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Transcranial Magnetic Stimulation and Electroencephalography Markers of Adolescent Depression and Suicidality

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Disclosures

Dr. Lewis

- Research grant support from the Mayo Clinic Foundation (Departmental Small Grant Program) and the Brain and Behavior Research Foundation (NARSAD Young Investigator Award)
- Site sub-investigator/treater for multi-site clinical trials sponsored by Neuronetics, Inc. and NeoSync, Inc.

Dr. Doruk Camsari

- Research grant support from Mayo Clinic Foundation Departmental Small Grant Program (co-investigator)

Will discuss a non-FDA-approved use of repetitive transcranial magnetic stimulation (rTMS) for treatment of adolescents

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Learning Objectives

- Understand how transcranial magnetic stimulation (TMS) can be used for both neurophysiologic research and as a neuromodulatory treatment
- Identify what has been learned from TMS research about brain physiology in adolescent depression and suicidality
- Review available evidence for TMS as a treatment for adolescent depression
- Learn about quantitative EEG (QEEG) and its potential applications in understanding the pathophysiology of adolescent depression and suicidality, as well as in guiding future treatments

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Transcranial Magnetic Stimulation (TMS): Investigational Tool of Cortical Physiology and Neuromodulatory Treatment

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What is Transcranial Magnetic Stimulation?

- High-intensity **magnetic field** induces **electrical current** in conductive material, including neural tissue
- **Geometry of electromagnetic coil** permits focusing magnetic field to a limited area
- Stimulation results in **action potentials in neurons** of stimulated area
- Effects of stimulation **propagated through neural circuits** connected to stimulated region

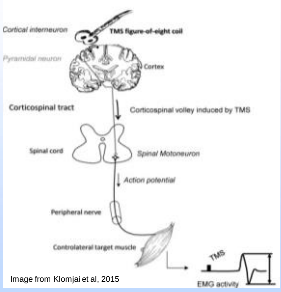

Image from Klomjai et al, 2015

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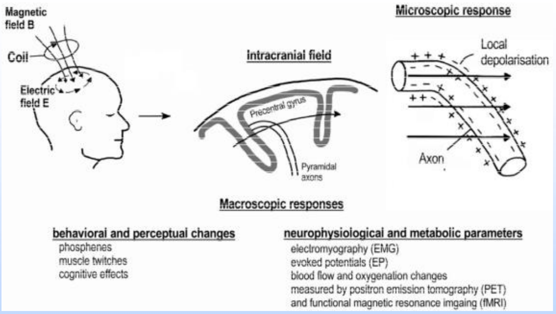

Image from Sack & Linden, *Brain Res Rev*, 2003.

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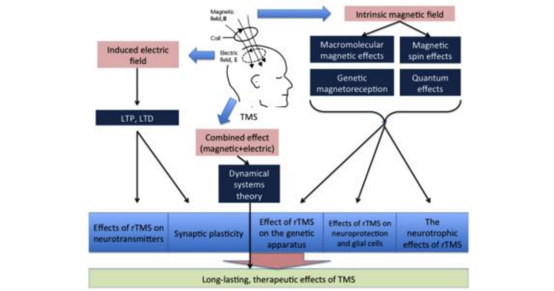
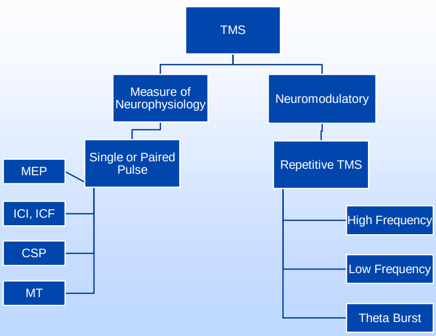


FIGURE 3 | The general scheme of the influence of magnetic and electric fields.

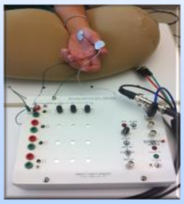
Image from Chervyakov et al., *Front Hum Neurosci*, 2015.



Transcranial Magnetic Stimulation (TMS): Brain Physiology in Adolescent Depression and Suicidality

TMS as a Neurophysiologic Probe

- Single or paired pulses can induce distinct and replicable effects on neural circuits by varying intensity, intervals between stimuli
- Can be measured by established objective methods (EMG, EEG)



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TMS-EMG Measures of Cortical Excitability and Inhibition

Measure	Pulse	Interstimulus Interval	Mechanism
Motor threshold (RMT/AMT)	single	(n/a)	NMDA, AMPA, voltage-gated Na^+ channels
Cortical silent period (CSP)	single	(n/a)	$GABA_A$, $GABA_B$
Short-interval intracortical inhibition (SICI)	paired	2 - 4 ms	$GABA_A$
Intracortical facilitation (ICF)	paired	7 - 20 ms	NMDA
Long-interval intracortical inhibition (LICI)	paired	50 - 200 ms	$GABA_B$

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Ziemann et al. *Clin Neurophysiol*, 2015.

TMS-EMG Measures of Cortical Excitability and Inhibition

TMS-induced Motor Evoked Potential (MEP)

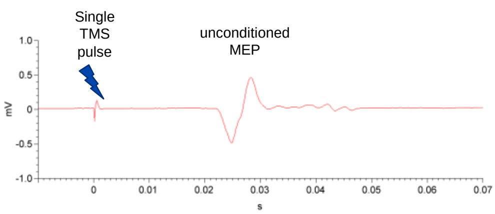

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Image adapted from Lewis et al. *Front Neural Circuits*, 2016.

TMS-EMG Measures of Cortical Excitability and Inhibition

Short-Interval Intracortical Inhibition (SICI)

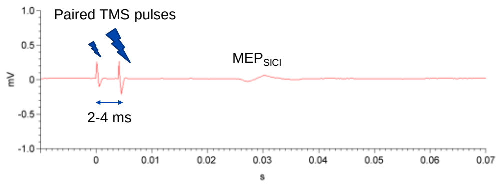


Image adapted from Lewis et al. *Front Neural Circuits*, 2016.

TMS-EMG Measures of Cortical Excitability and Inhibition

Intracortical Facilitation (ICF)

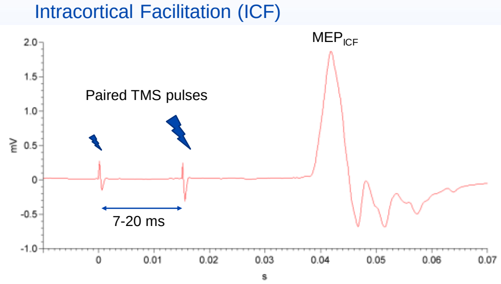
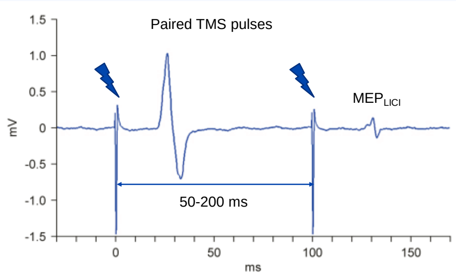


Image adapted from Lewis et al. *Front Neural Circuits*, 2016.

TMS-EMG Measures of Cortical Excitability and Inhibition

Long-Interval Intracortical Inhibition (LICI)



TMS-EMG Measures of Cortical Excitability and Inhibition

Cortical Silent Period (CSP)

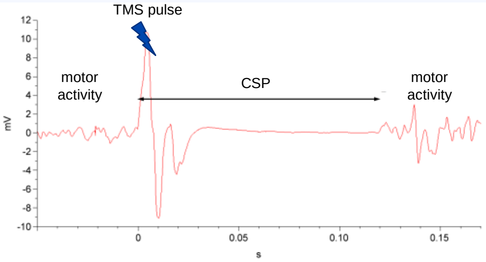


Image adapted from Lewis et al. *Front Neural Circuits*, 2016.

Cortical Excitability and Inhibition in Major Depressive Disorder

- Impaired cortical inhibition in adult MDD studies
  - Reduced CSP duration (Bajbouj et al., 2006; Lefaucheur et al. 2008); vs. increased (Steele et al., 2000)
  - Reduced SICI (Bajbouj et al., 2006; Lefaucheur et al., 2008)
  - Levinson et al. (2010): three MDD groups exhibited reduced CSP duration (vs. controls); treatment-resistant MDD group also showed reduced SICI amplitude
- Meta-analysis of adult MDD studies (Radhu et al., 2013)
  - Shortened CSP (g=-1.232, 95% CI -1.530 to -0.933, p=0.000)
  - Impaired SICI (g=0.641, 95% CI 0.384 to 0.898, p=0.000)

Steele et al. *Psychol Med*, 2000.
Bajbouj et al. *Biol Psychiatry*, 2006.
Lefaucheur et al. *J Psychiatr Res*, 2008.
Levinson et al. *Biol Psychiatry*, 2010.
Radhu et al. *Clin Neurophysiol*, 2013.

Cortical Excitability and Inhibition in Adolescents

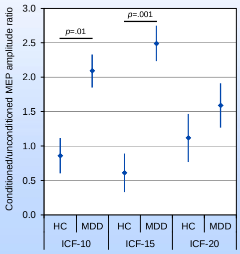
- GABA and glutamate systems are dynamic in youth
  - Subunit composition of receptors shifts throughout development, affecting functions
  - GABA receptors have excitatory effect in early life
  - Receptor density changes into young adulthood; rates vary across brain structures, with cortex among the last to develop into adult patterns
- Excitatory and inhibitory TMS measures (RMT, LICI) show developmental effects in depressed adolescents (Croarkin et al., 2014)

Duncan et al. *J Psychiatr Res*, 2010.
Chugani et al. *Ann Neurol*, 2001.
Rakhade and Jensen. *Nat Rev Neurol*, 1999.
Croarkin et al. *Front Hum Neurosci*, 2014.

Cortical Excitability in Adolescent MDD

- Medication-naïve adolescents with MDD (n=24) vs. healthy control adolescents (n=22)
- Increased cortical facilitation (10 ms, 15 ms) in both left and right hemispheres in MDD group

	Least Squares Mean (SE)		
TMS Measure	MDD Patients (n=24)	Healthy Controls (n=22)	p-value (p_{FDR})
ICF-10	2.09 (0.24)	0.86 (0.26)	.01
Right hemisphere	1.99 (0.26)	0.84 (0.28)	.03 (.11)
Left hemisphere	2.19 (0.25)	0.87 (0.27)	.01 (.05)
ICF-15	2.49 (0.26)	0.61 (0.28)	.001
Right hemisphere	2.46 (0.28)	0.53 (0.30)	<.001 (.005)
Left hemisphere	2.53 (0.27)	0.69 (0.29)	.001 (.007)
ICF-20	1.59 (0.32)	1.12 (0.35)	.47
Right hemisphere	1.51 (0.34)	1.12 (0.37)	.55
Left hemisphere	1.68 (0.33)	1.13 (0.36)	.41



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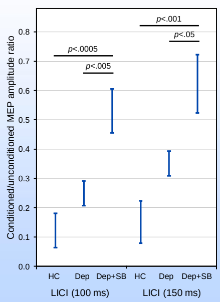
Croarkin et al. *JAMA Psychiatry*, 2013.

Impaired Cortical Inhibition in Adolescents with Lifetime Suicidal Behavior

	Least Squares Mean (SE)			
TMS Measure	**Healthy Control (n=20)**	**Depressed (n=37)**	**Depressed+SB (n=17)**	**p-value (p_{FDR})**
Cortical Excitability				
RMT	51.757 (3.193)	53.591 (1.607)	52.413 (2.738)	0.8484 (0.8484)
ICF				
ISI=10 ms	1.476 (0.128)	1.580 (0.086)	1.398 (0.102)	0.3601 (0.4801)
ISI=15 ms	1.407 (0.132)	1.658 (0.078)	1.553 (0.128)	0.3127 (0.4801)
ISI=20 ms	1.295 (0.147)	1.692 (0.087)	1.528 (0.138)	0.0945 (0.3780)
Cortical Inhibition				
CSP	0.184 (0.011)	0.166 (0.005)	0.150 (0.010)	0.1216 (0.2432)
SICI				
ISI=2 ms	0.505 (0.069)	0.430 (0.043)	0.406 (0.066)	0.6061 (0.6061)
ISI=4 ms	0.751 (0.091)	0.642 (0.052)	0.707 (0.074)	0.5158 (0.6061)
LICI				
ISI=100 ms	0.122 (0.059)	0.249 (0.042)	0.530 (0.075)	**0.0002 (0.0012)**
ISI=150 ms	0.151 (0.072)	0.351 (0.042)	0.623 (0.099)	**0.0013 (0.0039)**
ISI=200 ms	0.975 (0.143)	0.795 (0.084)	0.713 (0.147)	0.5147 (0.6061)



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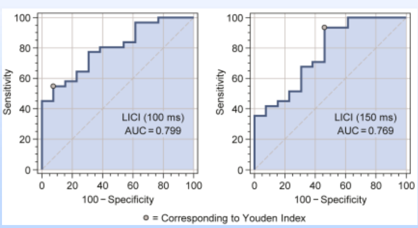
Lewis et al. *Neuropsychopharmacology*, 2018.

Impaired Cortical Inhibition in Adolescents with Lifetime Suicidal Behavior

- ROC analysis of LICI for discriminating Depressed from Depressed+SB youth



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Lewis et al. *Neuropsychopharmacology*, 2018.

Cortical Inhibition in Adolescent Suicidality

- Does impaired inhibition correspond to chronic risk (i.e., "suicidal trait") vs. fluctuating, state-dependent risk?
  - Partial correlation (controlling for change in depression severity) between change in LICI-100 and change in suicidal ideation intensity: ρ=.746, *df*=7, *p*=.021 (Lewis et al. 2019)
- Need for longitudinal studies tracking cortical inhibition and suicidal risk and behaviors over time

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Lewis et al. *J Affect Disord*, 2019.

Cortical Inhibition in Adolescent Suicidality

- How does impaired LICI correspond to higher-level behavioral characteristics of suicidal youth (e.g., impulse control, affect regulation, emotional salience processing)?
- How does motor cortex inhibition correspond to inhibition in other regions and networks?
  - LICI can be measured by TMS-EEG (Daskalakis et al., 2008; Farzan et al., 2010, 2016)
  - LICI correlates with connectivity measured by resting-state fMRI (Balzekas et al., 2018)

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Daskalakis et al. *Neuropsychopharmacology*, 2008.
Farzan et al. *J Neurophysiol*, 2010.
Farzan et al. *Front Neural Circuits*, 2016.
Balzekas et al. *Psychiatry Res Neuroimaging*, 2018.

TMS-Measured Cortical Excitability and Inhibition: Potential Clinical Applications

- Need to improve tools for clinical evaluation and interventions
- Risk assessment and stratification
- Prediction of treatment response
  - TMS-EEG-measured cortical inhibition predicted reduction of suicidal ideation with MST (Sun et al., 2016)
- Individualize targeting and dosing of neuromodulatory interventions

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Sun et al. *JAMA Psychiatry*, 2016.

Transcranial Magnetic Stimulation (TMS): Neuromodulatory Treatment for Depression

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TMS: Therapeutic Applications

- Repeated stimulation can modulate excitatory and inhibitory functions of neural circuits, including areas distant to stimulation site
- Considerations:
  - Frequency (high vs. low)
  - Patterned pulses (e.g., theta burst stimulation)
  - Placement of coil
  - Intensity of magnetic stimuli
  - Number of pulses
  - Scheduling of rTMS sessions

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rTMS

<5 Hz: inhibitory

>5 Hz: excitatory

TBS (50 Hz)

cTBS: inhibitory

iTBS: excitatory

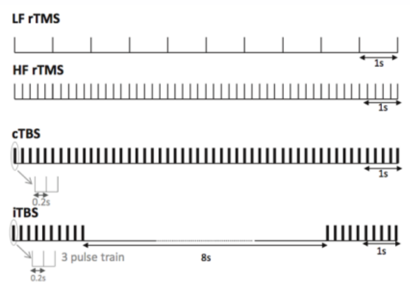

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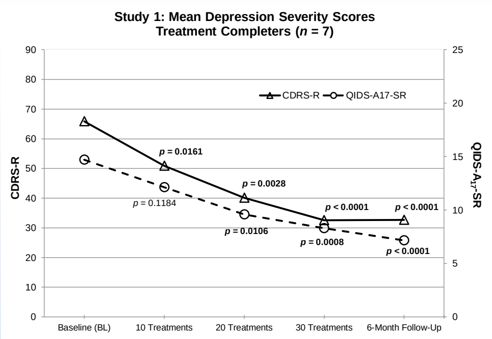
Image from Klomjai et al. *Ann Phys Rehabil Med*, 2015.

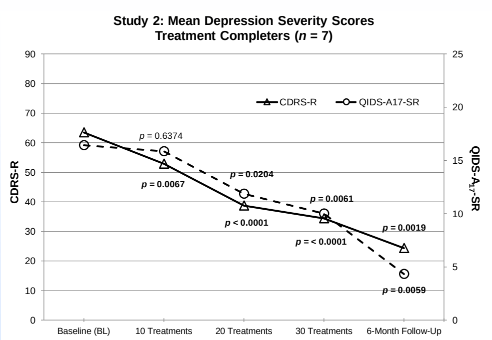
rTMS in Adolescent Depression
Case Series and Open-Label Trials

Study	Popul-ation	Age Range	*n*	Psycho-tropic Medic-ation	Coil Place-ment	Freq-uency	Stimulus Intensity (%MT)	Stimuli/ Train	Trains	Inter-train Interval	Stimuli/ Session	Sess-ions	Duration (weeks)	Antidepressant Outcomes
Walter et al. (2001)	TRD	16-17y	3	N	Left DLPFC	10 Hz	90-110%	40-80	20-40	52-56 s	1600	10	2	TRD: improvement on HDRS, BDI at end of treatment and 2 weeks post-treatment in 2/3 patients
	BD	18y	1	Y	Right DLPFC	1 Hz	110%	1600	1	n/a	1600	10	2	BD: no improvement on HDRS or CGI at end of rTMS; substantial improvement 2 weeks post-treatment
Loo et al. (2006)	MDD	16y	2	Y/N	Left DLPFC	10 Hz	110%	50	40	25 s	2000	29-36	6-11	Improvement in MADRS, BDI, CES-DC, and CGI-S at end of treatment and one month; symptomatic and functional improvements maintained at 3-4 months
Bloch et al. (2008)	TRD	16-18y	9	Y	Left DLPFC	10 Hz	80%	20	20	58 s	400	14	3	3/9 patients responded (≥30% reduction in CDRS); on continuous measures (CDRS, BDI, SCARD), improvement with study stage (all $p < .05$), continued improvement at 1 month after rTMS (all $p < .05$)
Mayer et al. (2012)														At 3 years post-rTMS, no significant change from 1-month post treatment on CDRS-R, BDI-II; 5/8 patients minimally depressed at 3 years
Wall et al. (2011)	TRD	14-17y	8	Y	Left DLPFC	10 Hz	120%	40	75	26 s	3000	30	6-8	Improvement in CDRS-R, QIDS-A_{17}-SR, and CGI-S at end of treatment (all $p < .001$); improvements maintained at 6 months (all $p < .001$)
Le et al. (2013)	TS	7-16y	25	Y	Bilateral SMA	1 Hz	110%	60	20	1 s	1200	20	4	Statistically significant improvement in CDI at end of treatment ($p = .001$), maintained at 3 and 6 months
Yang et al. (2014)	TRD	15-21y	8	Y	Left DLPFC	10 Hz	120%	40	75	26 s	3000	15	3	4/6 completers responded (≥50% reduction on HDRS), with mean decreases of 68% on HDRS, 84% on BDI, and 78% on HARS
Wall et al. (2016)	TRD	13-17y	10	Y	Left DLPFC	10 Hz	120%	40	75	26 s	3000	30	6-8	6/10 responded (CGI-I of 1-2, with CGI-S ≤ 3); improvement in CDRS-R, QIDS-A_{17}-SR, and CGI-S at end of treatment and 6 months after rTMS (all $p < .05$)

Adapted from Lewis et al., *Neurotechnology and Brain Stimulation in Pediatric Psychiatric and Neurodevelopmental Disorders*, (forthcoming 2018).



Wall et al. *J Clin Psychiatry*, 2011.



Wall et al. *J Child Adolesc Psychopharmacol*, 2016.

Adverse Effects of rTMS in Children and Adolescents

- Systematic review (Krishnan et al., 2015) of 35 rTMS studies in a total of 322 children/adolescents with a variety of neuropsychiatric conditions:
  - Headache (11.5%)
  - Scalp discomfort (2.5%)
  - Muscle twitching (1.2%)
  - Mood changes (1.2%)
  - Fatigue (0.9%)
  - Tinnitus (0.6%)
  - Seizure (0.6%, *n*=2)
  - Syncope (0.6%, *n*=2)

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Krishnan et al. *Brain Stimul*, 2015.

FDA Regulatory Approvals

- 2008:
  - First rTMS device approved for marketing by the U.S. FDA for the treatment of major depression (adults)
  - Other devices have subsequently obtained FDA clearance for MDD indication
- 2018:
  - Deep TMS approved for treatment of obsessive compulsive disorder
  - First approval of theta burst stimulation device for MDD
- No devices currently cleared for treatment of MDD in adolescents

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rTMS in Children and Adolescents: Ongoing and Future Research

- Multisite RCT
  - 10 Hz rTMS, 6 weeks (30 sessions), *n*=100
- Mayo Clinic (PI: Paul Croarkin)
  - Biomarker-stratified (ICF)
  - Phase I (6 weeks): 1 Hz vs. 10 Hz rTMS, left DLPFC
  - Phase II (2 weeks): cTBS vs. iTBS, left DLPFC
  - Weekly TMS neurophysiology and clinical measures
  - 7T magnetic resonance spectroscopy

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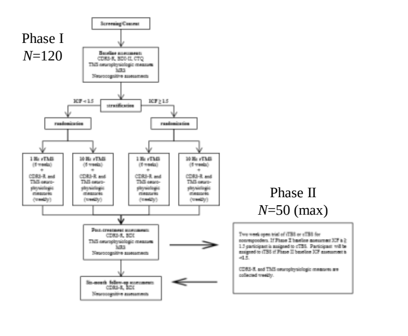
rTMS in Children and Adolescents: Ongoing and Future Research



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rTMS in Children and Adolescents: Ongoing and Future Research

- Future intervention for suicidal ideation/behavior?
  - Odds of suicidal ideation decreased over 6-week course of rTMS in open-label study of 19 adolescents (Croarkin et al., 2018)
  - Magnitude of decrease nonsignificant adjusting for illness severity
  - Need for studies designed specifically to target brain structures/networks implicated in suicidality
  - Need for measures and outcomes specifically designed to assess suicidal ideation/behavior and underlying constructs

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Croarkin et al. *J Affect Disord*, 2018.

Quantitative EEG (QEEG) and its potential applications in understanding the pathophysiology of adolescent depression and suicidality

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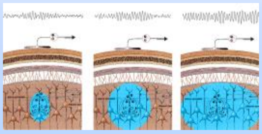
EEG

- Based on volume conduction of ionic currents generated by nerve cells through the extracellular space.
- Recorded EEG potentials arise from extracellular current flow from summated EPSPs and IPSPs.
- The EEG does not record activity from single neurons but is dependent on the summation of thousands to millions of postsynaptic potentials.
- Thalamocortical pathways along with cortical circuitry are the main neuroanatomical structures involved in EEG generation.



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Advantages

- Lower hardware cost
- Higher temporal resolution - ms
- Silent - better for auditory stimulus
- Relatively tolerant to movement
- No IV ligands
- No claustropobhia
- More flexible

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Disadvantages

- Lower spatial resolution
- Poor recording for layers below cortex
- Can be time consuming
- Poor signal to noise ratio- more sophisticated analysis and large number of subject is needed

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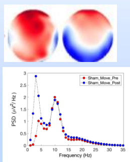
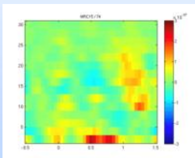
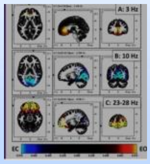
Quantitative EEG

Quantitative EEG (QEEG) is the mathematical processing of digitally recorded EEG in order to highlight specific waveform components, transform the EEG into a format or domain that elucidates relevant information, or associate numerical results with the EEG data for subsequent review or comparison.







Nuwer. *Neurology*, 1997.

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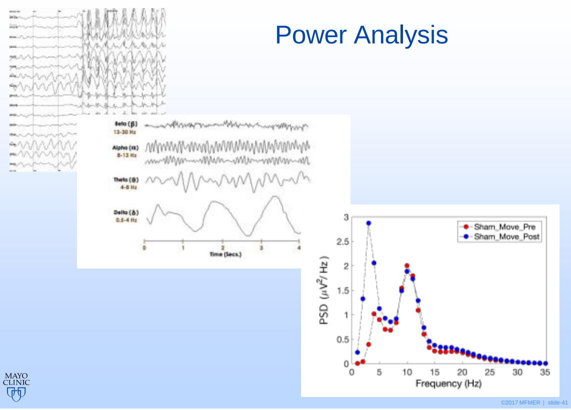
Power Analysis



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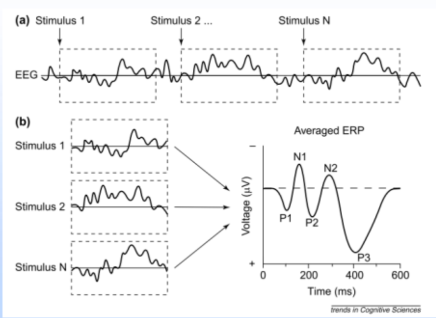
Event Related Potentials



Luck et al. *Trends Cogn Sci*, 2000

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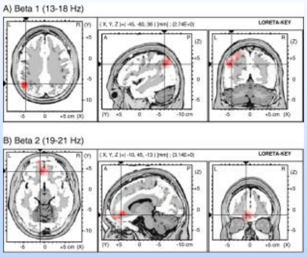
Source Localization
Low resolution electromagnetic tomography



Lee et al. *Schizophr Res*, 2006.

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QEEG in Psychiatry

- Depression
- ADHD, learning disabilities
- Dementia
- Schizophrenia
- Cognition

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QEEG in Psychiatry

QEEG is useful for research purposes and rare;y in a clinical context. No QEEG method has as yet become accepted as providing reliable, independent markers for psychiatric disease or treatment response

Diagnostic?

Discriminative?

Treatment outcome?

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Suicide

- Suicide is the second leading cause of death among young people (WHO 2014).
- Multiple risk factors: environmental factors, affective processes, cognitive processes, social factors and biological correlates (Cha et al., 2018)

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WHO, 2014. Preventing suicide: a global imperative.
Cha et al., *J Child Psychol Psychiatry*, 2018.

Suicide

- One-third of those who experience suicidal ideations proceed with suicide attempt or plan within one year of the onset of ideations (Nock et al., 2013; Glenn et al., 2017)
- Depends on subjective reports which could be concealed due to multiple reasons such as fear of stigma, avoiding involuntary treatment, lack of insight and transient nature of suicidal thoughts.
- It has been estimated that 78% of suicide completers deny any suicidal thoughts before they die (Bush et al., 2003).

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Nock et al. *JAMA Psychiatry*, 2013.
Glenn et al. *Depress Anxiety*, 2017.

Correlates of suicidality in adolescents

EEG
- Increased fronto-central theta power
- P300 amplitude
- Frontal and Posterior alpha asymmetry

TMS Neurophysiologic Measures
- LICI and other measures of cortical inhibition (CSP, SICI)

Neuroimaging (Resting-State fMRI)
- Attempters could be discriminated from non-attempters by their brain activity in the left superior medial frontal area, medial frontal/anterior cingulate and the right middle temporal area

Implicit Association Test
- Implicit associations between self and death/suicide had approximately six-fold increase in the odds of making a suicide attempt at 6-month follow-up (Nock 2010)

Psychosocial factors
- Internalizing and externalizing symptoms, maternal depression, socioeconomic status, trauma history

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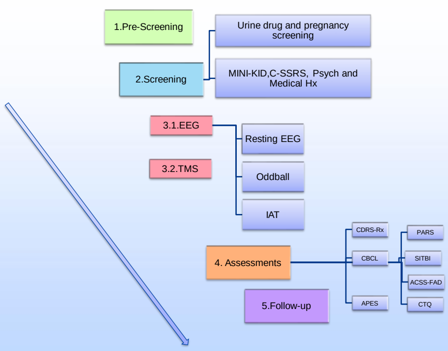
Quantitative EEG correlates of suicidality in adolescents

30 participants between ages 13-18 years old with suicidal behaviors (suicide attempt, suicidal ideations, intent, plan, and non-suicidal self-injurious behaviors) and 30 age- and gender- matched healthy controls will be recruited in this case-control study.



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Questions & Discussion