) Imputed as smoking (n=4)

Participants

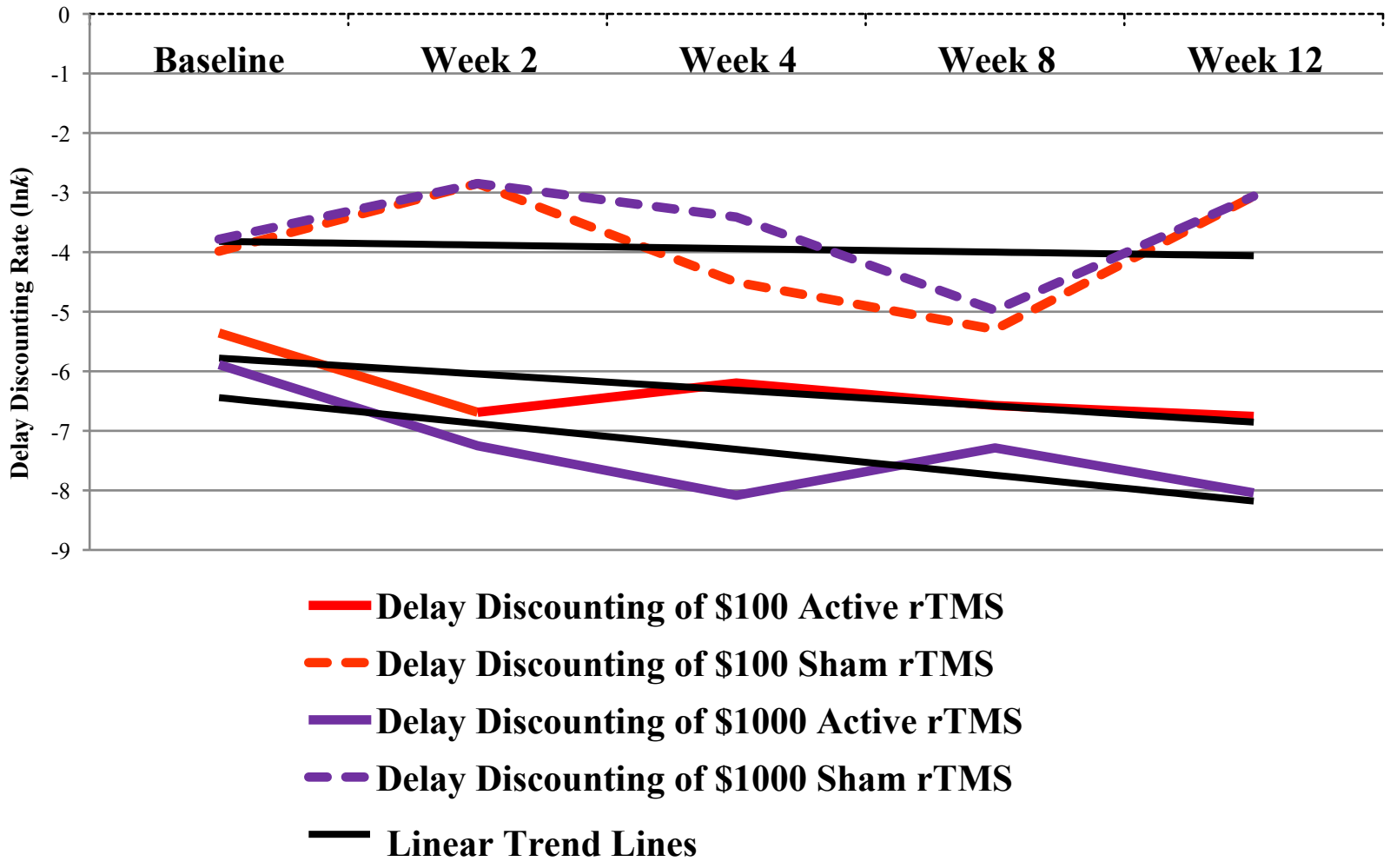
- Age 28-63
- 56% male
- 81% non-white
- Range of socioeconomic statuses
- Cigarettes per day
  - 10 or less 75%
  - 11-20 25%
- Mean Fagerstrom Test for Nicotine Dependence score 3.8
- Smoking for a mean of 19 years

Side effects reported immediately after stimulation session by condition

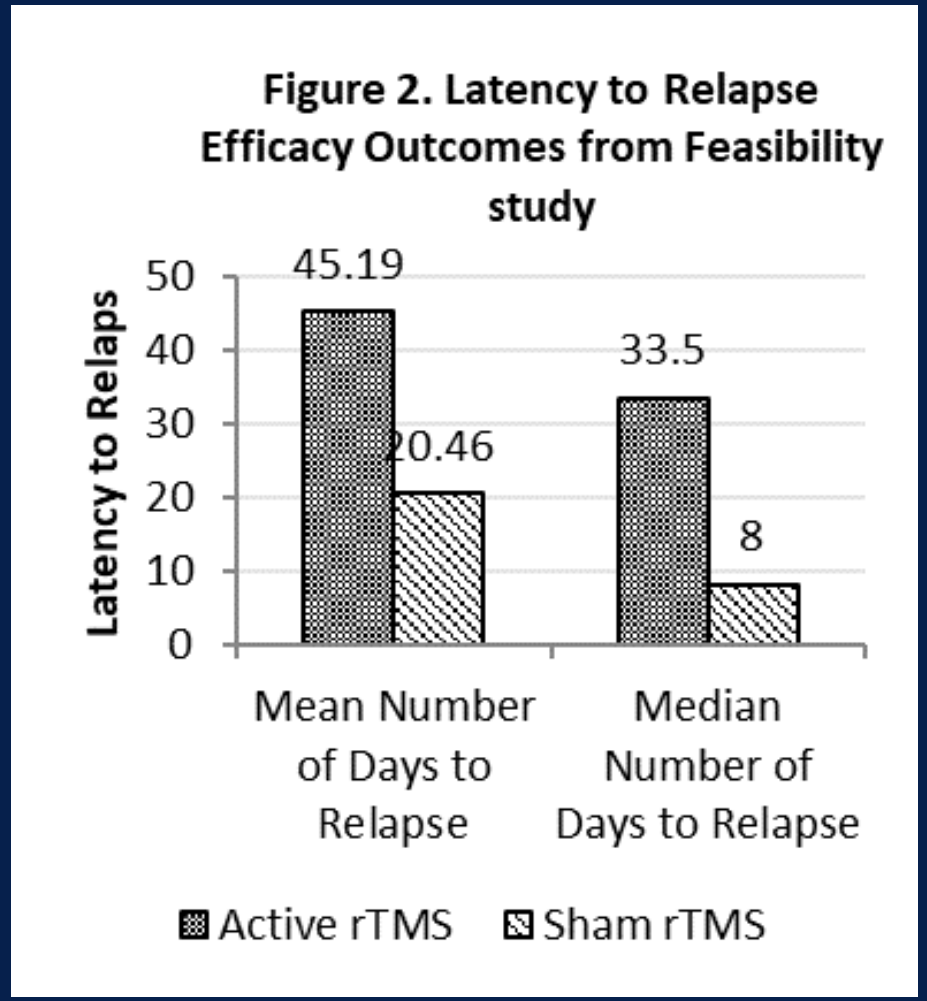
Session	Condition	No. of complaints	Specific complaints
1	Active (n=16)	25.0% (n=4)	Headache (n=3), Agitation/anxiety (n=1), Back pain (n=1)
	Sham (n=13)	None	
2	Active (n=14)	21.4% (n=3)	Headache (n=2), Increased positive mood (n=1)
	Sham (n=12)	None	
3	Active (n=13)	21.4% (n=3)	Headache (n=3)
	Sham (n=12)	None	
4	Active (n=13)	7.7% (n=1)	Headache (n=1)
	Sham (n=12)	8.3% (n=1)	Headache (n=1)
5	Active (n=12)	16.6% (n=2)	Headache (n=2)
	Sham (n=12)	None	
6	Active (n=12)	9.1% (n=1)	Headache (n=1)
	Sham (n=12)	None	
7	Active (n=10)	9.1% (n=1)	Blurry vision (n=1)
	Sham (n=12)	8.3% (n=1)	Headache (n=1)
8	Active (n=8)	12.5% (n=1)	Headache (n=1)
	Sham (n=12)	8.3% (n=1)	Neck pain (n=1)

Number of minutes devoted to and amount of content viewed/reviewed during the study

Timeline		**Minutes devoted to reading booklet content, mean (SD)**			**Percent of booklet content viewed/reviewed, mean (SD)**		
		Active	Sham	p-value	Active	Sham	p-value
Weeks 1-2 (during stimulation period)	Inside of treatment sessions	87.1 (42.9)	96.3 (30.1)	.52	69.4 (27.9)	76.8 (17.1)	.41
	Outside of treatment sessions	43.0 (38.5)	62.3 (76.0)	.41	9.3 (7.1)	16.3 (14.6)	.12
Weeks 3-4		8.9 (15.3)	1.3 (4.3)	.41	9.4(13.7)	0.9(3.1)	**.04**
Week 4-8		11.1 (12.1)	2.3 (5.2)	**.04**	7.2 (8.6)	3.3 (8.1)	.28
Weeks 8-12		37.3 (50.2)	0 (0)	**.02**	36.2 (37.1)	0 (0)	**<.01**
Sum weeks 4, 8, 12		45.6 (44.3)	3.6 (6.4)	**<.01**	46.0 (45.8)	3.9 (8.0)	**<.01**


0
-1
-2
-3
-4
-5
-6
-7
-8
-9
Baseline
Week 2
Week 4
Week 8
Week 12
Delay Discounting Rate (lnk)
Delay Discounting of $100 Active rTMS
Delay Discounting of $100 Sham rTMS
Delay Discounting of $1000 Active rTMS
Delay Discounting of $1000 Sham rTMS
Linear Trend Lines

Abstinence



- Latency to relapse – number of days to relapse
  - Relative Risk 0.29, CI 0.10-0.76, Likelihood ratio $\chi 2$ with 1 df = 6.40, p =.01)
    - Exploratory: Including FTND as covariate

      RR 0.40, CI: 0.13-1.10, Likelihood ratio $\chi 2$ with 1 df = 3.13, p =.08
- Point prevalence abstinence 12 weeks after the quit date:
  - Active 50% vs. Sham 15.4%, X^2 (df=1) = 3.80, p=.05

    Smoking imputed for missing data

Conclusions

- Feasible
- Well-tolerated
- Potential efficacy for supporting abstinence
- Evidence supports a larger randomized clinical trial
- More data is needed about optimal dosing

rTMS Dosing for Tobacco Use Disorder

rTMS Dosing Study Design

INTENSITY: SESSIONS PER DAY	DURATION: STIMULATION DAYS					
	8 active	***8 sham***	***12 active***	***12 sham***	***16 active***	***16 sham***
	Within 14 days		***Within 21 days***		***Within 28 days***	
1x per day (900 pulses per day)	8 sessions per person (n=32)	8 sessions per person (n=11)	12 sessions per person (n=32)	12 sessions per person (n=11)	16 sessions per person (n=32)	16 sessions per person (n=11)
2x per day (1800 pulses per day)	16 sessions per person (n=32)	16 sessions per person (n=11)	24 sessions per person (n=32)	24 sessions per person (n=11)	32 sessions per person (n=32)	32 sessions per person (n=11)

Intensity = number of pulses per day; Duration = number of days in which participant receives stimulation

Innovations

- Combining rTMS
  - Rendering circuits more susceptible to rTMS
    - Increasing learning
    - Decreasing cue-induced reactivity or craving
- Combining rTMS with evidence-based treatments
- Important to investigate new treatment elements that show efficacy and how TMS may or may not interact with them
- Combining with other methods to normalize delay discounting rates

Final Takeaways/Summary

- TMS therapy for the treatment of Tobacco Use Disorder is likely to be efficacious, but probably needs to be combined with behavioral treatment and/or other evidence-based treatments to be robust
- Many questions remain about dosing, stimulation target, frequency, timing, persistence of effects

References

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