An Introduction to Seizures
for the TMS Clinician or Investigator

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A 30-year-old woman with an episode of left facial twitching
Outline

• Definitions and epidemiology

• Seizures as an adverse effect of TMS

• Epilepsy as a therapeutic target of TMS

• Differential diagnosis and seizure types

• The acute response to an unexpected seizure

• Diagnostic workup and management
Seizures are defined by pathophysiology, not by specific symptoms

• Seizure
  – A clinical episode of neurologic dysfunction caused by the abnormal hypersynchronous activity of a group of neurons

• Epilepsy
  – Any disorder characterized by a tendency toward recurrent, unprovoked seizures
  – In practice, diagnosed after two unprovoked seizures
Seizures and epilepsy are common, and incidence is highest in the young and in the old

- Prevalence of epilepsy in the general population is about 0.5%, or 1 in 200 persons
- Cumulative lifetime incidence of one or more seizures is 5-10%, including febrile seizures

Annegers, 2001

Stephen and Brodie, 2000
Seizures occur when an imbalance of excitation and inhibition exists in the nervous system.

Examples:
- hypoxic-ischemic brain injury
- developmental brain malformation
- traumatic brain injury
- neurosurgery
- brain tumors
- alcohol-related
- strokes
- CNS infections
- neurodegenerative diseases
- CNS demyelination/inflammation
- inborn errors of metabolism
- systemic illness (metabolic, infectious)

Modified from White, 2001
The early literature highlighted seizures as a possible complication of TMS

- 1 stroke patient out of 150 developed a seizure within 30 secs after TMS (Homberg and Netz, 1989)

- 2 healthy subjects out of 9 developed seizures acutely during TMS (stimulation frequency 10 Hz, 25 Hz) (Pascual-Leone et al., 1993)
Data now suggest that TMS-associated seizures are rare in those without prior history

- It is unclear if single- or paired-pulse TMS have ever been associated with a seizure in a normal individual without risk factors (Kratz et al., 2011; Alonso-Alonso et al., 2011)

- As of a comprehensive 2008 review, there had been 16 total cases of seizures in individuals without an apparent prior history of seizures, 9 of which occurred since the 1998 safety guidelines, and most of which involved rTMS and some possible pro-epileptogenic risk factors (Rossi et al., 2009)

- One seizure was reported in a healthy individual without risk factors receiving continuous theta burst stimulation (Obermann and Pascual-Leone, 2009)
The risk of TMS-associated seizures even in those with known epilepsy is still quite low:

- All were typical seizures followed by typical recovery
- Impossible to be certain about their relationship to TMS
- No long-lasting adverse effects

Table 4
Crude risk of a seizure occurring in association with TMS in epilepsy subjects: a pooling of published data and UCLA experience

<table>
<thead>
<tr>
<th>Condition</th>
<th>Single-pulse TMS</th>
<th>Paired-pulse TMS</th>
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<tbody>
<tr>
<td>Risk of seizure during TMS</td>
<td>8 in 717 (1.1%)</td>
<td>1 in 120 (0.8%)</td>
</tr>
<tr>
<td>Risk if seizure during or within 4 min of TMS</td>
<td>8 in 463 (1.7%)</td>
<td>1 in 56 (1.8%)</td>
</tr>
<tr>
<td>Risk if seizure during TMS if AEDs were lowered</td>
<td>11 in 717 (1.5%)</td>
<td>2 in 120 (1.7%)</td>
</tr>
<tr>
<td>Risk if no change in AEDs</td>
<td>11 in 463 (2.4%)</td>
<td>2 in 56 (3.6%)</td>
</tr>
<tr>
<td>Risk if medically intractable epilepsy</td>
<td>6 in 213 (2.8%)</td>
<td>1 in 36 (2.8%)</td>
</tr>
<tr>
<td>Risk in well-controlled epilepsy</td>
<td>2 in 500 (0.4%)</td>
<td>0 in 84 (0.0%)</td>
</tr>
<tr>
<td>Risk if medically intractable epilepsy</td>
<td>8 in 525 (1.5%)</td>
<td>1 in 81 (2.2%)</td>
</tr>
<tr>
<td>Risk in well-controlled epilepsy</td>
<td>0 in 74 (0.0%)</td>
<td>0 in 31 (0.0%)</td>
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</tbody>
</table>

AED, antiepileptic drug; TMS, transcranial magnetic stimulation.

\(^a\) Excludes subjects from articles that did not specifically comment upon seizures or side effects.

Schrader et al., 2004
The risk is low even in patients with known epilepsy undergoing rTMS

- Crude risk of induced seizures in patients with known epilepsy during a rTMS session estimated to be 1.4% (4 out of 280 patients)

- Only one reported case of an atypical seizure, apparently arising from stimulation site (16 Hz)

- No instances of status epilepticus

- No TMS-linked seizures in 152 patients with epilepsy who had weekly rTMS at ≤1 Hz in therapeutic trials

Bae et al., 2007

tabulated in Rossi et al., 2009
In an epilepsy patient, it may be hard to know whether a seizure during TMS is causally related.

- Clinical seizure in a 22-year-old man with drug-resistant epilepsy of frontopolar onset

Vernet et al., 2012
But seizures are still important to learn about as part of TMS training

• They are the most dramatic and medically dangerous acute complication of TMS

• IRB/ethics boards expect them to be addressed as a risk of TMS research

• The world of TMS usage has expanded:
  – To researchers who are not physicians or clinicians who are not familiar with neurological disorders
  – To labs that are not located proximate to medical facilities
  – To patient or subject populations with known epilepsy or with neurological disorders that lead to an increased risk of seizures
Outline

• Definitions and epidemiology
• Seizures as an adverse effect of TMS
• Epilepsy as a therapeutic target of TMS
• Differential diagnosis and seizure types
• The acute response to an unexpected seizure
• Diagnostic workup and management
In selected epilepsy patients, low-frequency rTMS to cortical targets reduces seizures

Targeting the epileptogenic zone in 64 patients, 0.5 Hz rTMS high-intensity vs. low-intensity for 2 weeks

Targeting cortical malformations in 21 patients, 1 Hz rTMS vs. sham for 5 sessions

Sun et al., 2012; Fregni et al., 2006
TMS-evoked potentials recorded on EEG may be a useful and sensitive biomarker of epilepsy

This patient had no interictal epileptiform discharges (spikes) on 11 days of continuous EEG recording

Shafi et al., 2015
We are using MRI connectivity to guide rTMS targeting in epilepsy patients with deep lesions.
Seizures are classified by their origin in the brain and associated clinical features

- **Partial-onset or focal-onset**
  - Simple partial
  - Complex partial

- **Generalized-onset**
  - Generalized tonic-clonic
  - Absence
  - Myoclonic

- All partial-onset seizures can become secondarily generalized
Partial Motor and Somatosensory Seizures

Motor cortex arranged in specific zones. Body areas involved in seizure may help localize seizure focus.

Motor cortex
- Leg
- Trunk
- Arm
- Hand
- Face

Seizure initially involves facial portion of motor cortex.

Seizure spreads to involve hand portion of motor cortex.

Supplementary motor cortex

Affected areas may remain paralysed for several hours (Todd paralysis).

Partial Sensory and Autonomic Seizures

Formed visual hallucinations (posterior temporal, parietal, occipital, visual association cortex, temporal limbic cortex)

Formed auditory hallucination: ringing, buzzing

Simple auditory illusion or hallucination: music, voices

Unformed visual hallucination (occipital lobe)

Olfactory seizures (uncinate gyrus)

Abnormal or disagreeable taste: metallic, garlicky

Epigastric fullness

Abdominal rising sensation

Visceral

Visceral and autonomic seizures (insular, cingulate gyrus, and frontal temporal areas)

Simple partial seizure (rost motor seizure with Jacksonian spread)

Clonic facial grimace

Tonic-clonic movements of upper limb

Usually disagreeable odor, such as burnt rubber

Head and eyes turn to side opposite lesion

Typical posturing with contralateral arm

Simple partial seizure originates in supplementary motor cortex

Sensory symptoms may spread in Jacksonian fashion (Jacksonian sensory march)

Sensory cortex

Dumbness and tingling

Involvement of supplementary motor cortex results in versive movements

Somatosensory cortex also arranged in anatomic zones

Gustatory seizures (parietal and insular areas)

Nausea

Sweating

Flushing

Autonomic

Netter F, Ciba collection of medical illustrations
Generalized Tonic–Clonic Seizures

Tonic phase

- Simultaneous bilateral cortical seizure activity
- Loss of consciousness, fall, cry, and generalized tonic stiffening, often with bladder incontinence
- Cyanosis

Clonic phase

- Jerking of limbs
- Salivary frothing

Postictal phase

- Patient lethargic and confused after seizure, often sleeps
- Postictal period may last minutes to hours

Stages of generalized tonic–clonic seizure

- Tonic phase
- Clonic phase
- Postictal phase

- Generalized fast repetitive spikes with muscle artifact
- Generalized spike and slow wave activity
- Generalized attenuation of activity

Netter F, Ciba collection of medical illustrations
Temporal Lobe Epilepsy

Simple partial seizure
- Consciousness preserved. Fear and déjà vu sensation

Complex partial seizure
- Spread to opposite hippocampus results in altered consciousness

Secondary generalized tonic-clonic seizure
- Ipsilateral arm waves in circular fashion
- Secondary generalization of temporal lobe seizure
- Central lateral hand in dystonic position

Spread to entire cortex, thalamus, and midbrain structures results in secondary generalized tonic-clonic seizure

Simple partial seizure (aura: epigastric fullness)

Complex partial seizure (altered consciousness, hand posturing)

Secondary generalized tonic-clonic seizure

EEG. Progression of seizures in temporal lobe epilepsy
Most seizures in adults are focal-onset, even those that end up generalized tonic-clonic

Seizure types in the elderly population

- Complex partial, 43%
- Partial, secondarily generalized, 42%
- Primary generalized, 12%
- Simple partial, 4%

Holt-Seitz et al., 1999
Complex partial seizures of temporal lobe origin can have fairly distinct characteristics.
Some focal seizures may have minimal motor manifestations and be misdiagnosed, however
All focal-onset seizures can become secondarily generalized tonic-clonic seizures
The generalized tonic-clonic phase has a fairly stereotyped appearance.
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There is little to do acutely for most types of seizures

• Absence, myoclonic, simple partial seizures
  – Usually no intervention necessary except reassurance when event ends

• Complex partial seizures
  – Allow event to run its course while preventing patient from encountering harm
  – Patients may become hostile or violent if actively restrained
Some standard measures are taken for generalized tonic-clonic seizures

<table>
<thead>
<tr>
<th>Action 1</th>
<th>Action 2</th>
</tr>
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<tbody>
<tr>
<td>Cushion Head</td>
<td>Loosen Necktie</td>
</tr>
<tr>
<td>Turn On Side</td>
<td>Nothing In Mouth</td>
</tr>
<tr>
<td>Look For ID</td>
<td>Don't Hold Down</td>
</tr>
<tr>
<td>As Seizure Ends</td>
<td>...Offer Help</td>
</tr>
</tbody>
</table>
Life-threatening complications of isolated seizures are rare

- Vast majority of generalized tonic-clonic seizures last less than 120 seconds
- Vomiting, aspiration, face-down positioning
- Cardiac arrest or prolonged respiratory arrest
What are the initial elements in evaluating a possible seizure?

• History
  – Details of the event
  – Past history of seizure-like symptoms or similar events
  – History of head trauma, febrile seizures, CNS infection
  – Family history of seizures

• Exam
  – General exam: evidence of head injury, meningismus, tongue bite
  – Neurologic exam: evidence suggesting a focal brain lesion

• Labs
  – Evidence of infection or metabolic disturbance: CBC, electrolytes, toxicologic screen, drug levels
Many unexpected events, including other TMS adverse effects, can appear similar to seizures

- Seizure
- TIA
- Confusion/delirium
- Syncope
- Medication side effects
- Cardiac arrhythmia
- Migraine (without headache)
- Hallucinations from sensory deprivation
- Myoclonus
- Transient global amnesia
- Vertigo
Further neurodiagnostic testing could be indicated in certain cases

- **Neuroimaging (MRI/CT)**
  - All new partial-onset seizure patients should have a nonurgent MRI
  - If acute neurologic lesion is suspected, obtain an urgent CT or MRI

- **EEG**
  - Most new seizure patients should have an EEG
  - Can help to clarify partial- vs. generalized-onset and prognosticate risk of recurrence
There are many antiepileptic drugs, and many have multiple indications

- **“Older”**
  - 1912 Phenobarbital
  - 1938 Phenytoin (Dilantin)
  - 1974 Carbamazepine (Tegretol)
  - 1978 Valproic acid (Depakote)

- **“Newer”**
  - 1993 Gabapentin (Neurontin)
  - 1994 Lamotrigine (Lamictal)
  - 1996 Topiramate (Topamax)

- **“Newest”**
  - 1999 Levetiracetam (Keppra)
  - 2000 Oxcarbazepine (Trileptal)
  - 2000 Zonisamide (Zonegran)
  - 2006 Pregabalin (Lyrica)
Status epilepticus is a medical emergency

• Either a state of continuous seizure activity or a state in which seizures are recurring so frequently that there is no recovery in between

• The operational definition (when to begin acting) is 5 minutes
There are many precipitating risk factors for status epilepticus

- Preexisting epilepsy
  - Medication noncompliance
  - Sleep deprivation or alcohol
  - Worsening underlying disease

- Metabolic / toxic disturbances
  - Hyperglycemia, hyponatremia, etc.
  - Drug intoxication

- Structural neurological causes
  - Acute stroke, hemorrhage
  - Head trauma
3 questions to think about for your use of TMS

• **WHO are my TMS patients or subjects?**
  (different individuals have different seizure risk levels)
  Do any of them:
  ◦ have epilepsy?
  ◦ have neurological disorders that increase the risk of seizures?
  ◦ take medications which may lower the seizure threshold?
  ◦ take antiepileptic medications, and if so, are they changing their dosage?

• **WHAT type of TMS am I using?**
  (different protocols have different seizure risks/benefits)
  • Am I using rTMS? At high or low frequencies?

• **WHERE am I using TMS?**
  (different settings require different responses if a seizure occurs)
  • What would I do if a seizure occurred in my TMS lab?
  • Who is responsible for the medical care of my TMS subjects or patients who experience adverse effects?
Summary

• Seizures are quite common in the population, but rare as a direct complication of TMS

• Low-frequency rTMS can be used therapeutically in patients with epilepsy if accurate targeting is achievable

• Seizures have some distinguishing characteristics, but can be confused with other types of events that may occur with TMS

• There is little to do other than ensure safety in the setting of an acute seizure

• TMS parameters, subjects/patients, and settings all need to be considered in estimating seizure-related risks and benefits