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D.I.U. Théorie et pratique de l'ECT et rTMS

NIBS et réseaux neuronaux (rTMS et ECT/ MDD)

Bordeaux, 15 janvier 2020

Christophe DAUDET
psychiatre et médecin du sommeil
Centre d'évaluation approfondie et de neuromodulation
Clinique Mirambeau, Anglet

The University of Bordeaux logo is located in the bottom right corner of the slide. It consists of the text 'université de BORDEAUX' in a dark blue serif font, with a small blue 'U' logo to the right.

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Recommandations françaises (Lefaucheur, 2011)

- rTMS vs. Sham rTMS (placebo)
 - 35 études, >2000 sujets (dont 500 en 2 études)
- rTMS vs. Médicaments
 - 2 études, 102 sujets



MISE ALL POINT / REVIEW

Recommandations françaises sur l'utilisation de la stimulation magnétique transcrânienne répétitive (rTMS): règles de sécurité et indications thérapeutiques[☆]

French guidelines on the use of repetitive transcranial magnetic stimulation (rTMS): Safety and therapeutic indications

J.-P. Lefeaucure^{a,b,b,†}, N. André-Obadia^{c,d,†}, E. Poulet^{e,f,†}, H. Devanne^{g,h,i,†}, E. Haffen^{j,k}, A. Londero^{l,m}, B. Cretinⁿ, A.-M. Lerol^{o,p}, A. Radtchenko^q, G. Saba^{r,s}, H. Thal-Van^{t,u}, C.-F. Litré^v, L. Vercuelli^{w,x}, D. Bouhassira^y, S.-S. Ayache^z, W.-H. Farhat^{a,b}, H.-G. Zouari^{a,b}, V. Mylius^a, M. Nicollier^j, L. Garcia-Larrea^{a,z}

- **Grade A de preuve**
 - Analgésie HF rTMS M1 controlatérale à douleur
 - Halucination auditive LF rTMS T 3P3
- **Dépression HF rTMS**
CPFDL gauche
- **Grade B de preuve**
- **Dépression LF rTMS**
CPFDL droit
- **Potentialisation**
antidépresseur
médicamenteux rTMS
CPFDL gauche
- **Symptômes négatifs schizophrénie HF**
rTMS CPFDL gauche

Significativité statistique mais clinique...? (Downar 2013)

- dIPFC rTMS:
rémission 17%
réponse 25%
(O'Reardon 2007,
Lam 2008)
- VS ECT rémission
65-75 % (Sackeim
2008)
- DBS rémission >40
% (Kennedy 2011)
- Post 2008
- dIPFC rTMS: rémission
30-35%, réponse 40-
55%
- (Downar 2013)
- Sham 5 et 10 % (Lam
2008)
- VS STAR D : rémission
23-33% (Thase 2007)
- Switch CBASP
rémission 22%
réponse 33%
(Schatzberg 2005)

One fit sizes all? Ou le problème de l'hétérogénéité de la dépression

- Formes cliniques:
- Unipolaire/bipolaire (Leonhard 1957)
- Mélancolique/atypique (Davidson 2007)
- (non)suppression test DXM (Rush 1996)
- Agitée ou caractéristique de mixité (Benazzi 2006)
- Modèle d'interaction entre régions impliquées dans la régulation des émotions (neuroimagerie)
- Différents sous-types ou biotypes, différentes anomalies d'interaction, différentes cibles

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Cibles potentielles du PFC (dlPFC = 10%) (Downar 2013)



New Targets for rTMS in Depression: A Review of Convergent Evidence

Jonathan Downar^{a,b,c}, Z. Jeff Daskalakis^{a,c,1}^aDepartment of Psychiatry, University of Toronto, Canada^bMRI Centre for Clinical Neuroimaging, University Health Network, 706-420, 390 Adelaide Street, Toronto, Ontario, Canada M5T 2M8^cBrain Stimulation Treatment and Research Program, Centre for Addiction and Mental Health, 250 College Street, 10th Floor, Toronto, Ontario, Canada M5T 1A6

Back to the past:

1990s/2000s: dépression et hyperactivité du sgCCA (BA 25) → DBS

1980s/1990s: Dépression et hypoactivité dlPFC gauche (BA 9, 43) → rTMS dlPFC gauche HF

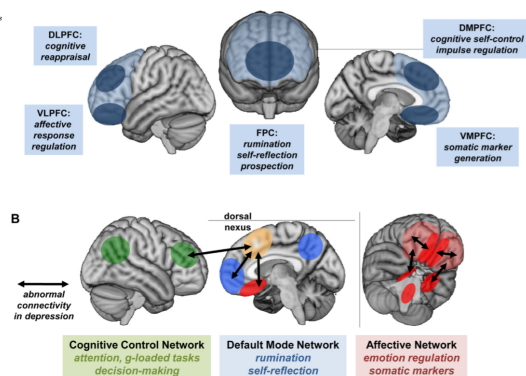


Figure 1. Cortical nodes and networks involved in the pathophysiology of depression. (A) In patients with depression, 20 years of FDG-PET studies have revealed a network of prefrontal regions whose resting metabolic activity shows a general reduction over the ~1 h timescales required for scan acquisition using this technique. The prefrontal nodes of this network include DLPFC, DMPFC, VLPFC, and FPC. DLPFC, dorsolateral prefrontal cortex. The proposed contributions of each region to emotion regulation in depression are shown in the panel. (B) Abnormal network activity in depression. Resting-state functional MRI in depression reveals a "dorsal nexus" in the DMPFC linking networks for cognitive control (DLPFC), default-mode reflection (FPC), and somatic marker generation (VMPFC). VLPFC also shows abnormal connectivity to VMPFC in depression. DMPFC, dorsomedial prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; VMPFC, ventromedial prefrontal cortex; FPC, frontopolar cortex.

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Études de lésions (Koenigs 2008, 2009)

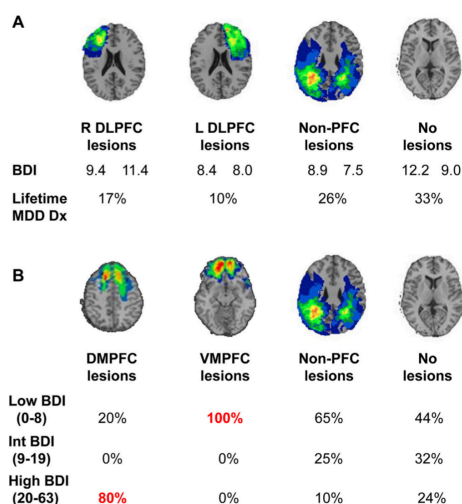
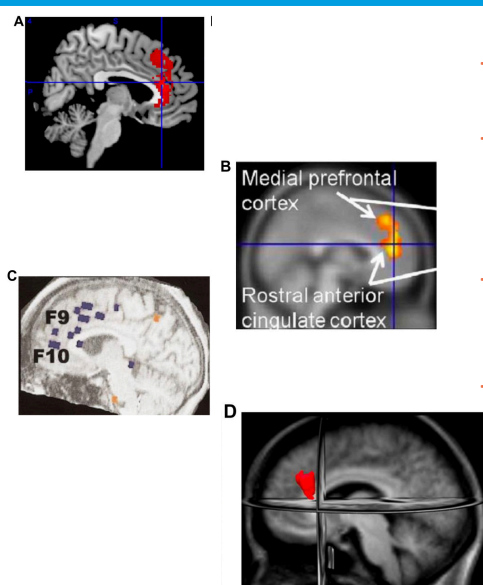


Figure 2. Lesion evidence for a more central role of DMPFC and VMPFC over DLPFC in the pathophysiology of depressed mood. (A) In veterans with focal brain injury, neither left nor right DLPFC lesions produce significant increases in depressive symptomatology, or in the lifetime prevalence of major depressive disorder, when compared to non-prefrontal lesions or to a control group with no lesions. (B) In veterans with focal brain injury, DMPFC lesions confer a strong risk of severe depressive symptomatology, while VMPFC lesions have the opposite effect, when compared against control groups with non-prefrontal lesions or no lesions. DLPFC, dorsolateral prefrontal cortex. DMPFC, dorsomedial prefrontal cortex. PFC, prefrontal cortex. BDI, Beck Depression Inventory. Adapted from refs. [60,63].

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Convergence d'études de stimulation, volumétriques, de connectivité et de lésions → dmPFC (Downar 2013)



- Études VBM: dmPFC et ACC (Bora 2012)
- Étude PET: moindre métabolisme chez non répondeurs dPFC rTMS (Li 2010)
- Inadvertant DBS-induced inhibition (Stefurak 2003)
- « dorsal nexus » increased FC rsNW self-reflection, affect regulation, cognitive control (Sheline 2010)

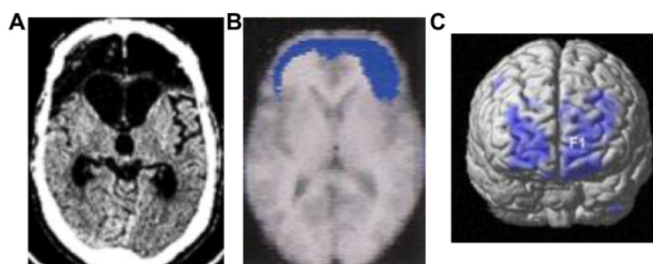
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Convergence d'études de lésion, corrélation et stimulation → FPC (BA 10) (Downar 2013)

- A : lésion sévère par arme à feu (conduite suicidaire):
rémission durable (Koenigs 2008)
B: corrélation réduction activité frontopolaire et amélioration
symptomatique ECT (Henry 2001)
C: Nacc DBS inhibe cortex frontopolaire(Bewernick 2010)



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Obstacle aux cibles non dl PFC (Downar 2013)

→ (Lu 2017)

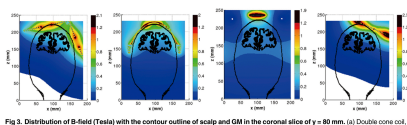


Fig 3. Distribution of B-field (Tesla) with the contour outline of scalp and GM in the coronal slice of $y = 80$ mm. (a) Double cone coil, (b) H-coil, (c) HCA coil and (d) Fob coil.

<https://doi.org/10.1371/journal.pone.0179422.g003>

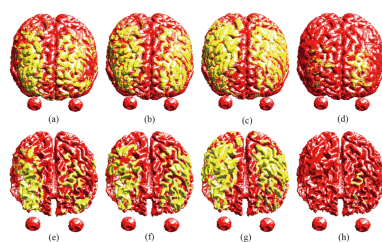


Fig 5. Electric field distributions on the cortical surfaces. Top row: Gray matter. Double cone coil (a), H-coil (b), HCA coil (c) and Fob coil (d). Bottom row: White matter. Double cone coil (e), H-coil (f), HCA coil (g) and Fob coil (h).

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Profondeur/ scalp:
vmPFC 7 cm
dm PFC 3-5 cm
FPC 2 cm

Douleur:
Lidocaine injection ou
patch
Titration de l'intensité
Protocoles plus courts
(theta burst)

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Anhédonie et circuit de la récompense (Downar 2014)

ARCHIVAL REPORT

Anhedonia and Reward-Circuit Connectivity Distinguish Nonresponders from Responders to Dorsomedial Prefrontal Repetitive Transcranial Magnetic Stimulation in Major Depression

Jonathan Downar, Joseph Geraci, Tim V. Salomons, Katharine Dunlop, Sarah Wheeler, Mary Pat McAndrews, Nathan Bakker, Daniel M. Blumberger, Zafiris J. Daskalakis, Sidney H. Kennedy, Alastair J. Flint, and Peter Giacobbe

BIOL PSYCHIATRY 2014;76:176–185 181

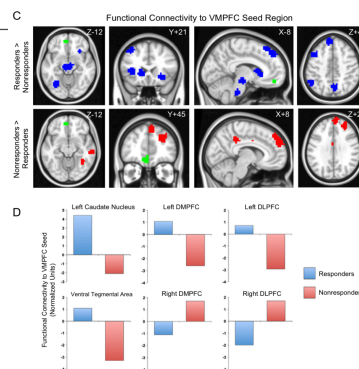
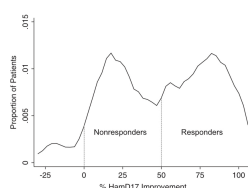


Figure 4. Neuroimaging correlates of response to dorsomedial prefrontal cortex (DMPFC)-repetitive transcranial magnetic stimulation. A comparison of betweenness centrality values in nonresponders versus responders to treatment revealed a single region whose betweenness centrality was significantly higher in nonresponders (A). This region lay in left ventromedial prefrontal cortex (VMPFC) at a location similar to that observed in previous meta-analyses of reward- versus loss-related activation in healthy control subjects (B) [reprinted from Diekhof *et al.* (53) with permission from Elsevier, copyright 2012]. Compared with responders, nonresponders showed significantly lower functional connectivity between the VMPFC seed and the ventral tegmental area and striatum, as well as between the VMPFC seed and a left-lateralized network of cortical regions including left DMPFC, dorsolateral prefrontal cortex (DLPFC), and anterior insula (C,D). Conversely, nonresponders showed significantly higher functional connectivity from the VMPFC seed to a right-lateralized network of cortical regions including right DMPFC, DLPFC, and posterior cingulate cortex.

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Si on n'augmente pas la réponse, peut-on la prédire ? (Salomons 2014)

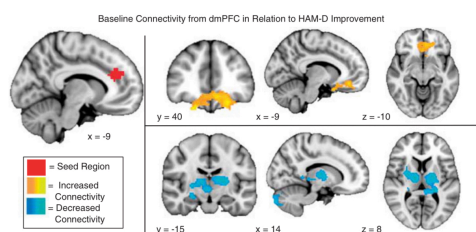
- À partir de l'activité d'une seule région (sgACC et dmPFC):
- CBT (Siegle 2006, Ritchey 2011)
- ADP (Mayberg 1997, Pizzagaly 2001, Kennedy 2001, Davidson 2003)
- DI PFC rTMS (Li 2010)
- rsFC ventral ↔ dorsal ACC
- ADP (Kozel 2011)
- Doit-on alors cibler ce réseau?
- Cela améliore-t'il la réponse?
- Cela en change-t'il la connectivité?

Resting-State Cortico-Thalamic-Striatal Connectivity Predicts Response to Dorsomedial Prefrontal rTMS in Major Depressive Disorder

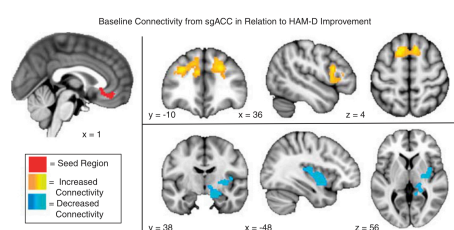
Tim V Salomons^{1,2,3,7}, Katharine Dunlop^{1,4,7}, Sidney H Kennedy^{2,5}, Alastair Flint^{2,5}, Joseph Geraci^{2,4}, Peter Giacobbe^{1,2,5} and Jonathan Downar^{1,2,5}

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Baseline predictors (Salomons 2014)



- High FC cortical nodes (executive control & emotion regulation)
- sgACC – dl or dmPFC
- Low FC cortico-thalamic & striatal (dmPFC- mdthalamus, putamen), cortico-limbic (sgACC-amgdala & hippocampus)



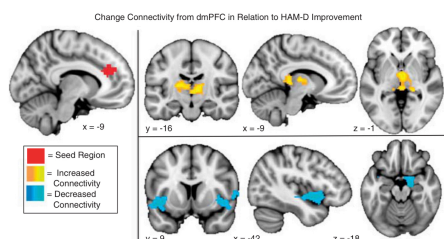
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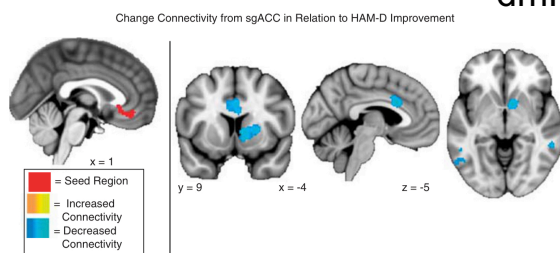


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Connectivity changes predictors (Salomons 2014)



- Increase dmPFC-thalamus
- Decreases sgACC-caudate & posterior midcingulate cortex, dmPFC- insula



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potentiel mécanisme d'action de la rTMS (dmPFC)?

- « increased influence of cognitive control networks over thalamic and striatal regions (core emotional functions), possibly linked with improved facilitation of goal-directed behavior (by integrating cognitive information with associated rewards and punishments (Shakman 2011))
- (Corbetta & Shulman 2002, Price & Drevets 2010, Sheline 2010)
- Général ou spécifique?
- Network-based model of major depression (Seminowicz 2004) suggère des voies neuronales différentes pour des approches différentes (Top-down vs bottom-up)
- ADP response with FC similar cingulate regions (Kozel 2011) mais en direction inverse!!!

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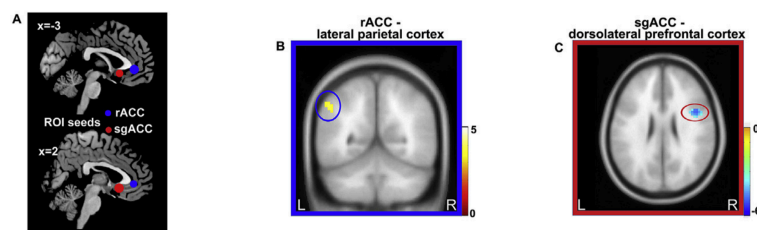
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fMRI predictors of dlPFC rTMS response in TRD



Functional connectivity of the anterior cingulate cortex predicts treatment outcome for rTMS in treatment-resistant depression at 3-month follow-up

Ruiyang Ge^a, Jonathan Downar^{b,c}, Daniel M. Blumberger^{b,d}, Zafiris J. Daskalakis^{b,d}, Fidel Vila-Rodriguez^{a,*}



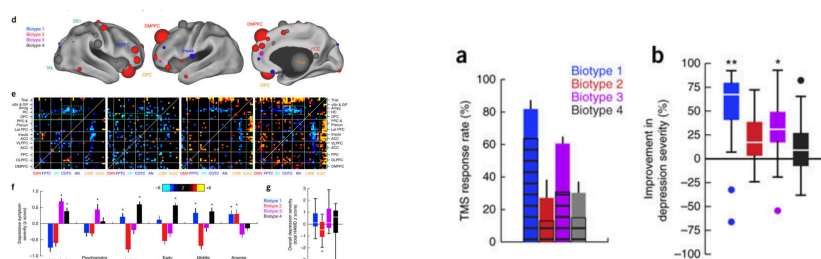
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4 sous types de dépression

Resting-state connectivity biomarkers define neurophysiological subtypes of depression

Andrew T Drysdale^{1,2,3}, Logan Grosenick^{4,5}, Jonathan Downar⁶, Katharine Dunlop⁶, Farrokh Mansouri⁶, Yue Meng¹, Robert N Fetho¹, Benjamin Zebley⁷, Desmond J Oathes⁸, Amit Etkin^{9,10}, Alan F Schatzberg⁹, Keith Sudheimer⁹, Jennifer Keller⁹, Helen S Mayberg¹¹, Faith M Gunning^{2,12}, George S Alexopoulos^{2,12}, Michael D Fox¹³, Alvaro Pascual-Leone¹³, Henning U Voss¹⁴, BJ Casey¹⁵, Marc J Dubin^{1,2}, and Conor Liston^{1,2,3}



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Bon vs mauvais répondeur DMPFC-rTMS

- Perte envahissante de contrôle cognitif
- Impulsivité, dysrégulation, cluster B
- Éléments de bipolarité, TDAH, traits borderline
- Atcdt hyperphagie/purge
- Atcdt abus/dépendance
- Éléments de TSPT, TOC
- Pensées intrusives, reviviscences
- Manque de contrôle: émotion, cognition, action
- N'est pas chroniquement dysrégulé/impulsif
- Cluster C/ traits TGP obsessionnel compulsif
- Dysthymie chronique, anhédonie
- Tristesse « compulsive », pessimisme
- Restrictif, ou pure anorexie mentale
- Contrôle cognitif intact
- Absence de perte de contrôle envahissante

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Psychiatric common core regions

Trends in Cognitive Sciences

CellPress

Opinion The Neural Crossroads of Psychiatric Illness: An Emerging Target for Brain Stimulation

Jonathan Downar,^{1,2,3,4,*} Daniel M. Blumberg,^{1,2,5} and
Zafiris J. Daskalakis^{1,2,5}

Recent meta-analyses of structural and functional neuroimaging studies are converging on a collective core of brain regions affected across most psychiatric disorders, centered on the dorsal anterior cingulate cortex (dACC) and anterior insula. These nodes correspond well to an anterior cingulo-insular (ACIN) or "salience" network, and stand at a crossroads within the functional architecture of the brain, acting as a switch to deploy other major functional networks according to motivational demands and environmental constraints. Therefore, disruption of these "hubs" may be disproportionately disabling, even when other networks remain intact. These regions may represent promising targets for a new generation of anatomically directed brain stimulation treatments. Here, we review the potential of the psychiatric core areas as targets for therapeutic brain stimulation in psychiatric diseases.

Keywords:
The structure and functional connectivity of the brain's psychiatric core areas are becoming increasingly well characterized, including the involvement of neuroimaging studies and new brain stimulation analysis techniques. A common core of areas is affected across most categories of psychiatric illness. We review these key ACC and anterior insula. The psychiatric core areas are located in the dorsal anterior cingulate cortex and anterior insula. These regions are part of the salience network, which is a core of the resting state network of the brain. Downar et al. (2018) 10.1016/j.tics.2018.05.001

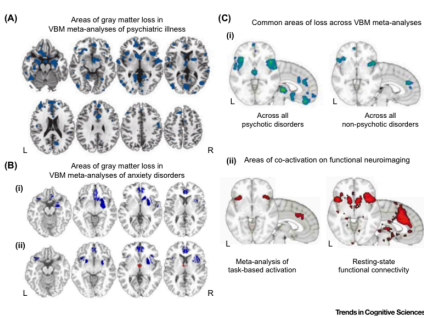
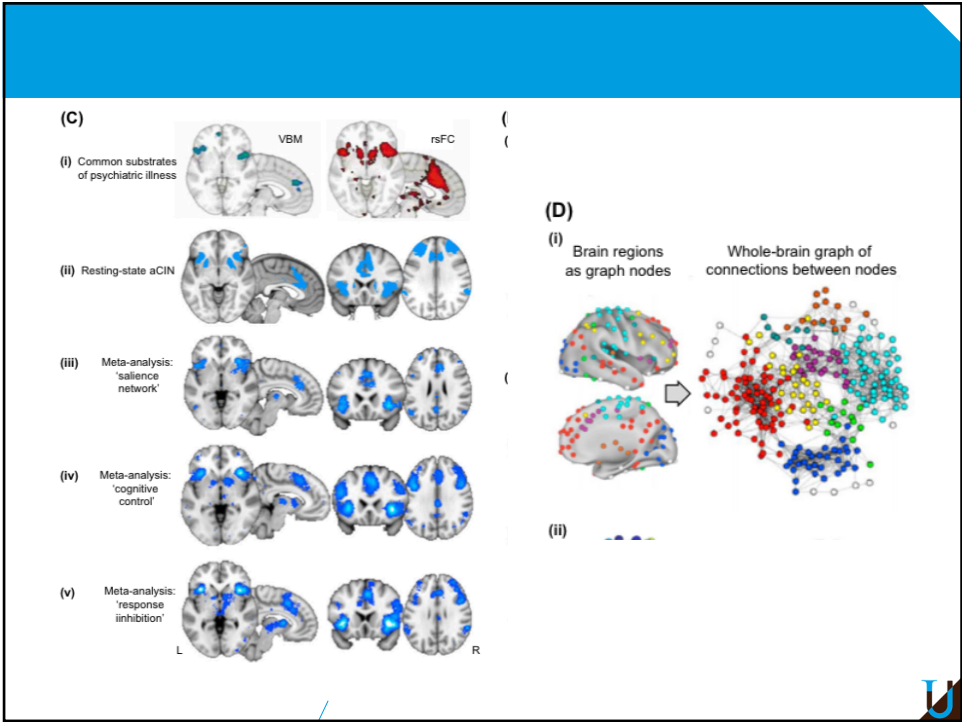


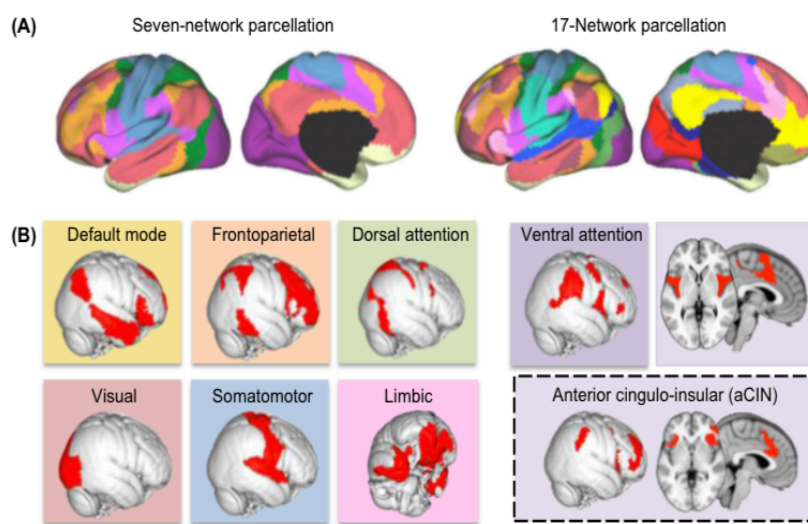
Figure 2. A Common Core of Regions with Structural Abnormalities in Psychiatric Illness. (A) Brain regions showing consistent loss of gray matter across a selection of voxel-based morphometry (VBM) studies of diverse psychiatric illnesses, including schizophrenia (SCZ), bipolar disorder (BD), obsessive-compulsive disorder (OCD), panic disorder (PD), post-traumatic stress disorder (PTSD), attention deficit hyperactivity disorder (ADHD), autism spectrum disorders, and anorexia. (B) Brain regions showing consistent loss of gray matter across a variety of anxiety disorders [generalized anxiety disorder (GAD), social anxiety disorder (SAD), PD with and without agoraphobia, and specific phobias], shown in blue. (C) Brain regions showing consistent loss of gray matter across multiple categories of psychotic and nonpsychotic psychiatric disorders. Combining both groups, three nodes emerge: the left and right anterior insula/horizontal operculum, and the dorsal anterior cingulate cortex. (D) These three nodes belong to a common network of co-activating brain regions seen in meta-analyses of brain activation across multiple tasks; on resting-state activity, these nodes belong to a larger common network that also includes a circuit of connected regions in the striatum, thalamus, subthalamic nucleus, and brainstem. Adapted from [24] (A), [20] (B), and [25] (C).

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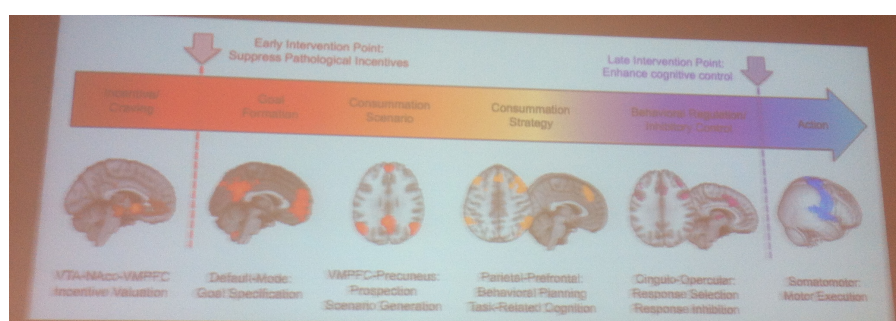
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Saliience network in whole brain network parcellation (Yeo 2011, Power 2011)

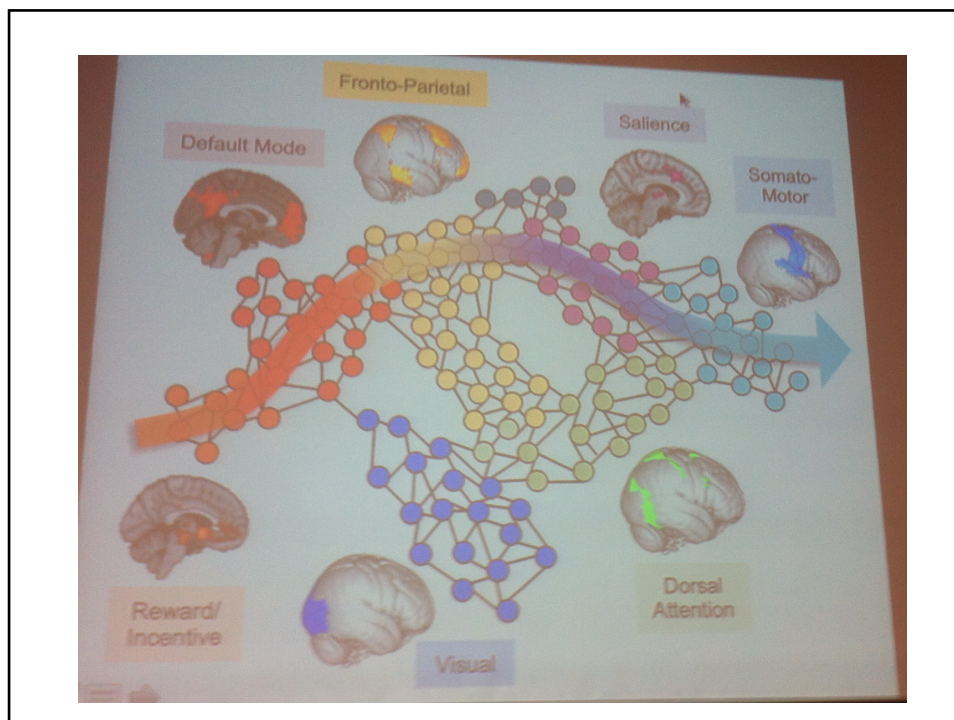


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A pathway from drives to action (Downar 2016)



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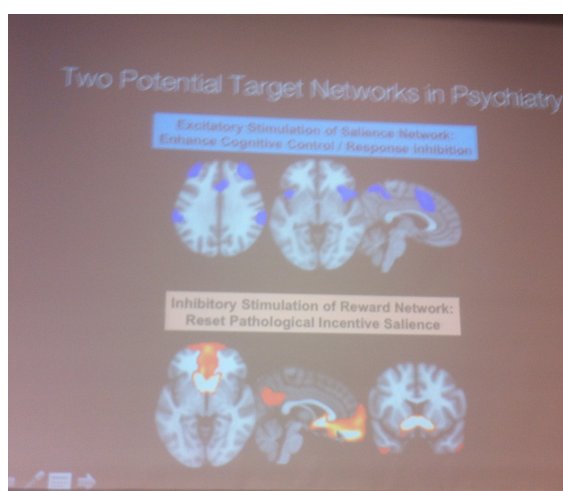


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Excitatory stimulation of salience network; enhance cognitive control/response inhibition

Inhibitory stimulation of reward network; reset pathological incentive salience



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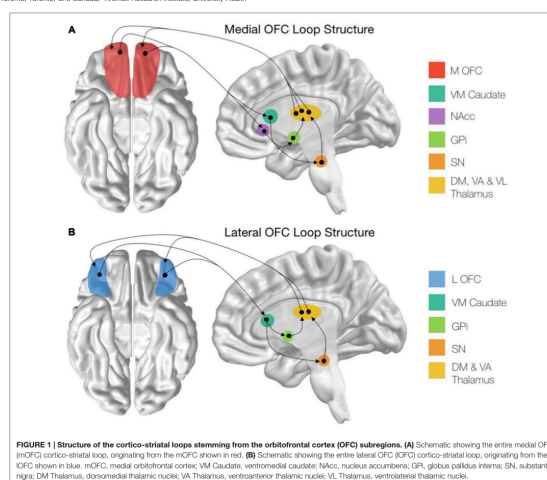
Taking together these lines of evidence, recent reviews have suggested that the therapeutic effects of rTMS may be best understood not as “antidepressant” *per se*, but more generally as enhancement of cognitive control via improved SN integrity (Downar et al., 2016; Dunlop et al., 2016). This would account for its transdiagnostic efficacy across a range of psychiatric disorders involving cognitive control deficiency (McTeague et al., 2016).

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Cortico-Striatal-Thalamic Loop Circuits of the Orbitofrontal Cortex: Promising Therapeutic Targets in Psychiatric Illness

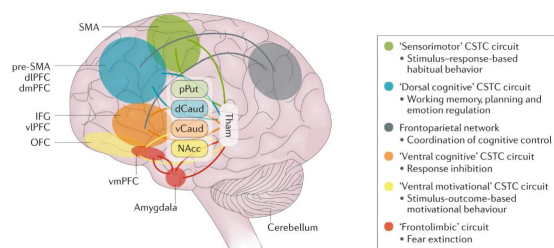
Peter Fettes¹, Laura Schulte¹ and Jonathan Downar^{1,2,3,4*}

¹Institute of Medical Science, University of Toronto, Toronto, ON, Canada; ²Krembil Research Institute, University Health



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Différents réseaux cortico striato thalamo corticaux



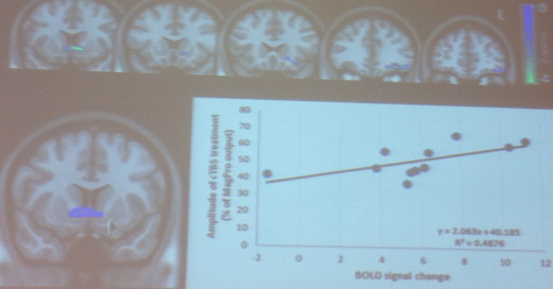
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Frontopolar rTMS: effects on Ventral Striatum

A) Design



B) TMS-evoked BOLD signal after cTBS

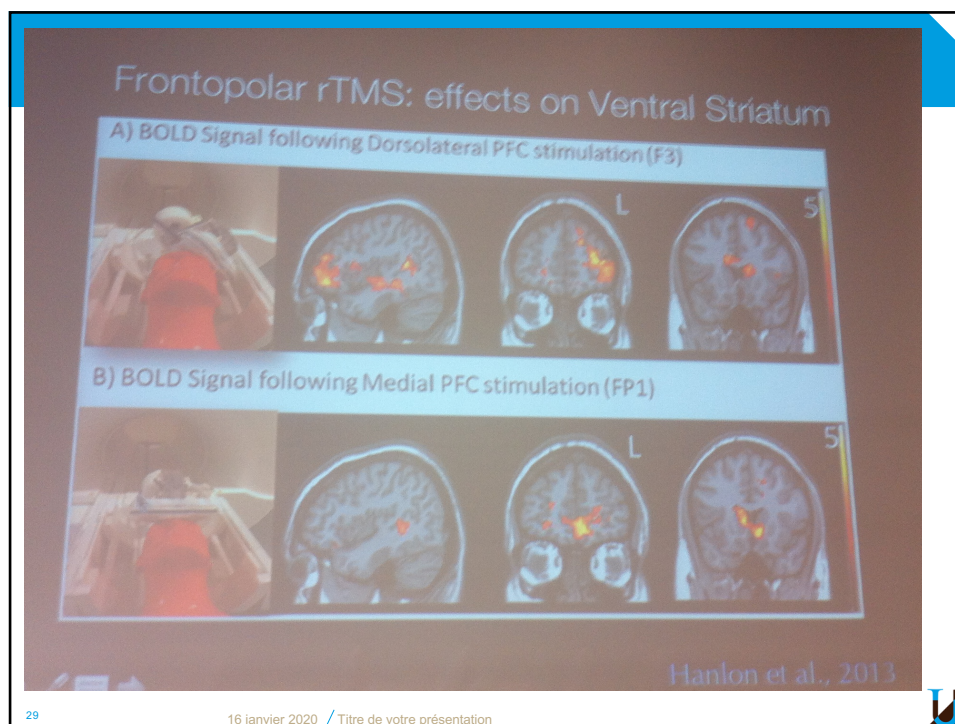


Hanlon et al., 2013

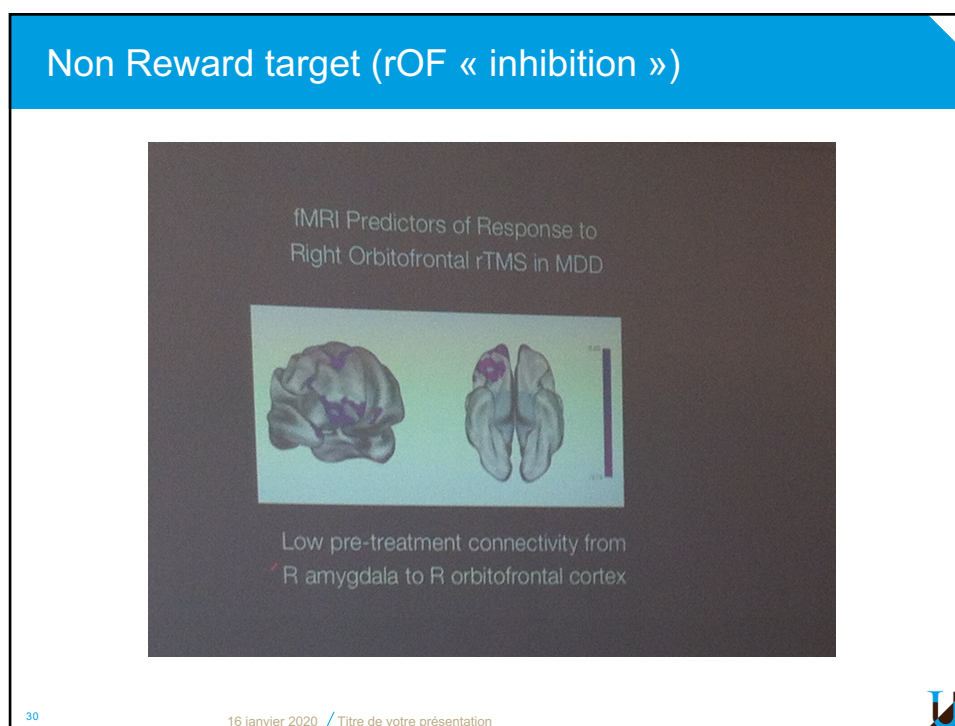
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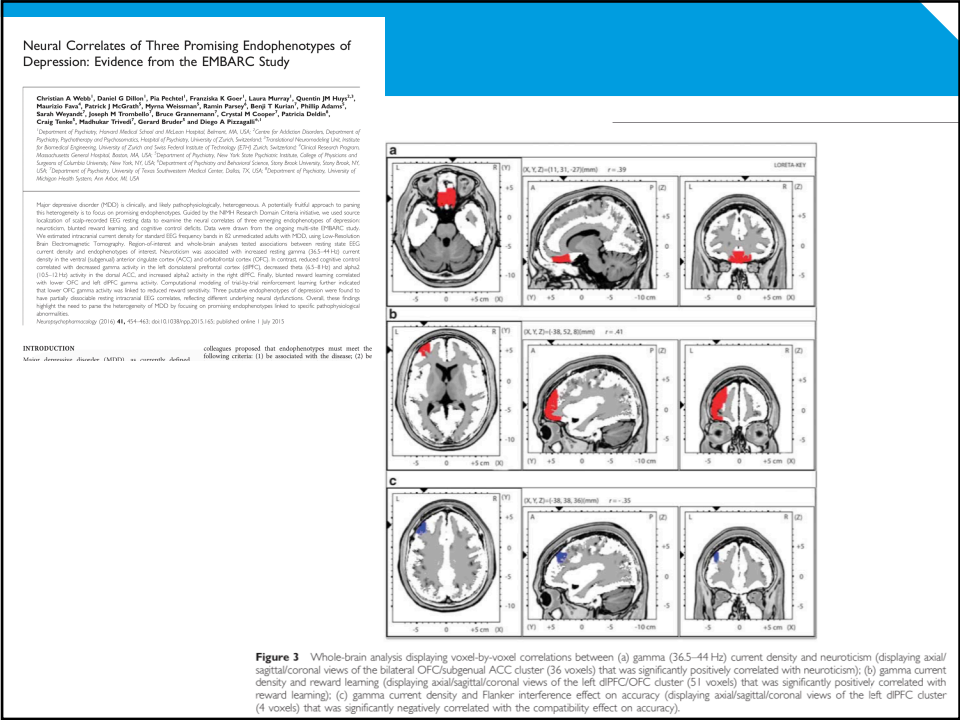
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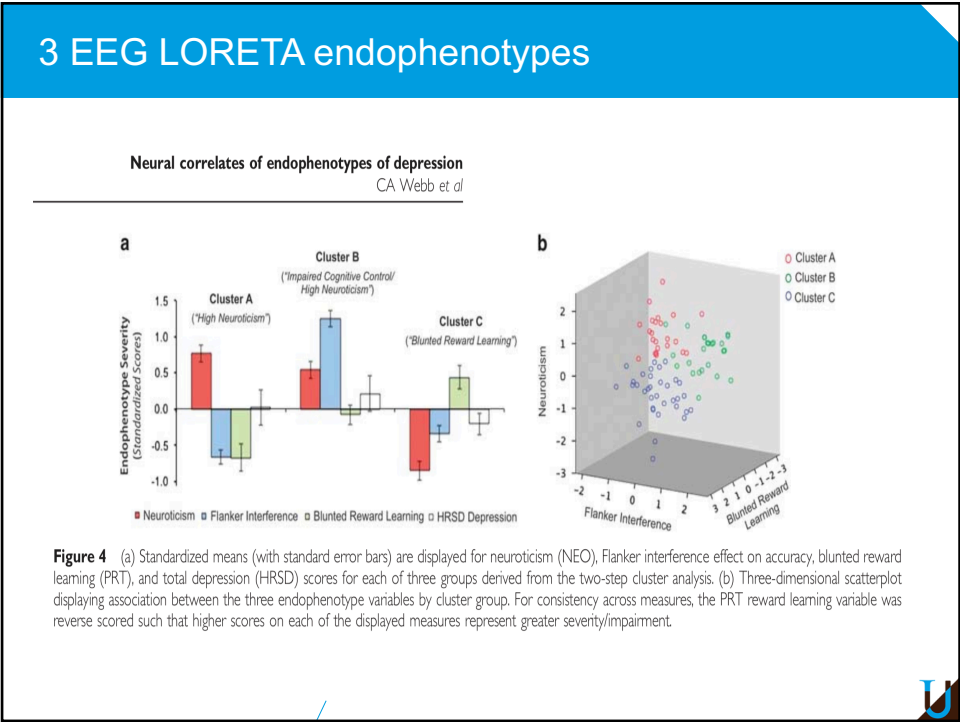
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Three Neural Endophenotypes of Depression:

1. Cognitive control deficits – Salience Network
2. Anhedonia/Reward problems – Reward Network
3. Neuroticism/anxiety – Non-reward Network

1. The Salience Network

The most important network is the Salience Network (our current target in cTMS), which enables cognitive control.

The cortico-striatal-thalamic loop of the Salience Network is:

The DLPFC/DMPFC → Striatum (Caudate/Putamen) → Thalamus → back up to the DLPFC/DMPFC again.

2. The Reward Network

The Reward Network enables motivation and pleasure.

The cortico-striatal-thalamic loop of the Reward Network is:

The ventromedial prefrontal cortex (VMPFC)/Frontal Polar cortex → Ventral striatum (nucleus accumbens) → Thalamus → back up to the VMPFC again.

3. The Non-Reward Network

The Non-reward network is involved in the generation and regulation of negative affect

The cortico-striatal-thalamic loop for the Non-reward network is:

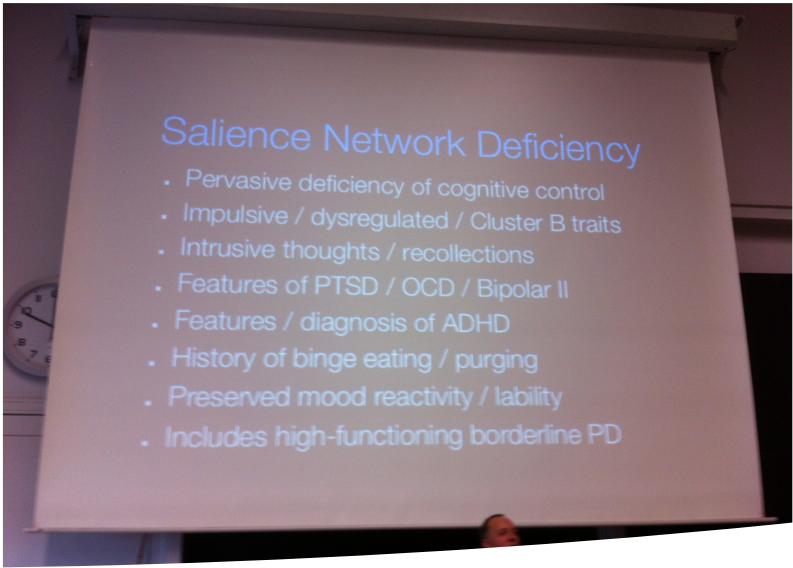
The right OFC/Temporal pole → Amygdala → Thalamus → OFC/Temporal pole.

Figure 1: Brain maps showing voxel-to-voxel correlations between gamma (36.5-44.0 Hz) current density and neuroticism (A), gamma current density and the lateral OFC/ventral ACC cluster (B), gamma current density and the left dlPFC cluster (C), and gamma current density and the right dlPFC cluster (D). Each panel shows axial, sagittal, and coronal views of the brain with significant clusters highlighted in red.

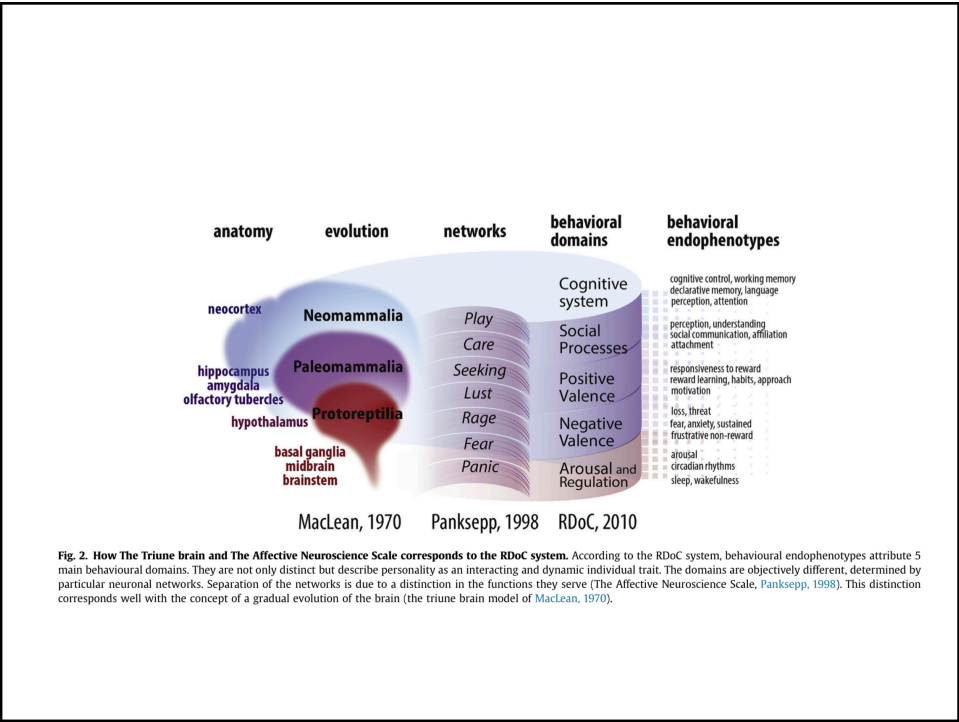
Bon répondeur rOF-rTMS

- Activité « anti-récompense » compulsive, envahissante
- Forte anxiété chronique, pessimisme
- Peu d'éléments d'impulsivité
- Négativisme obsédant, préoccupation
- Peut comporter des idées suicidaires obsédante
- Amélioration marquée de l'anxiété
- Amélioration marquée des IS obsédante
- Obtention de rémissions complètes parmi les non répondeurs à la rTMS conventionnelle

36/01/2020



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