L'impiego della rTMS nelle presentazioni resistenti di spettro Ossessivo-Compulsivo

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19 giugno 2017

L'arte della medicina consiste nel divertire il paziente mentre la natura cura la malattia. (Voltaire)

Outline

Neuromodulazione:

- Disturbi psichiatrici come disturbi della connettività
- Research Domain Criteria
- OCD Assessment secondo RDoC:
-

Protocolli e dimensioni

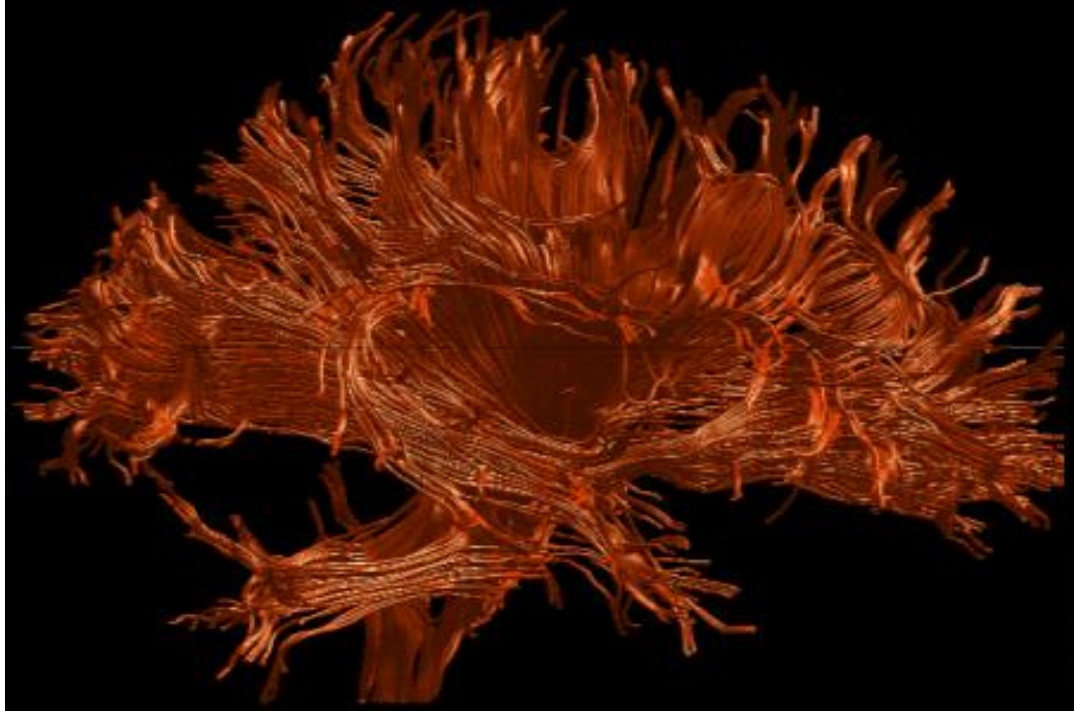
- Protocolli TMS in oCd
- Pre SMA , DLPFC e ACC,

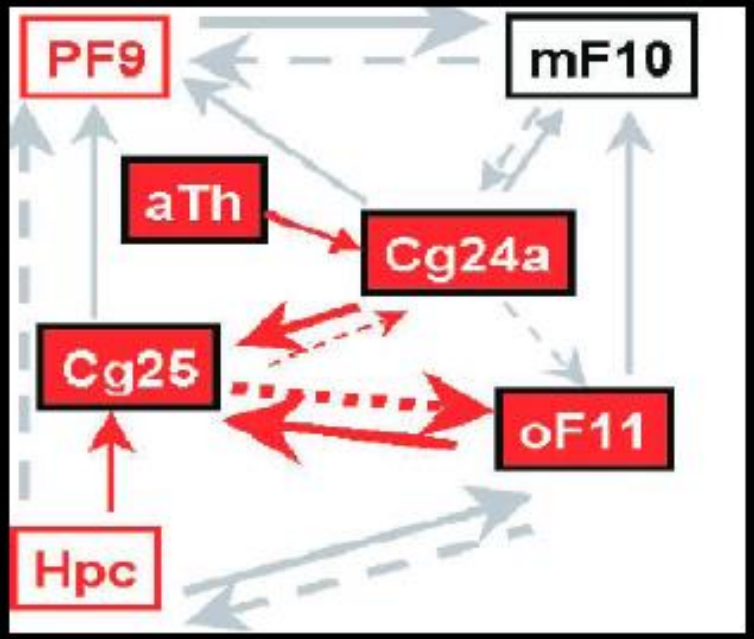
Integrare Tms e CBT

- Case report
- Dati preliminari

- Conclusioni
-

Psychiatry: Disorders of Connectivity





Mayberg et al. 2005

Courtesy by N Makris

Subgenual Cingulate Cortex (BA 25)

Increased activity with sadness and depression (a, b) (using PET)

Decreased activity with chronic fluoxetine treatment for depression (c) or natural placebo recovery (d)

Decreased activity in responders vs non-responders to CBT and citalopram for social phobia (e, f)

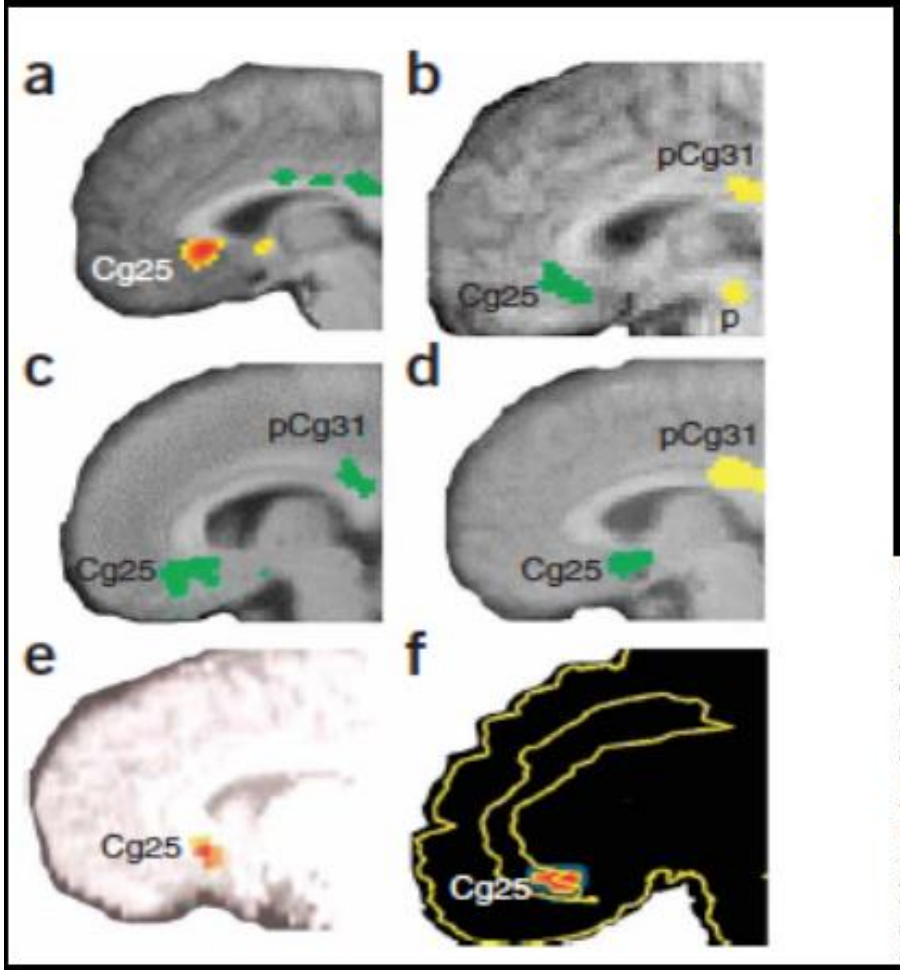


Figure 1 Subgenual cingulate cortex activation across studies. (**a**) Transient sadness in healthy volunteers increases activity (red) in Cg25 (arrow) measured with positron emission tomography (PET) (from ref. 12. Reprinted with permission from the *American Journal of Psychiatry*, copyright 1999, American Psychiatric Association.). (**b**) Decreased Cg25 activity (green) with chronic fluoxetine treatment for depression. (**c**) Cg25 decrease (green) in recovery with chronic fluoxetine from Parkinson's disease–related depression. (**d**) Natural recovery with decreased Cg25 activity (green) in patients treated with placebo. Panels **b**–**d** reprinted from ref. 11 by permission of Oxford University Press. (**e**) Predictors of response in subjects responding to CBT for depression included low pretreatment Cg25 activity (red) (from ref. 15. Reprinted with permission from the *American Journal of Psychiatry*, copyright 1999, American Psychiatric Association.). (**f**) Subgenual cortical decreased activity (red) was common in responders compared with nonresponders for those responding both to citalopram and to CBT for social phobia (from ref. 16. Reprinted from *Archives of General Psychiatry*, copyright 2002, American Medical Association. All rights reserved.).

Ressler and Mayberg, Nature Neuroscience, 2007

Courtesy by N Makris

Why is Brain Connectivity so Important?
A new paradigm: Brain Circuitry

- RDoC: Brain Circuitry underlies specific Behavioral Domains
- Domains are affected across Psychiatric Disorders
- Neuromodulation: Pacemakers in the Brain

Courtesy by N Makris

From psychopathology to RDoC

Commentary

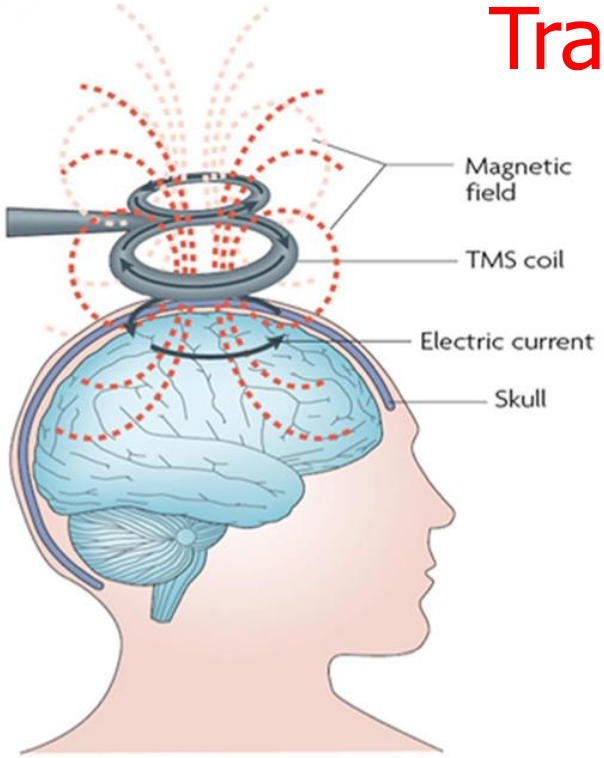
Research Domain Criteria (RDoC): Toward a New Classification Framework for Research on Mental Disorders

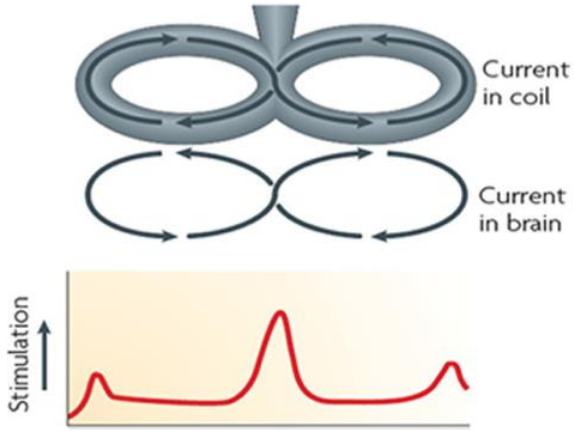
- A plan to "…develop new ways of classifying mental disorders based on behavioral dimensions and neurobiological measures".
- A framework for researchers to investigate the mechanisms of psychopathology.

"Our expectation . . . is that identifying syndromes based on pathophysiology will eventually be able to improve outcomes."

Insel T. Research Domain Criteria (RDoC): Toward a new classification framework for research on mental disorders. Am J Psychiatry. 2010

Transcranial magnetic stimulation





- Un campo magnetico induce una corrente elettrica che penetra nello scalpo e modula il firing neuronale della popolazione di neuroni nell'area sottostante al coil (bobina).

- Generalmente, le basse frequenze (<1 Hz) inibiscono l'attività neuronale, mentre le alte frequenze aumentano l'attività neuronale e l'eccitabilità corticale.

Gorelick et al. Transcranial magnetic stimulation in the treatment of substance addiction. Ann. N.Y. Acad. Sci (2014)

Fisiologia della TMS

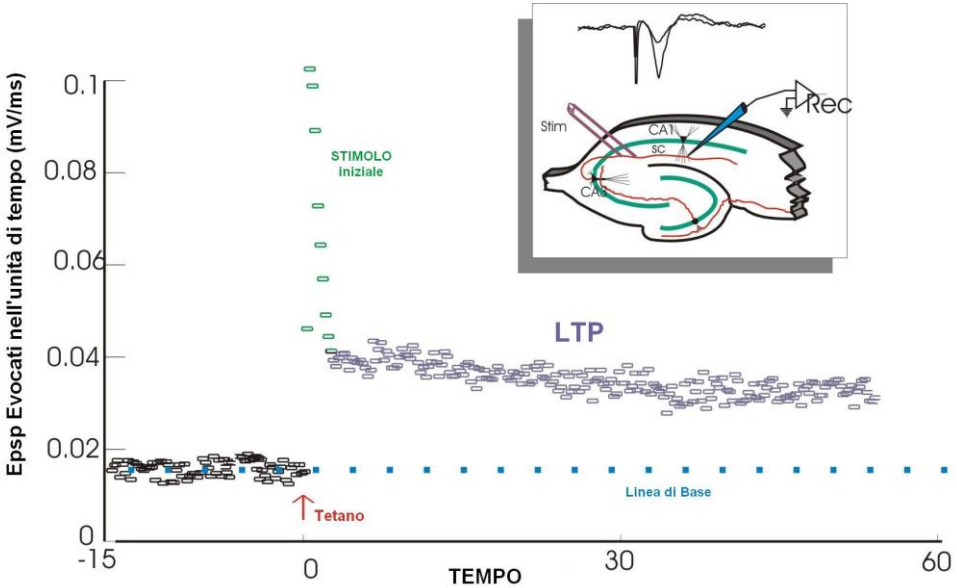
Sebbene l'esatto meccanismo d'azione non sia completamente chiarito…

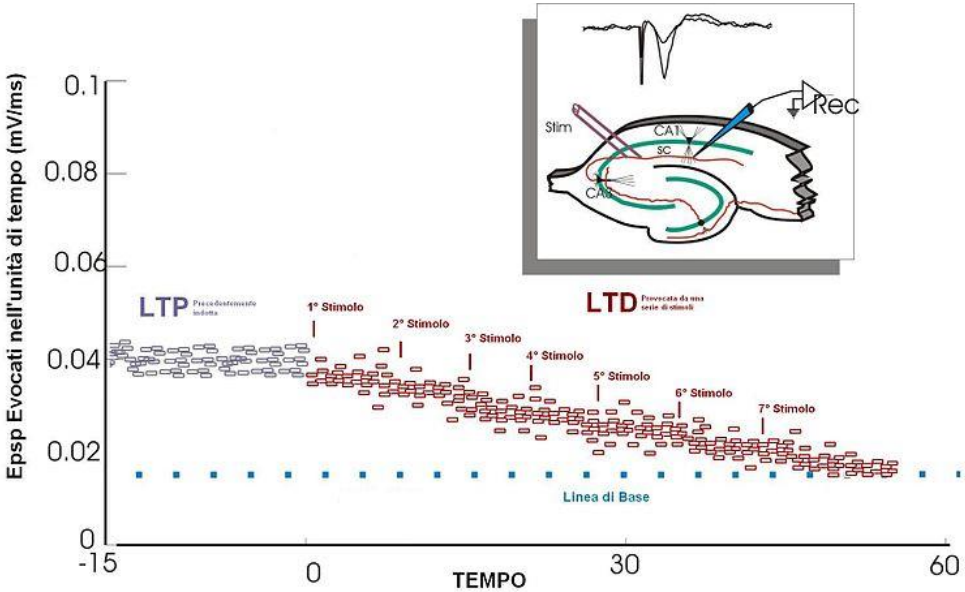
- INIZIALE AUMENTO e successiva DIMINUZIONE A LUNGO TERMINEdell'ossigenazione tissutale

- Modifiche nel TEMPO DI SPIKE NEURONALE e Local Field Potential (LFP) = facilitazione di effetti SIMIL-PLASTICI

- RISPOSTA DOSE-DIPENDENTE – Incremento con aumento della durata o dell'intensità di stimolazione

Fenomeni LTP e LTD: Learning





Long-term potentiation (LTP): fenomeno che induce una forma di plasticità sinaptica che consiste in un aumento a lungo termine della trasmissione del segnale tra due neuroni, ottenuto stimolandoli in maniera sincrona.

Long-term depression (LTD): Fenomeno che induce una forma di plasticità sinaptica che consiste in una riduzione a lungo termine della trasmissione del segnale tra due neuroni, che riporta la comunicazione a livello di partenza se esercitato in seguito ad un LTP.

Brain Stimulation 10 (2017) 1–18

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Neurobiological after-effects of non-invasive brain stimulation

G. Cirillo [a], G. Di Pino [b,c,d], F. Capone [c,d], F. Ranieri [c,d], L. Florio [c,d], V. Todisco [a], G. Tedeschi [a], K. Funke [e], V. Di Lazzaro [c,d,*]

Fenomeni di **long-term potentiation (LTP)** e **long-term depression (LTD)** non sono di per sé sufficienti a spiegare le modifiche a breve e a lungo termine che si verificano dopo brevi trattamenti di neuromodulazione non invasiva.

Studi sperimentali preliminari presentano uno scenario complesso potenzialmente rilevante per comprendere gli effetti di tali tecniche, che include il ruolo di:

- **Attivazione/regolazione genica**
- **Espressione de novo di proteine**
- **Modifiche morfologiche**
- **Modifiche nelle proprietà di firing neuronale**
- **Modifiche nelle proprietà a livello di network che dipendono da modifiche nell'inibizione, nei processi omeostatici e nella funzione gliale.**

- **Cortical excitability**

High-frequency increases cortical excitability
Low-frequency decreases cortical excitability

- **Neurotransmitters and sinaptic plasticity**

High-frequency increases DA striatal levels
TBS decreases DA striatal levels

- **Neurotrophic factors**

High-frequency increases BDNF in blood plasma

- **Apoptotic mechanisms (mice models)**

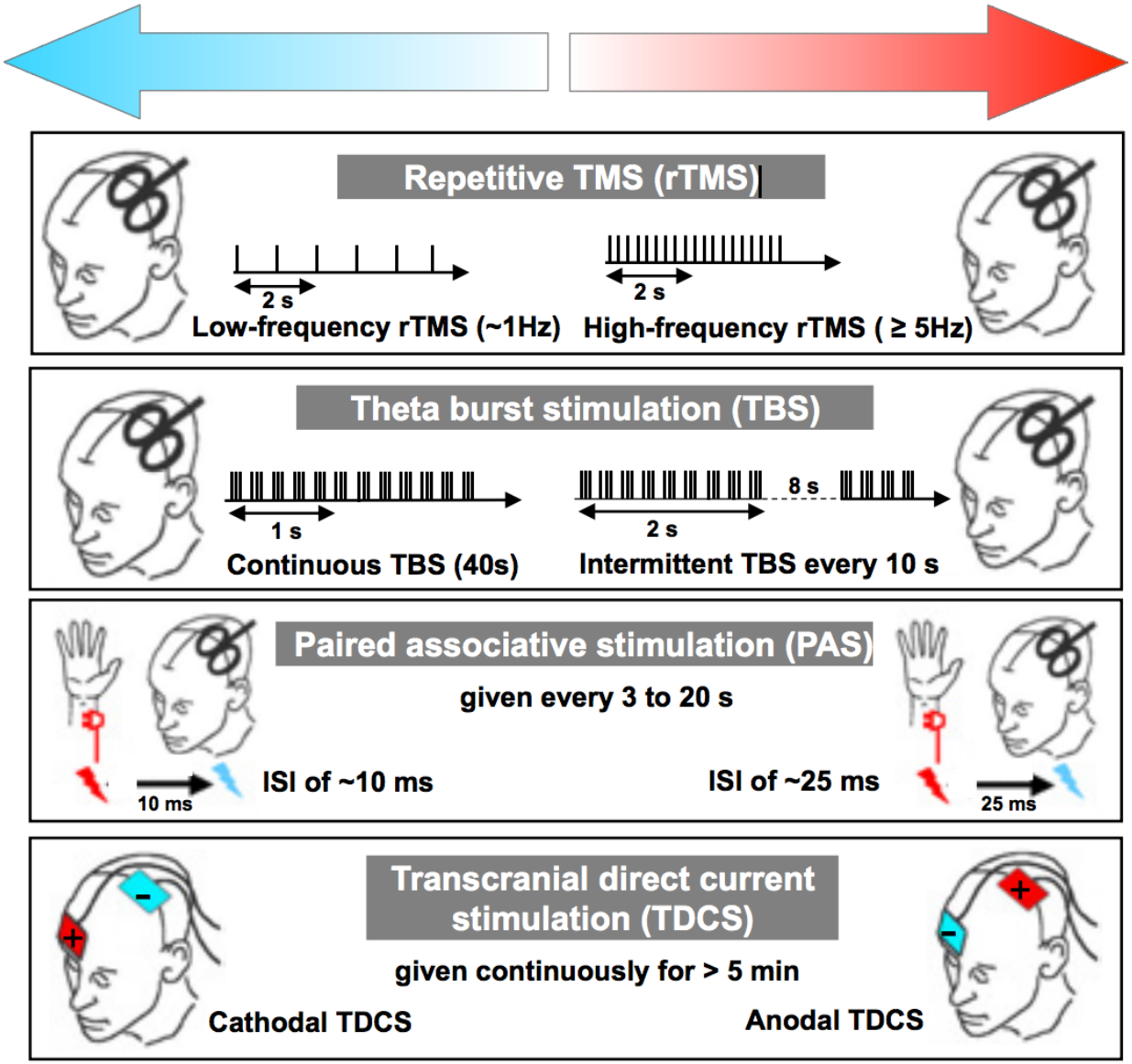
Low-frequency activates anti-apoptotic mechanisms on the zone surrounding infarct
Activation and migration of astrocytes toward the CNS damage focus

- **Genetic apparatus of neurons (mice models)**

Increase of mRNA c-FOS expression

Chervyakov et al. (2015). Possible mechanisms underlying the therapeutic effects of transcranial magnetic stimulation. Frontiers in Human Neurosciences.

Protocolli e dimensioni



TMS: Aspetti ancora da chiarire

rTMS ha effetti terapeutici su un ampio spettro di disturbi neuropsichiatrici.

Quali sono i meccanismi sottostanti?

Gli effetti benefici della rTMS possono perdurare fino a 6 mesi dopo la fine del trattamento.

Quali sono le cause di tali effetti a lungo termine?

Precision medicine and TMS target

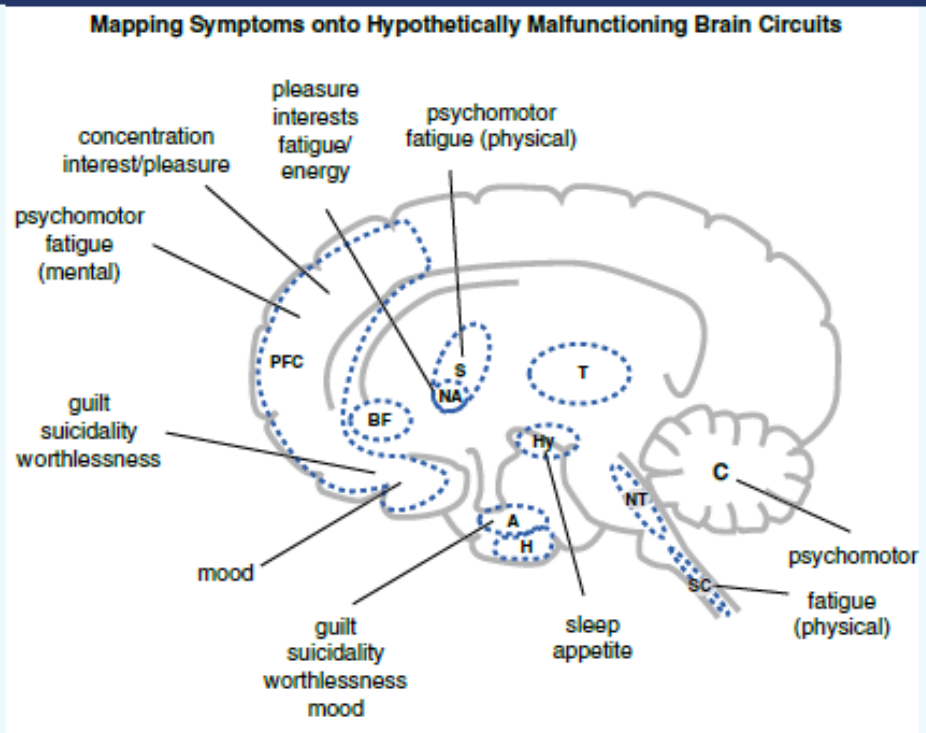
Precision medicine for mental disorders could be even more transformative than for cancer. Will subdiving syndromes based on molecular signatures, neuroimaging patterns, inflammatory biomarkers, cognitive style, or history give us subgroups that are more responsive to certain medications or psychosocial treatments?

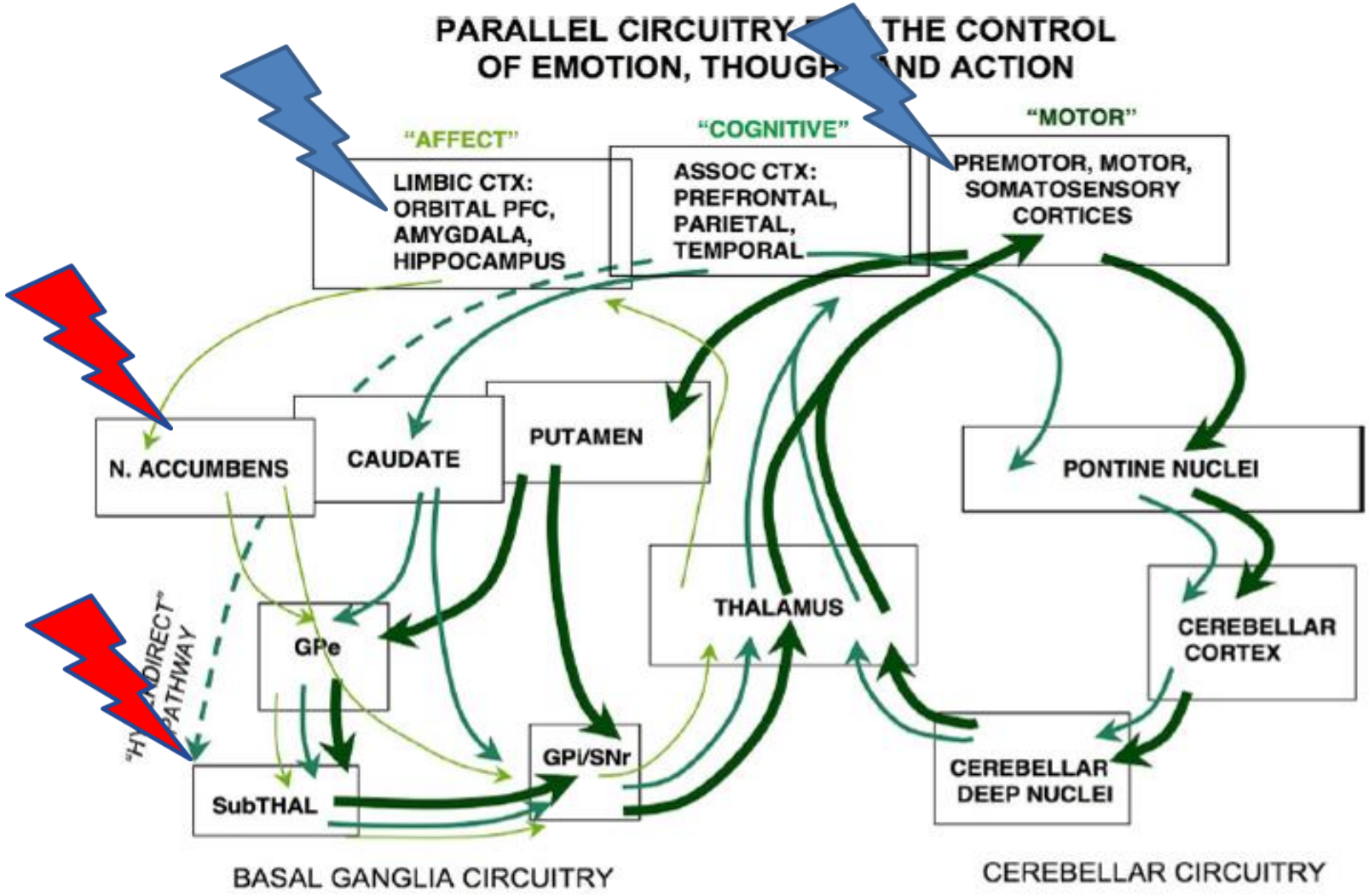
Behavior → **Neural networks** → **Individual patients**

Insel T. The NIMH Research Domain Criteria (RDoC) Project: Precision Medicine for Psychiatry. American Journal of Psychiatry. 2014.

Mapping Symptoms onto hypotetically malfunctioning brain circuits

Figure 3 Mapping symptoms onto hypothetically malfunctioning brain circuits. A = amygdala, BF = basal forebrain, C = cerebellum, H = hippocampus, Hy = hypothalamus, NA = nucleus accumbens, NT = monoamine neurotransmitter centers, PFC = prefrontal cortex, S = striatum, SC = spinal cord, T = thalamus.

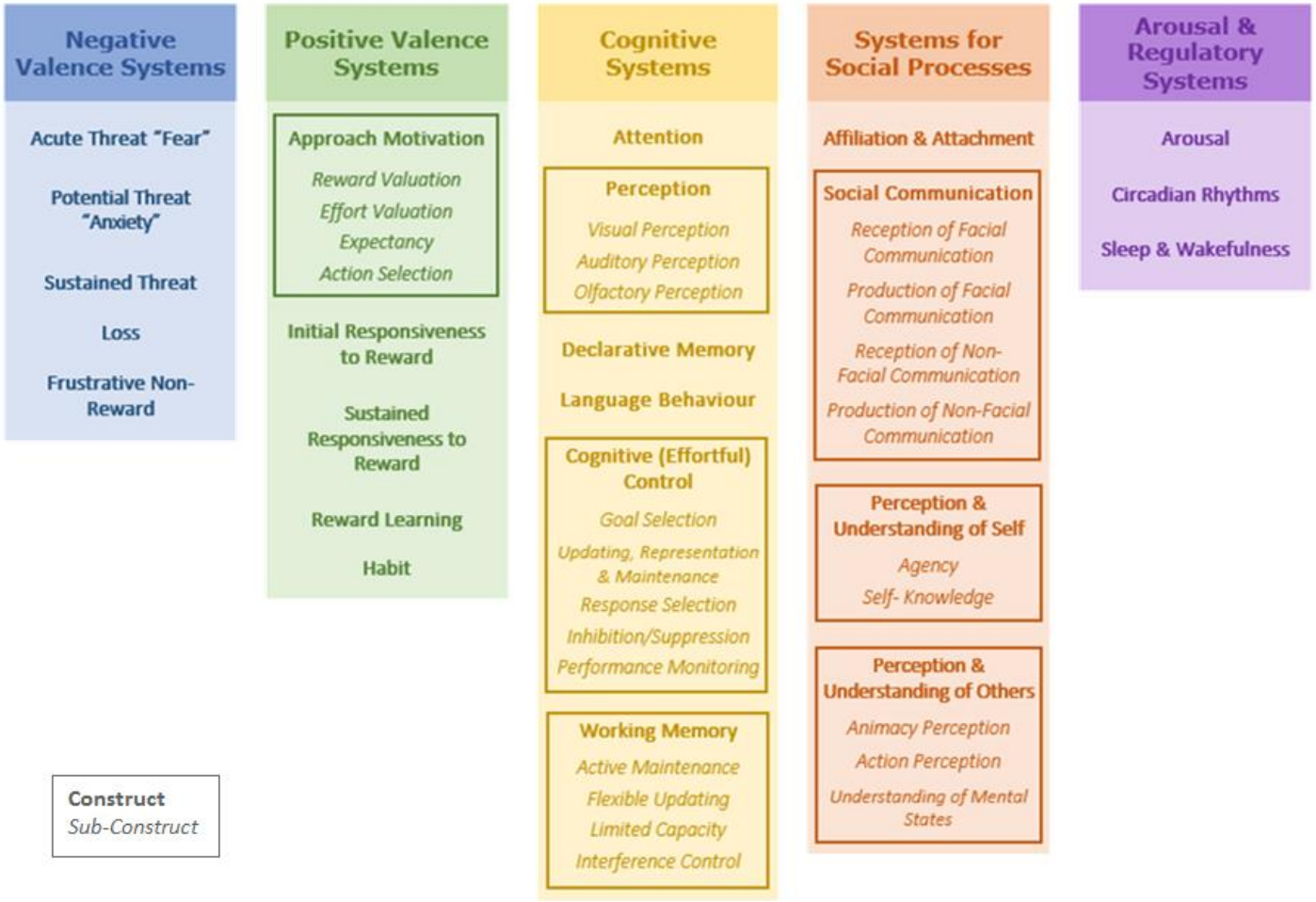




Arnsten AF, Casey BJ. Biological Psychiatry, 2011 Jun 15. PMID: 21640860

In OCD and related disorders, convergent evidence suggests insufficient top-down control in pre-frontal loops coupled with excess habit generation in dorsal striatum

RDoC Domains



OCD in the Research Domain Criteria

OCD patients are impaired in multiple Research Domain constructs:

Sustained Threat

Circuits

- Attention network
- Dysregulation of amygdala reactivity
- Dysregulation of cingulate reactivity
- Habit systems (Striatum/caudate/accumbens)
- Hypothalamic nuclei
- PVT
- Vigilance network

Reward learning

Circuits

- Amygdala
- dorsal striatum
- Medial prefrontal
- OFC
- Ventral striatum
- VTA/SN

Habit

Circuits

- dorsal striatum
- Medial prefrontal
- SN/VTA
- Ventral striatum

Makris N et al. Variability and anatomical specificity of the orbitofrontothalamic fibers of passage in the ventral capsule/ventral striatum (VC/VS): precision care for patient specific tractography-guided targeting of deep brain stimulation (DBS) in obsessive compulsive disorder (OCD). Brain Imaging and Behavior 2015

Neuromodulation in OCD

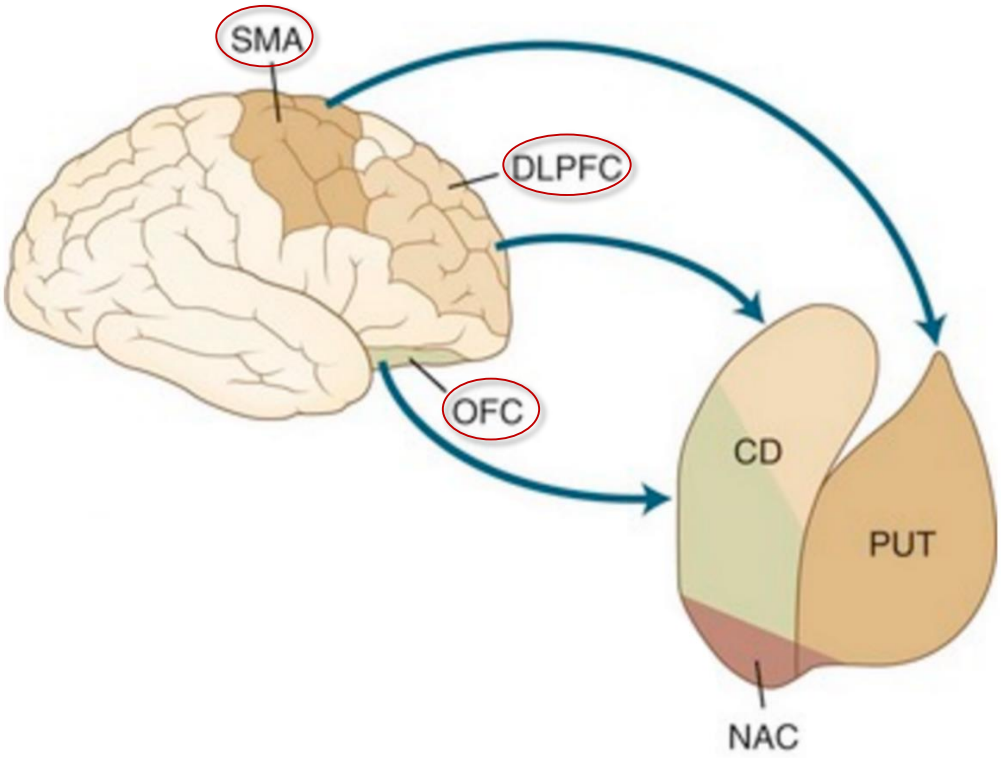
rTMS targets

- **DLPFC (BA 9/46)**
- **OFC (BA 11/14)**

Executive functions/decision-making

- **SMA (BA 6)**

Inhibitory control



Brody AL, Saxena S (1996). Brain imaging in obsessive-compulsive disorder: evidence for the involvement of frontal-subcortical circuitry in the mediation of symptomatology. CNS. Spectr. 1, 27–41.

The functional roles of the SMA and pre-SMA

- **Self-initiated vs externally triggered movements**

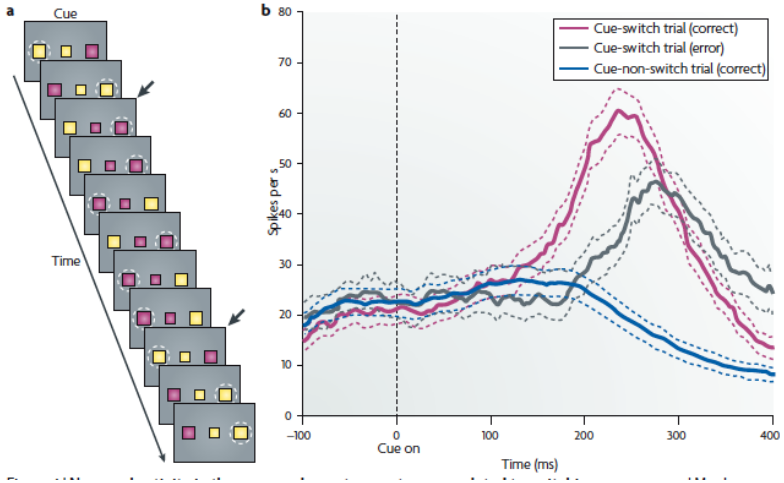
Imaging studies have reported greater activity in the pre-SMA when participants are free to choose their actions than when they are instructed by external signals.
In monkeys, SMA neurons respond to both self-initiated and externally cued movements.

- **Movement sequences**

SMA and pre-SMA neurons respond before some sequences but not others. They also respond in a specific manner in the interval between actions.

- **Learning**

Cells that show learning-related activity for a complex sequence of hand movements: such activity was more prominent in the pre-SMA than in the SMA.



- **Cognitive control**

It is likely that conflict-related activity in the medial frontal cortex is more attributable to pre-SMA, rather than nearby ACC, activation.

Nachev P, et al. Functional role of the supplementary and pre-supplementary motor areas. Nature Reviews Neuroscience. 2009.

Outcomes with neuromodulation in OCD

TABLE 2.

rTMS Outcomes in Obsessive-Compulsive Disorder

Target	Patients (n)	Response Rates (mean)
Left DLPFC	70	38% (19 of 50)
Right DLPFC	54	24% (6 of 25)
Pre-SMA	31[a]	52% (11 of 21)

Abbreviations: DLPFC, dorsolateral prefrontal cortex; rTMS, repetitive transcranial magnetic stimulation; SMA, supplementary motor area.
[a] Of which 10 were also treated with pre-SMA rTMS.

TABLE 3.

dTMS Outcomes in Obsessive-Compulsive Disorder

Target	Patients (n)	Response Rates (mean)
OFC	35	25% (4 of 16)

Abbreviations: dTMS, deep transcranial magnetic stimulation; OFC, orbitofrontal cortex.

- **Low-frequency** (1Hz) protocols more effective.
- **Pre-SMA** and **OFC** as the most promising targets.

Pallanti S, Marras A, Grassi G. Outcomes with neuromodulation in Obsessive-Compulsive Disorder. Psychiatr Ann 2015; 45(6):316-20.

rTMS targets in OCD: MINI REVIEW

Study	Active rTMS			Sham rTMS				rTMS Parameters			Psychiatric comorbidity	Treatment strategy	Resistant OCD?
	n	Age ± SD (yrs)	Female/ male (*n*)	*n*	Age ± SD (yrs)	Female/ male (*n*)	Strategy	Brain target	Frequency (Hz)/sessions	% rMT[a]/total pulses			
Alonso et al., 2001	10	39.2 ± 13.0	8/2	8	30.3 ± 9.5	4/4	90°	R-DLPFC	1/18	110/21,600	None	Mixed[a]	Yes[b]
Prasko et al., 2006	20	28.4 ± 7.4	5/15	14	33.6 ± 8.4	8/6	N/A	L-DLPFC	1/10	110/?	None	Augmentation	Yes[c]
Sachdev et al., 2007	10	29.5 ± 9.9	3/7	8	35.8 ± 8.2	5/3	Sham coil	L-DLPFC	10/10	15,000	None	Mixed[d]	Yes[e]
Kang et al., 2009	10	28.6 ± 12.7	2/8	10	26.2 ± 10.5	1/9	45°	R-DLPFC + Pre-SMA	1/10	110/12,000	35% (*n* = 7) with MDD	Augmentation	Yes[f]
Ruffini et al., 2009	16	41.5 ± 9.06	6/10	7	39.3 ± 9.55	3/4	90°	L-OFC	1/15	80/9000	None	Augmentation	Yes[e]
Badawy et al., 2010	40	26.9 ± 6.7	18/22	20	28.9 ± 5.7	13/7	Unspeci-fied angle	L-DLPFC	20/15	?/12,000	Unknown	Mixed	Yes
Mantovani et al., 2010	9	39.7 ± 8.6	4/5	9	39.4 ± 10.2	3/6	Sham coil	Pre-SMA	1/20	100/24,000	55.5% (*n* = 10) with MDD	Mixed[g]	Yes[h]
Sarkhel et al., 2010 [i]	21	29.4 ± 6.5	11/10	21	31.9 ± 7.8	8/13	45°	R-DLPFC	10/10	110/8000	Mild depressive symptoms[j]	Augmentation	N/A
Mansur et al., 2011	13	42.1 ± 11.9	6/7	14	39.3 ± 13.9	8/6	Sham coil[k]	R-DLPFC	10/30	110/60,000	Multiple[l]	Augmentation	Yes[m]
Gomes et al., 2012	12	35.5 ± 7.5	8/4	10	37.5 ± 6	5/5	Sham coil	Pre-SMA	1/10	100/12,000	77.3% (*n* = 17) with MDD	Augmentation	Yes[g]

Conclusions: Our exploratory analyses show that active rTMS seems to be efficacious for treating OCD. Moreover, LF-rTMS and protocols targeting the orbitofrontal cortex or the supplementary motor area seem to be the most promising. Nevertheless, future RCTs on rTMS for OCD should include larger sample sizes and be more homogeneous in terms of demographic/clinical variables as well as stimulation parameters and brain targets.

Berlim et al. (2013): Repetitive transcranial magnetic stimulation (rTMS) for obsessive-compulsive disorder (OCD): An exploratory meta-analysis of randomized and sham-controlled trials.

Original Paper

Better than treated as usual: Transcranial magnetic stimulation augmentation in selective serotonin reuptake inhibitor-refractory obsessive–compulsive disorder, mini-review and pilot open-label trial

Journal of Psychopharmacology
2016, Vol. 30(6) 568–578

DOI: 10.1177/0269881116628427
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Stefano Pallanti[1,2,3], Anna Marras[1,4], Luana Salerno[4], Nikos Makris[5] and Eric Hollander[3]

Abstract

Objective: 1 Hz repetitive transcranial magnetic stimulation (rTMS) over the supplementary motor area has been shown to be effective in a subset of obsessive–compulsive disorder (OCD) subjects, yet these results are still to be confirmed. This preliminary study compares the efficacy of augmentation with 1 Hz rTMS over the supplementary motor area and the usual augmentation treatment (TAU; treated as usual) with antipsychotics in a sample of selective serotonin reuptake inhibitor (SSRI)-refractory OCD patients.

Method: Fifty SSRI-refractory OCD patients consecutively admitted were studied: 25 were treated with a three-week trial of 1Hz, bilateral rTMS over the supplementary motor area and 25 with antipsychotic drugs. Yale–Brown Obsessive–Compulsive Scale (Y-BOCS; primary outcome measure), Hamilton Depression and Hamilton Anxiety scales were administered at first, second and third week of treatment.

Results: Y-BOCS showed a statistically significant time effect from the baseline to the third week, with a 68% of responders (Y-BOCS score reduction of ≥ 25%), in comparison with 24.0% in the TAU group. In the rTMS group, 17.6% of patients achieved remission.

Conclusions: 1 Hz rTMS over the supplementary motor area appeared to be effective in approximately 2/3 of SSRI-refractory OCD subjects, whereas in the TAU group only 1/4 of subjects were responders. The supplementary motor area might be a new target area to be further explored with neuromodulation for OCD treatment.

Keywords

Repetitive transcranial magnetic stimulation, rTMS, obsessive–compulsive disorder, OCD, supplementary motor area, SMA, SSRI-refractory OCD

Better than TAU: rTMS over the pre-SMA vs antidopaminergic augmentation

AIM:

Comparing the effectivenes of 3 weeks of 1Hz rTMS over the bilateral pre-SMA vs antidopaminergic augmentation (TAU: treatment as usual)

DESIGN:

50 treatment-resistant OCD patients (previous failure of 2 SRIs trials, including clomipramine, and one CBT trail of 16 sesisons) were randomized to

15 sessions of 1Hz rTMS bilateral pre-SMA

antidopaminergic augmentation (risperidone (n:21), paliperidone (n:2), aripiprazole (n:2))

Pallanti et al. Better than treated as usual: Transcranial magnetic stimulation augmentation in selective serotonin reuptake inhibitors refractory obsessive–compulsive disorder, mini-review and pilot open-label trial. Journal of Psychopharmacology, 2016.

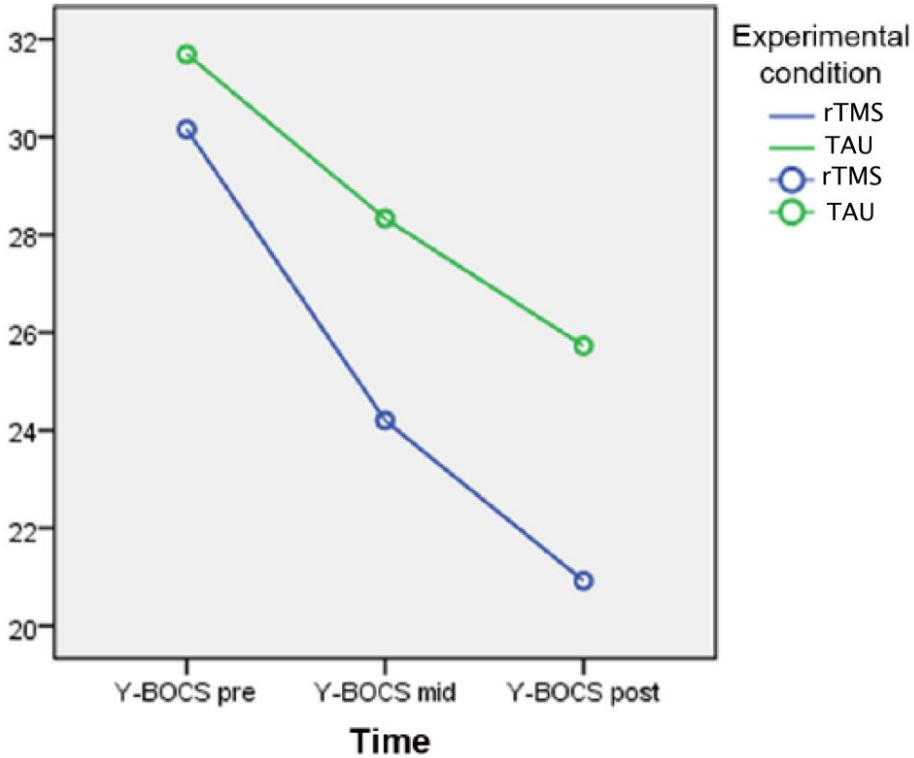
Better than TAU: rTMS over the pre-SMA vs antidopaminergic augmentation

rTMS PROTOCOL:

1Hz, 1200/pulses per session, 100% of the motor treshold, 5 sessions per week for 3 weeks (total of 15 sessions)

RESULTS:

68% responders in the rTMS group
24% responders in the TAU group
17.6% remitters in the rTMS group
0% remitters in the TAU group



Pallanti et al. Better than treated as usual: Transcranial magnetic stimulation augmentation in selective serotonin reuptake inhibitors refractory obsessive–compulsive disorder, mini-review and pilot open-label trial. Journal of Psychopharmacology, 2016.

Enhancing extinction learning through LTP with rTMS after CBT/ERP

Brain Stimulation 8 (2014) 160–167

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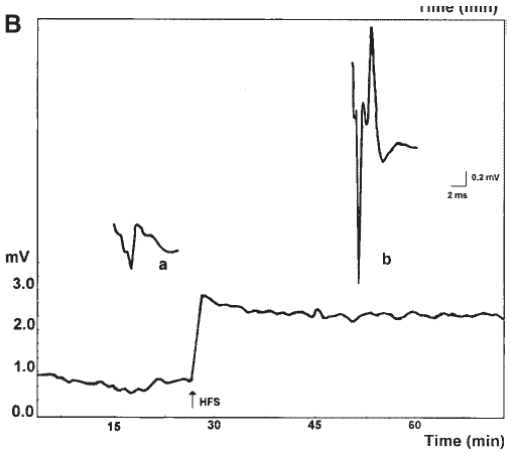
journal homepage: www.brainstimjrnl.com

Letters to the Editor

Enhancing Cognitive-behavioral Therapy With Repetitive Transcranial Magnetic Stimulation in Refractory Obsessive-compulsive-disorder: A Case Report

no change in her global functioning was observed. For this reason, we decided to enroll the patient in a rTMS-CBT trial. The patient underwent an intensive 16 sessions CBT trial (3 sessions per week, 50–60 min per session). The first 6 sessions were dedicated to establishing an individual hierarchy of obsessions and compulsions and to a cognitive restructuring of meta-cognitions. The following 10 sessions focused on in vivo ERP exercises. Each exposure session was immediately preceded by an HF-rTMS session over the left DLPFC (10 stimulation sessions). During the treatment, 100-s trains has been applied at 10 Hz and at 80% of the right RMT over the left DLPFC, with a 50 s inter-train interval (a total of 1800 stimuli per session). Each rTMS session ended 5–15 min before the CBT session starts.



LTP induced by HF-rTMS on rats hyppocampal slices

ENHANCING LEARNING

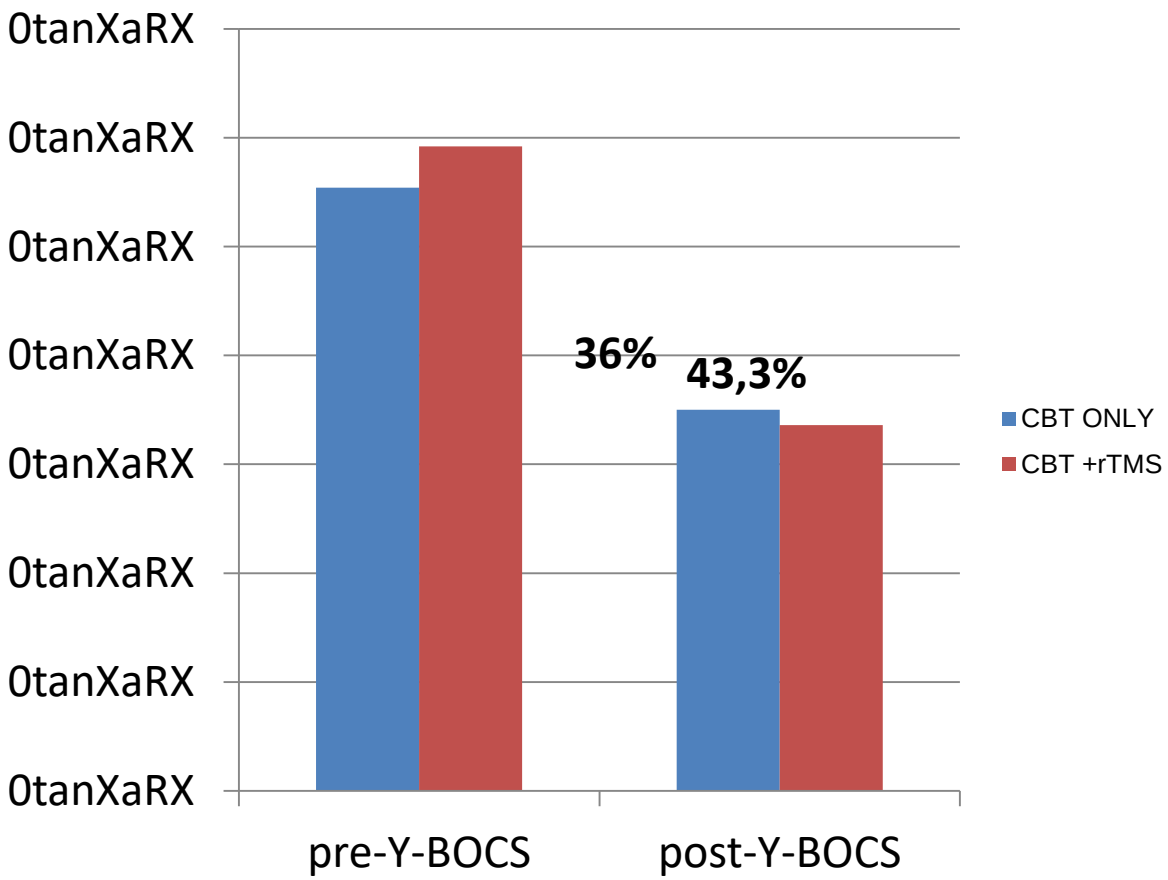
HF-rTMS over the **left DLPFC** after each successfull ERP sessions

ENHANCING COGNITION

HF-rTMS over the **left DLPFC** before cognitive reconstruction sessions

Grassi et al. Enhancing cognitive-behavioral therapy with repetitive transcranic magnetic stimulation in refractory obsessive-compulsive disorder: a case report. Brain Stimulation, 2014.

Enhancing inhibition during ERP with SMA-rTMS (preliminary data)



ENHANCING INHIBITION

LF-rTMS over the **pre-SMA** during or before ERP sessions

Combining rTMS with CBT/ERP: putative protocols

ENHANCING COGNITION

HF-rTMS over the **left DLPFC before cognitive** reconstruction sessions

ENHANCING LEARNING

HF-rTMS over the **left DLPFC after each** successfull ERP sessions

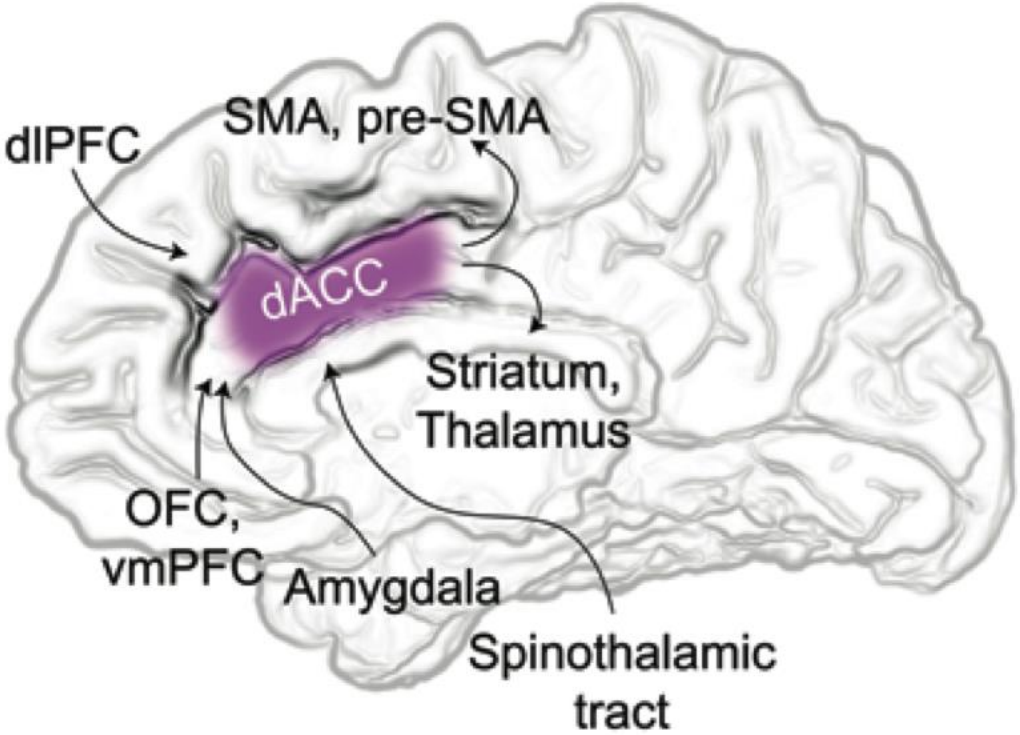
LF-rTMS over the **pre-SMA** during or before ERP sessions

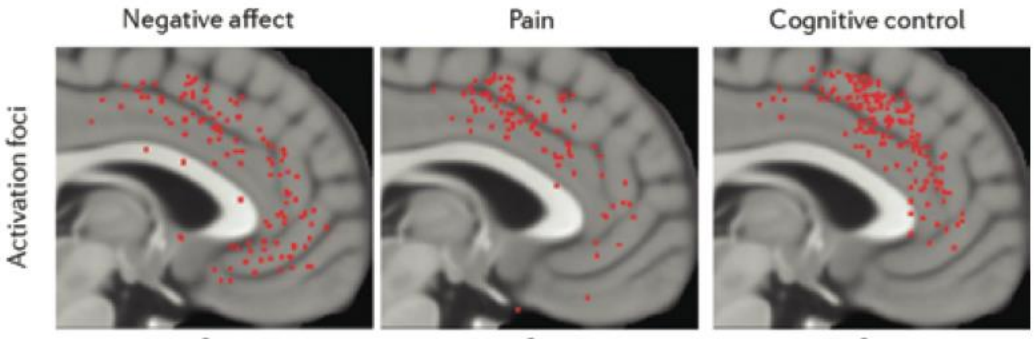
ENHANCING INHIBITION

The role of dACC in OCD

- dACC: extensive reciprocal cortical connections with the **DLPFC and motor regions**: an ideal position to both receive incoming sensory information and act on that information via downstream motor regulators.

- dACC: involved in the RDoC construct of **"Cognitive Control": performance monitoring, action selection, and goal-directed behavior**. Specifically activated in tasks that require significant cognitive effort, as well as negative feedback, pain, and other aversive cues.





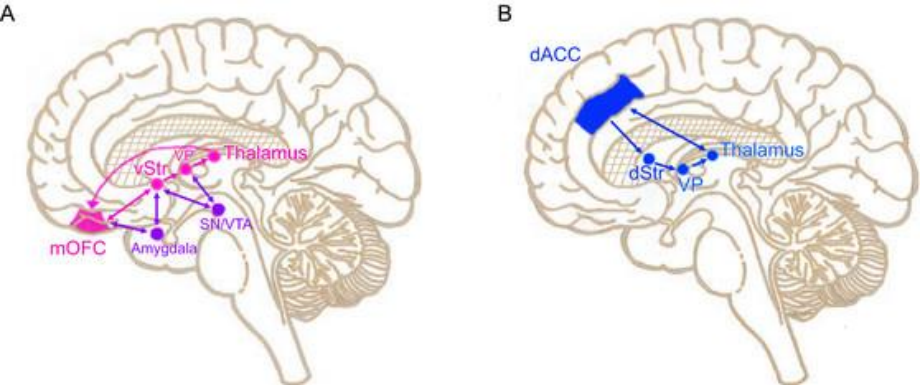
McGovern et al. Role of the dorsal anterior cingulate cortex in obsessive-compulsive disorder: converging evidence from cognitive neuroscience and psychiatric neurosurgery. J Neurosurg 2016.

Going deep and “high” in OCD: dTMS over the ACC

Protocol:
6 weeks (5 sessions per week) over the left ACC
20 Hz stimulation

38,1% full responders in the active group vs 11,1% in the sham group

54,8% partial responders in the active group vs 26,7% in the sham group



Zangen et al. 2017

Neuropsychobiology

Original Paper

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Positron Emission Tomography Imaging of Risperidone Augmentation in Serotonin Reuptake Inhibitor-Refractory Patients

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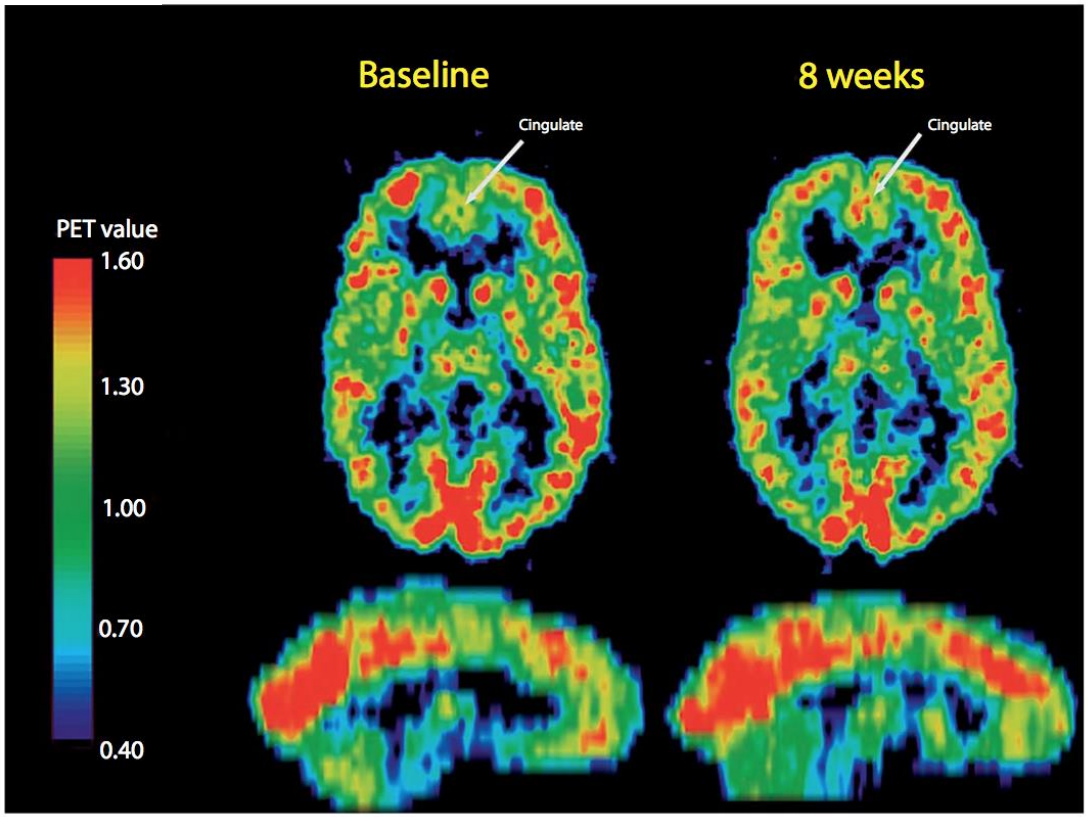
- **Highly refractory patients:**
  The importance of staging

- **ACC Anterior cingulate gyrus:**
  High relative metabolic rate is a predictor of clinical response to the augmentation with RISPERIDON



FDG-PET at baseline and following risperidone treatment for typical representative subject. Increase in cingulate is prominent but little change is seen in occipital cortex.

Laerning and Mental Imaginery: the new frontiers of integration

(SSRIs) have immediate effects on synaptic levels of serotonin but their therapeutic effects are often delayed. This delay has been suggested to reflect time required for new learning and therefore that SSRIs might be having effects on the learning process.(Msetfi et al 2016) Brain area involved are disoder" specific

TMS enhance learning , but there is a "inter-pulse interval issue "A control experiment revealed that identical TMS pulses at identical frequencies caused no change in fMRI-measured functional connectivity when the inter-pulse-interval was too long for Hebbian-like plasticity. (Johnen et al 2015)

Conclusions

- rTMS and RDoC OCD models reveals new treatment targets to focused and personalized treatment (According to types and staging)
- Neuromodulation, coupled with CBT and pharmacological treatment may improve treatment outcome in resistant OCD patients
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- LTP and LTD and other synaptic plasticity modulation related to learning are the “matter of integration”