



Apathie

neurocognitieve basis en neurostimulatie

André Aleman



rijksuniversiteit
groningen



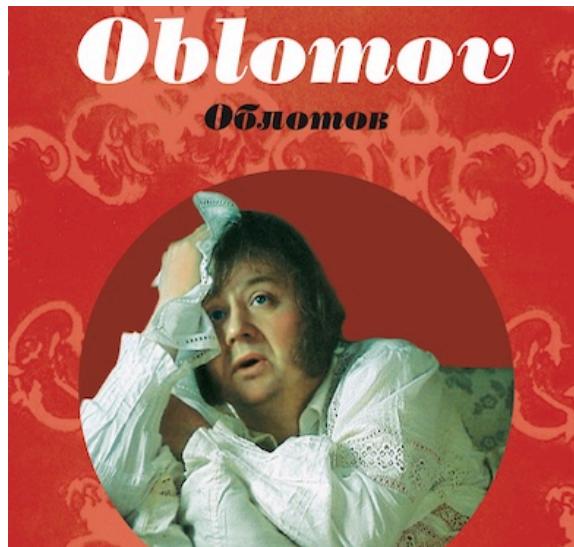
umcg



apathy
study



Het apateam



Oblomov: inactivity, inertia, apathy

Ten Days With Oblomov: A Journey in My Bed







Kort videofragment



- “I know I need to be doing something, and I feel it in my heart, but I just can’t make myself do anything. I’m just so dead inside, something I am really struggling with, I am going to have to talk to my doctor about, because this is absolutely horrible.”

Definition of apathy

(Levy & Dubois , 2006)

NEUROIMAGING CENTER GRONINGEN

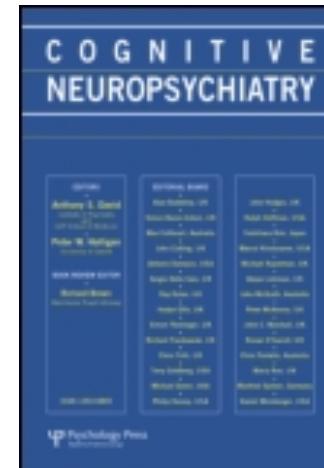


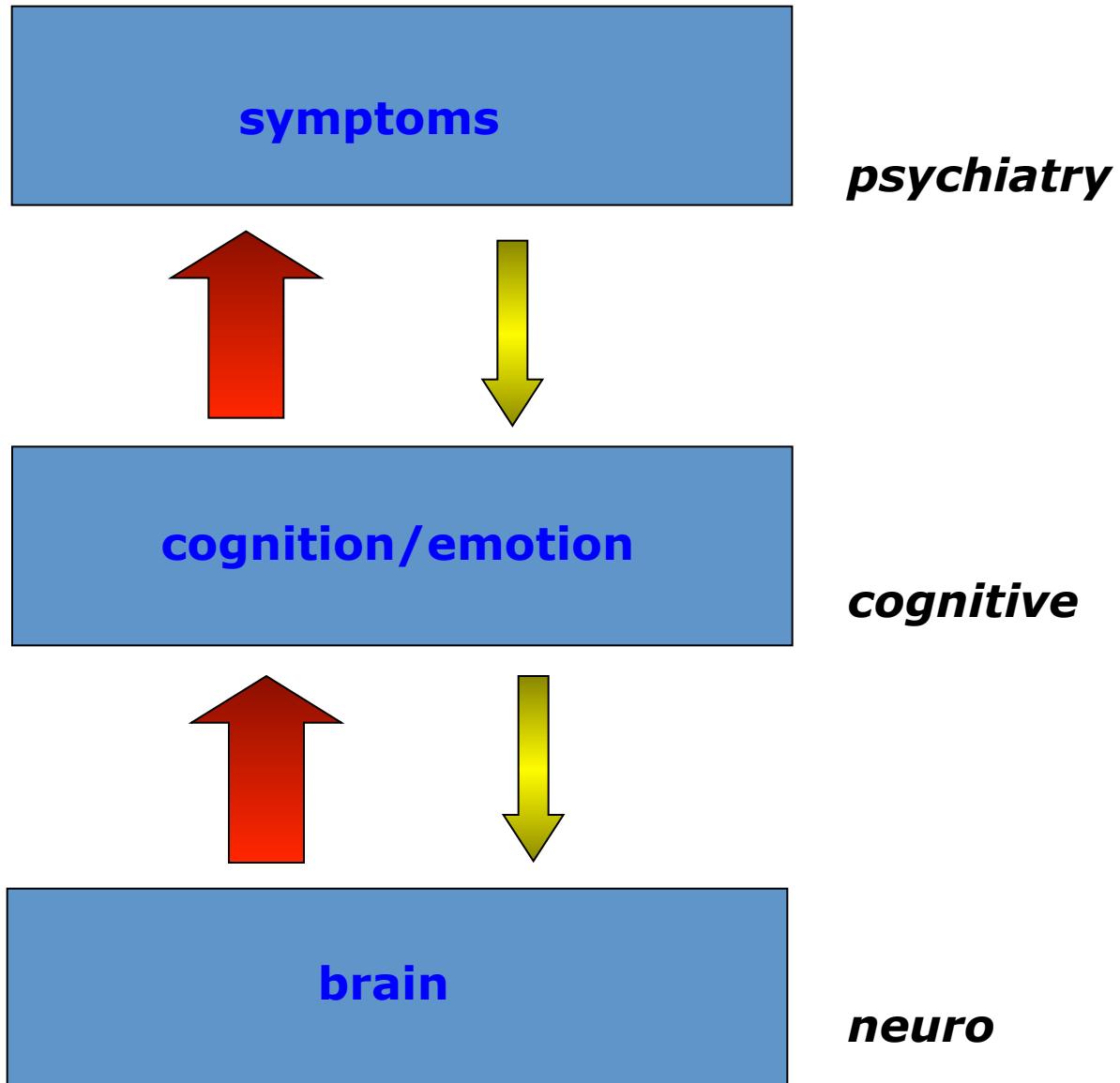
“Quantitative reduction of self-generated voluntary and purposeful behaviors.”

Cognitive neuropsychiatry

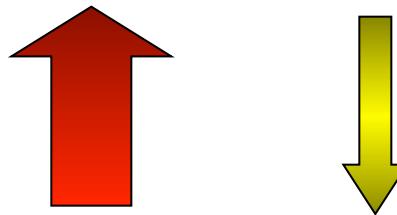
- A theory-driven approach that attempts to explain psychiatric symptoms in terms of cognitive brain processes
- Connects clinical psychiatry with cognitive psychology and the neurosciences

Halligan & David (2001) *Nature Reviews Neuroscience*

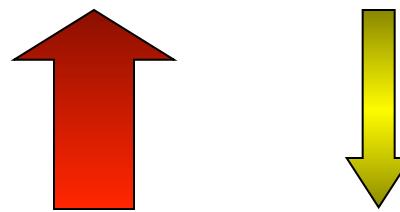




Cognitive apathy

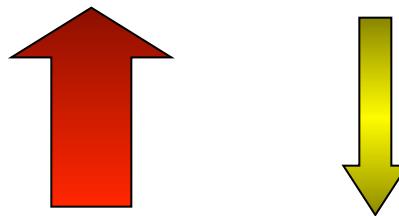


Reduced initiation of action due
to diminished cognitive control

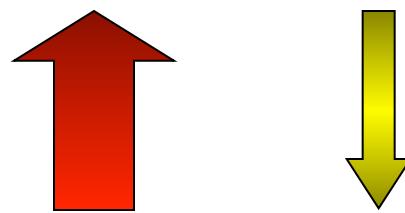


Dorsal frontostriatal/ parietal circuit

Emotional apathy



failure to signal the salience of
positive events

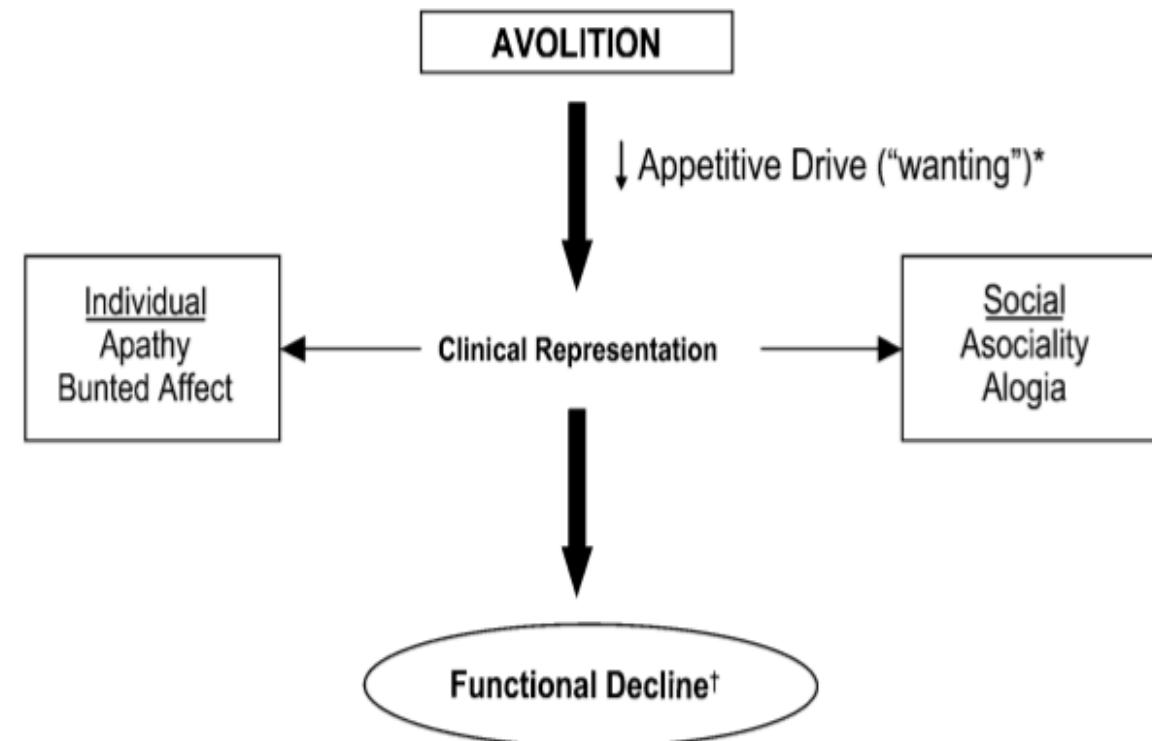


Ventral frontostriatal circuit

Negative Symptoms in Schizophrenia: Avolition and Occam's Razor

George Foussias^{1,2,3} and Gary Remington^{2,3}

²Centre for Addiction and Mental Health and Department of Psychiatry, Faculty of Medicine; ³Institute of Medical Science, Faculty of Medicine, University of Toronto, Toronto, ON, Canada



apathy

- common in schizophrenia patients
- Understanding apathy is important, as apathy is the strongest predictor of poor functioning, unemployment, severity of illness and worse outcome in routine clinical practice

Negative symptoms: two factors

Journal of Psychiatric Research 47 (2013) 718–725



ELSEVIER

Contents lists available at SciVerse ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires



Two subdomains of negative symptoms in psychotic disorders: Established and confirmed in two large cohorts

Edith Liemburg^{a,b}, Stynke Castelein^{b,c}, Roy Stewart^d, Mark van der Gaag^{e,f}, André Aleman^{a,g}, Henderikus Knegtering^{a,b,c,*}, Genetic Risk and Outcome of Psychosis (GROUP) Investigators¹

Expl FA in 664 patients
Confirm FA in 2172 pts

- Factor 1: Expressive deficits/
lack of initiative

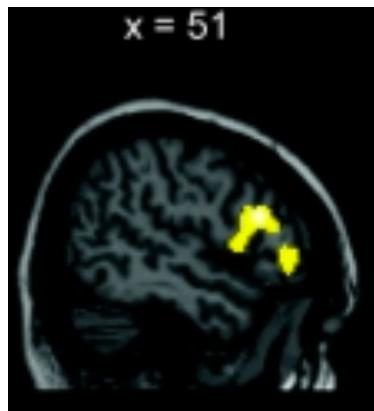
-Factor 2: Social amotivation

Table 2

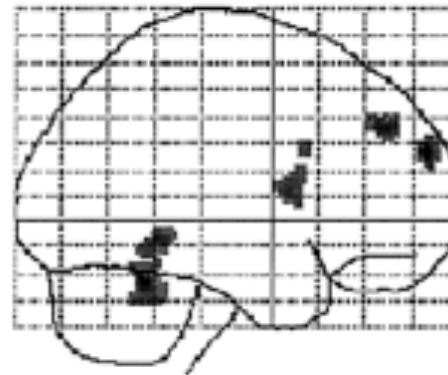
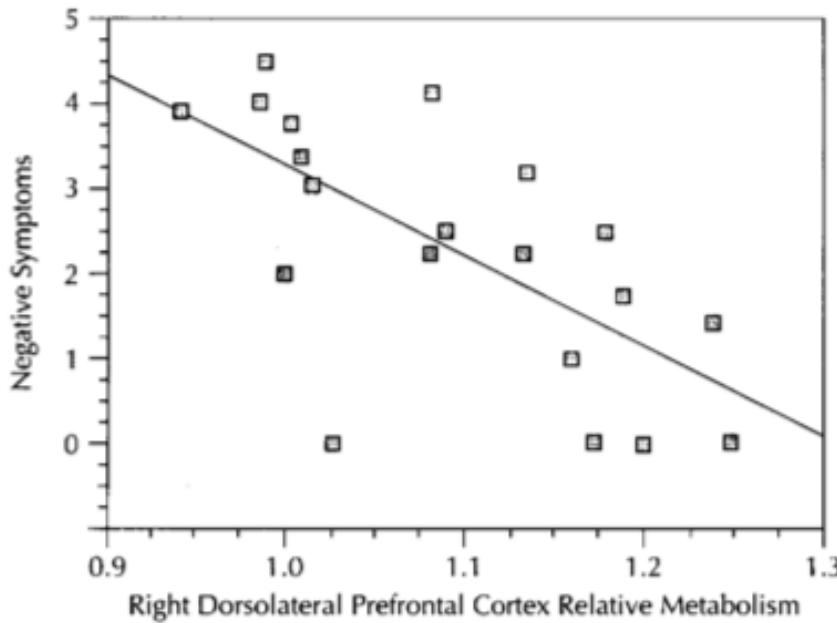
Factor structure of factor analysis on items N1, N2, N3, N4, N6, G5, G7, G13 and G16 of the PANSS after Varimax rotation; Bold values indicate that the item loaded strongest on this factor.

	Factor 1		Factor 2	
	Unrotated loading	Rotated loading	Unrotated loading	Rotated loading
N6 Lack of spontaneity	0.756	0.807	0.357	0.202
N3 Poor rapport	0.744	0.759	0.297	0.257
N1 Flat affect	0.713	0.594	0.080	0.403
G7 Motor retardation	0.645	0.571	0.124	0.325
G5 Mannerisms and posturing	0.443	0.460	0.189	0.144
G13 Avolition	0.435	0.406	0.117	0.194
N4 Passive/apathetic social withdrawal	0.807	0.287	-0.503	0.906
N2 Emotional withdrawal	0.777	0.386	-0.315	0.744
G16 Active social avoidance	0.431	0.158	-0.261	0.478

Right DLPFC: major hub?



Neural correlates of apathy in frontotemporal dementia (Zamboni et al. 2008): right DLPFC



fMRI in neuroleptic-naive patients, Riehemann et al. (2011)

Negative Symptoms and Hypofrontality of glucose metabolism in Chronic Schizophrenia (Wolkin et al. 1992 Arch Gen Psychiat)

Review

Neuroanatomical abnormalities in schizophrenia: A multimodal voxelwise meta-analysis and meta-regression analysis

Emre Bora ^{a,*}, Alex Fornito ^a, Joaquim Radua ^b, Mark Walterfang ^a, Marc Seal ^c, Stephen J. Wood ^{a,d}, Murat Yücel ^{a,e}, Dennis Velakoulis ^a, Christos Pantelis ^a

Schizophrenia Research 127 (2011) 46–57

In chronic samples, more severe negative symptoms were associated with smaller GM in the bilateral medial frontal gyrus/orbitofrontal cortex ($-2, 32, -16$, SDM = -0.48 , $p = 0.0009$, 79 voxels) and left insula ($-42, 2, 2$ SDM = -0.61 , $p = 0.00003$, 271 voxels).

Voxel-based morphometry meta-analysis

Parietal cortex and negative symptoms in drug-free scz patients

Am J Psychiatry. 2001 Nov;158(11):1797-808.

Abnormal patterns of regional cerebral blood flow in schizophrenia with primary negative symptoms during an effortful auditory recognition task.

Lahti AC, Holcomb HH, Medoff DR, Weiler MA, Tamminga CA, Carpenter WT Jr.

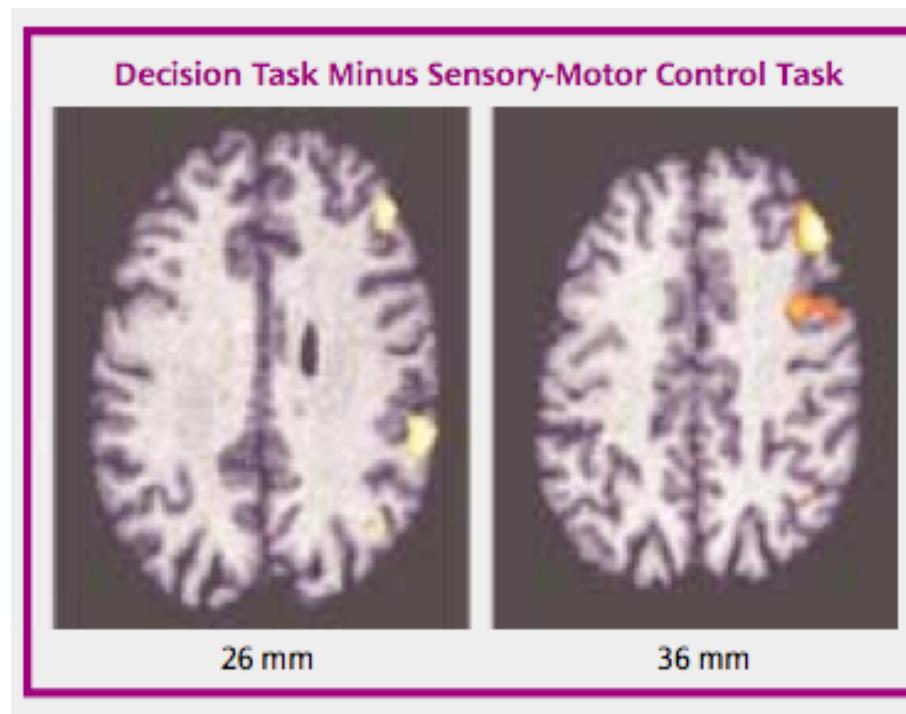


FIGURE 4. Brain Regions Activated More in 10 Schizophrenic Patients Without Primary Negative Symptoms Than in Eight Patients With Primary Negative Symptoms (Deficit Schizophrenia) During a Sensory-Motor Control Task and a Decision Task^a

First findings: Tower of London



Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

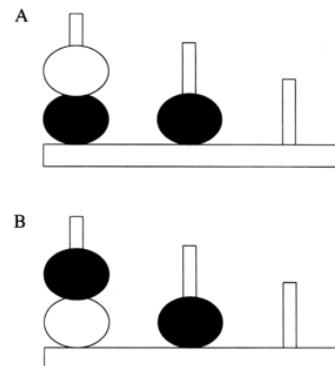


Neural correlates of planning performance in patients with schizophrenia – Relationship with apathy



Edith J. Liemburg ^{a,b,*}, Jozarni J.L.A.S. Dlabac-De Lange ^a, Leonie Bais ^{a,c}, Henderikus Knegtering ^{a,b},
Matthias J.P. van Osch ^d, Remco J. Renken ^a, André Aleman ^{a,e}

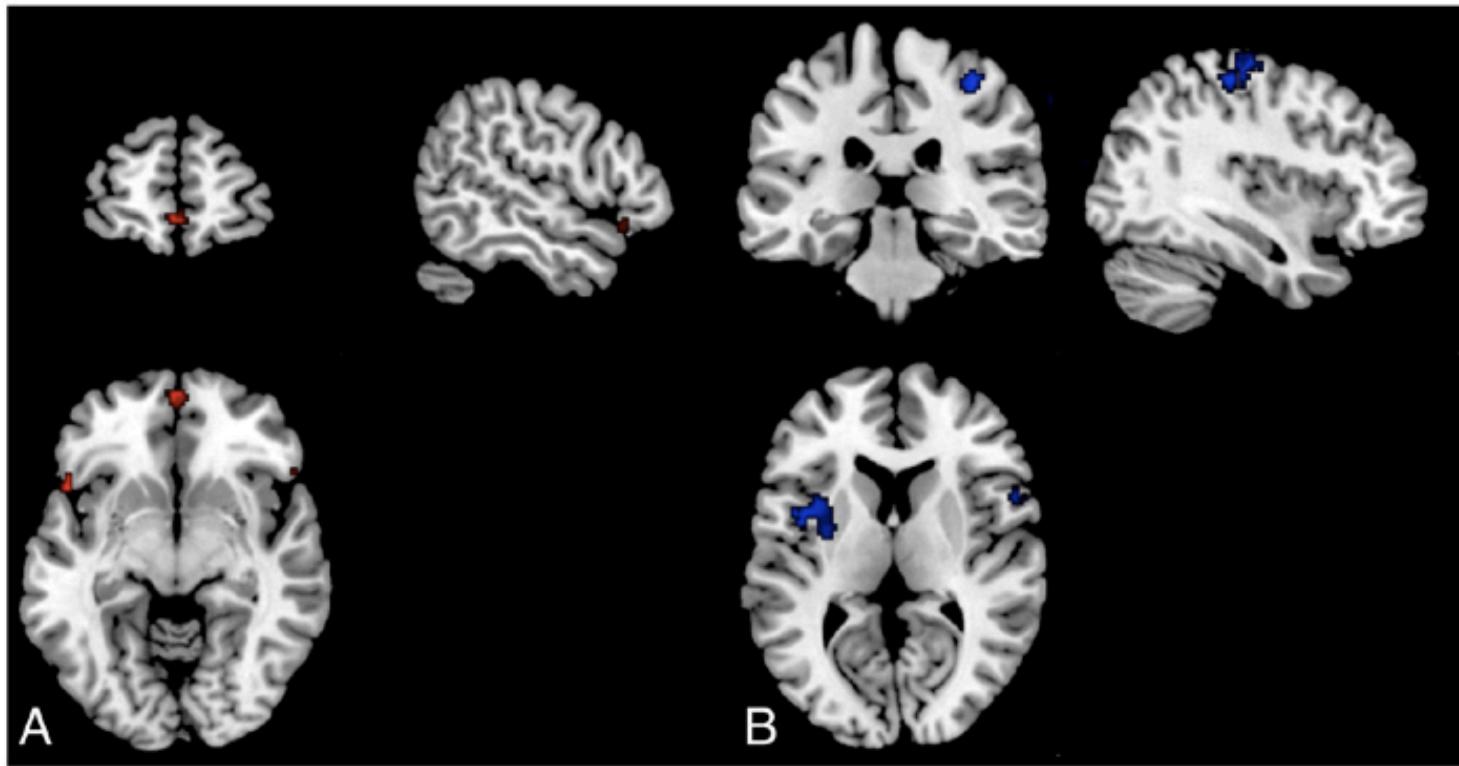
^a Department of Neuroscience, and BCN Neuroimaging Center, University of Groningen, University Medical Center Groningen, FA32, Antonius Deusinglaan 2, 9713 AW Groningen, The Netherlands



Healthy controls, N=14
Schiz pts, low apathy, N=14
Schiz pts, high apathy, N=13



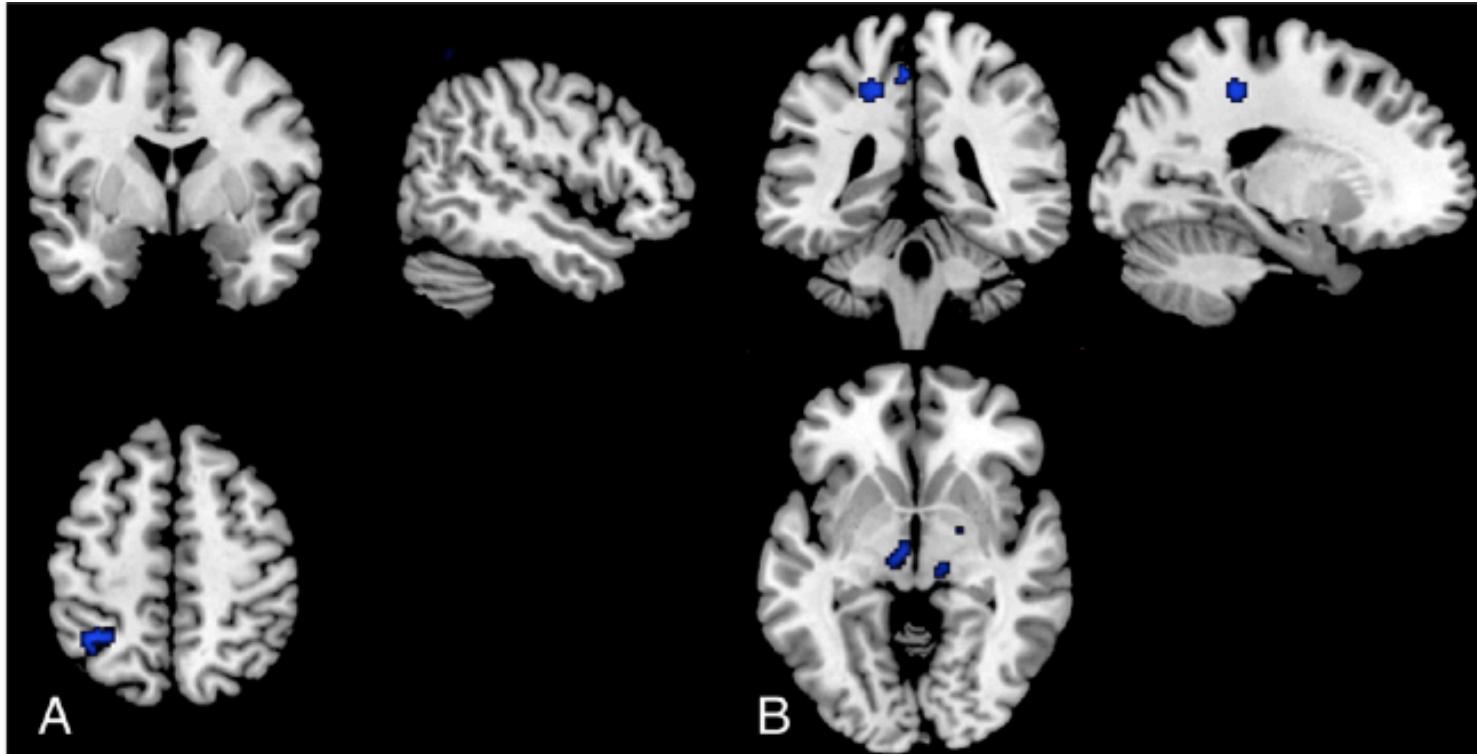
umcg



activation between schizophrenia patients and healthy controls in the Tower of London. red = patients – controls, blue = controls – patients nodulation.

Higher levels of apathy were associated with less task-related activation within the inferior parietal lobule, precuneus and thalamus. Compared to controls, patients showed lower activation in lateral prefrontal regions, parietal and motor areas, and a higher activation of medial frontal areas.

Association with apathy

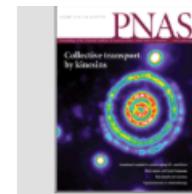




click for updates

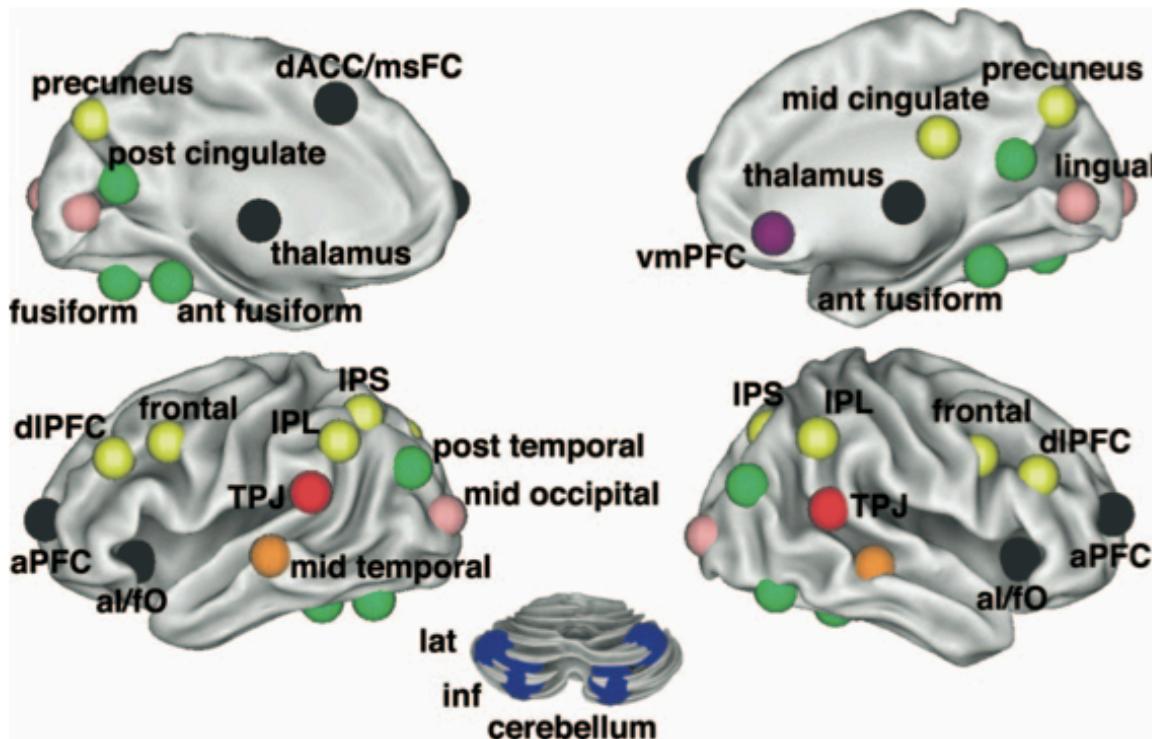
Distinct brain networks for adaptive and stable task control in humans

Nico U. F. Dosenbach * , † , Damien A. Fair ‡ , Francis M. Miezin * , ‡ , Alexander L. Cohen * ,



June 26, 2007
vol. 104 no. 26
Masthead (PDF)
Table of Content

this network may control goal-directed behavior through the stable maintenance of task sets.

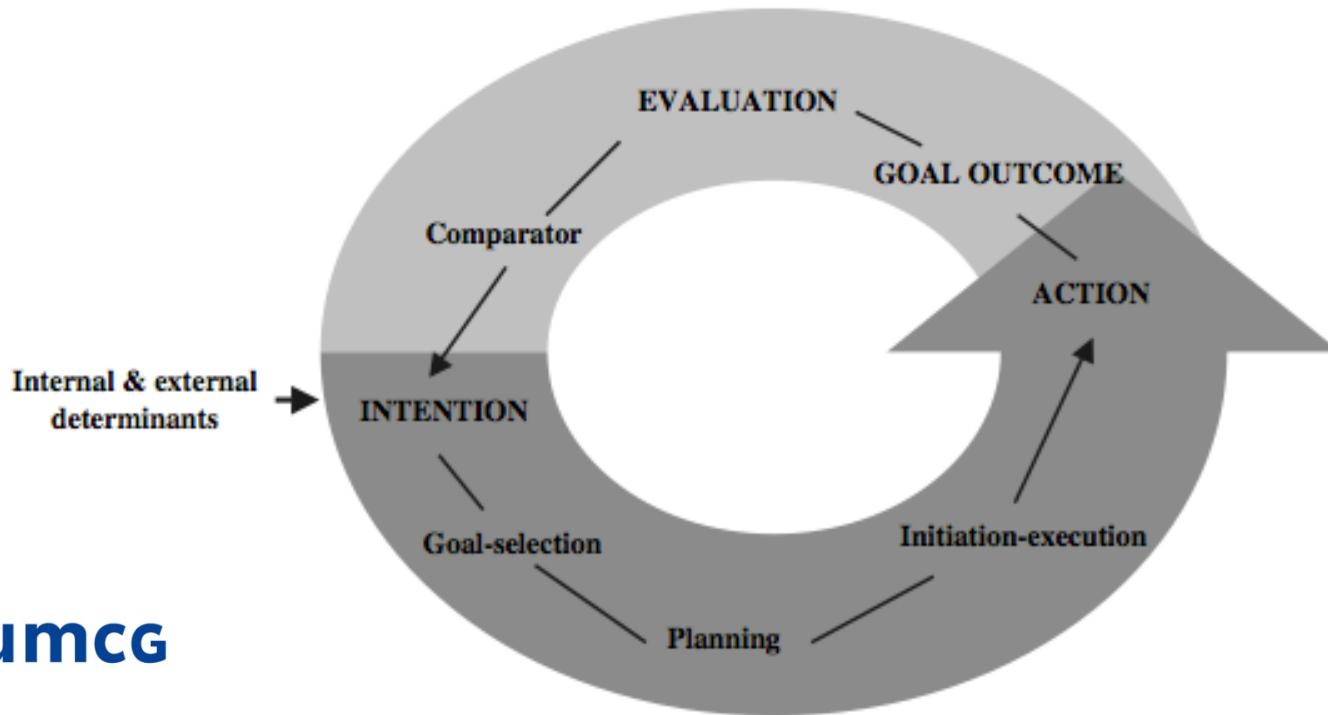


Cerebral Cortex July 2006;16:916-928
doi:10.1093/cercor/bhj043
Advance Access publication October 5, 2005

Apathy and the Functional Anatomy of the Prefrontal Cortex–Basal Ganglia Circuits

Richard Levy and Bruno Dubois

Fédération de Neurologie and INSERM U610, Hôpital de la Salpêtrière, Paris, France



umcg

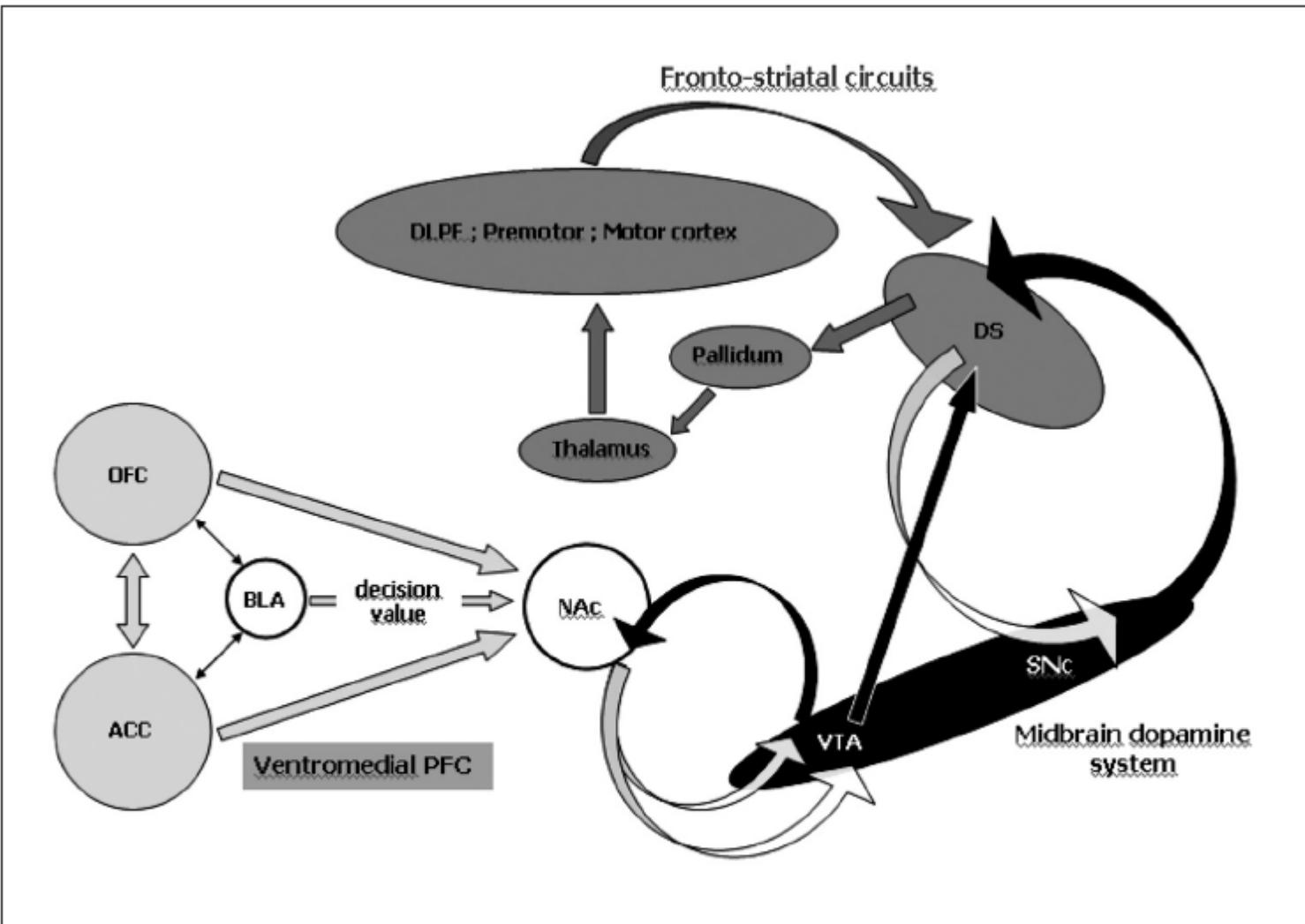


Figure. Proposed model of ventromedial PFC top-down influence on behavior generation. OFC, orbito-frontal cortex; ACC, anterior cingulate cortex; BLA, basolateral amygdala; NAc, nucleus accumbens core; VTA, ventral tegmental area; SNC, substantia nigra pars compacta; DS, dorsal striatum; DLPF, dorsolateral prefrontal.

Types of apathy

Stuss, van Reekum & Murphey, 2000; Levy & Dubois, 2006)

NEUROIMAGING CENTER GRONINGEN



Cognitive apathy
(CA)

Social-emotional apathy
(SEA)

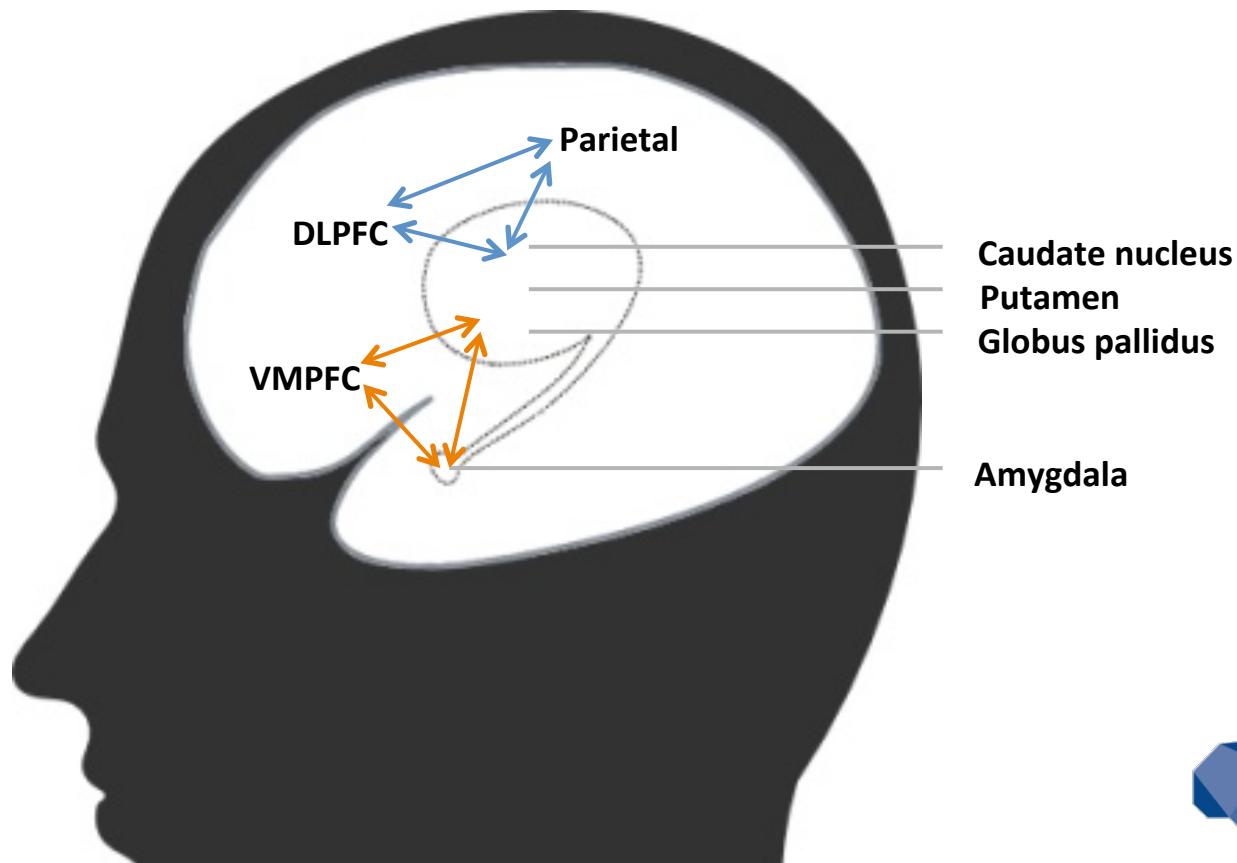
- Different cognitive deficits
- Different underlying neural substrates
- Different approaches/ treatment?

Objective

NEUROIMAGING CENTER GRONINGEN



Differential neural base for CA and SEA?

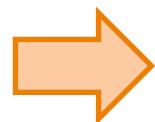


Social-emotional apathy (SEA)

NEUROIMAGING CENTER GRONINGEN



- Interest/ motivation
- Signaling salience of positive events

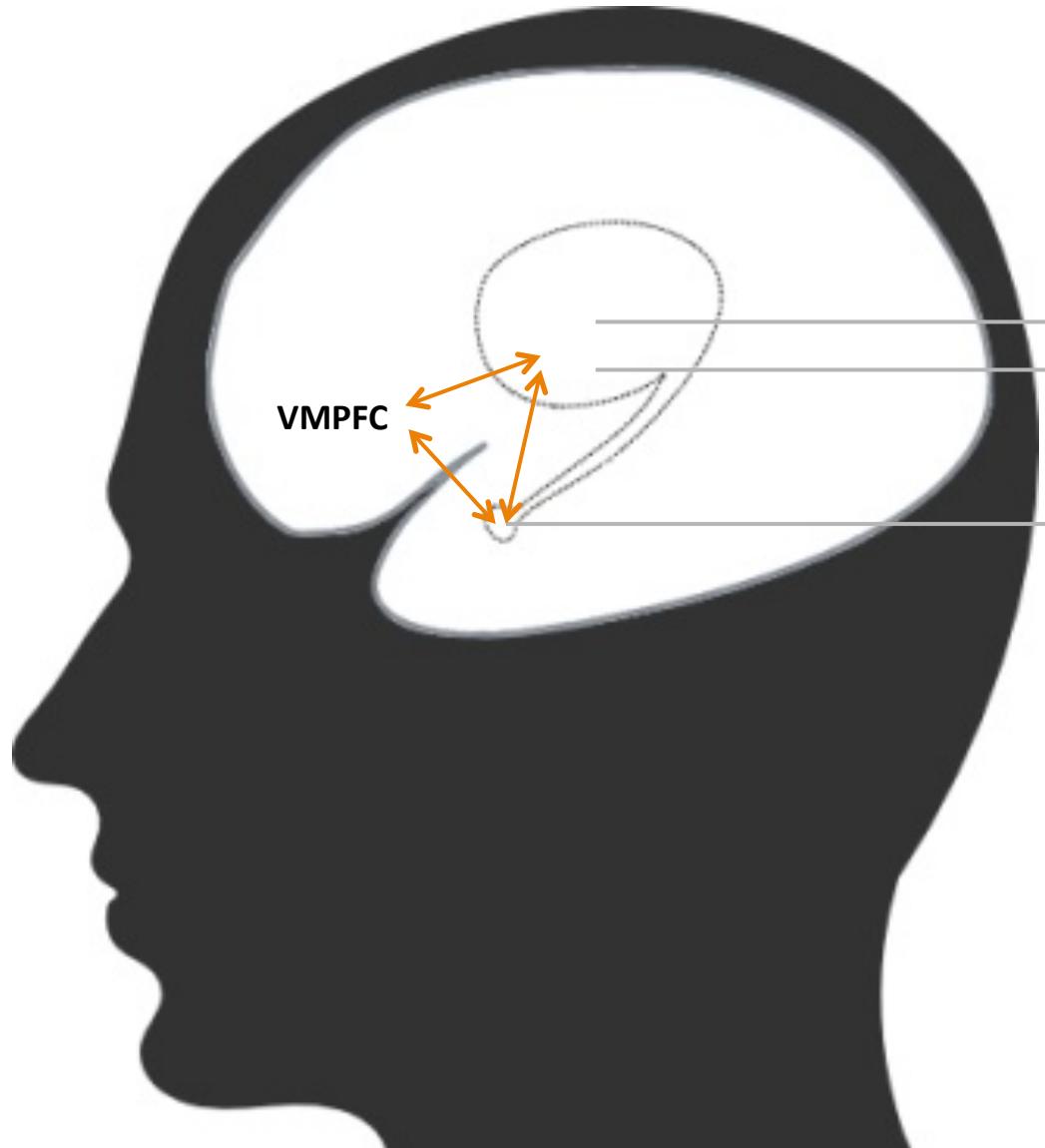


Difficulties anticipating pleasure



Neural base of SEA

NEUROIMAGING CENTER GRONINGEN



Putamen
Globus pallidus

Amygdala

Effort task

(Pessiglione et al., 2007; Schmidt et al., 2012)

NEUROIMAGING CENTER GRONINGEN



+ 500ms	Reward cue 1500ms	Response 3500ms	Effort rating 2500ms	Result Cumulative result 1500ms
	IAPS picture 		0 1 2 3 4 5 6	



Effort task

(Pessiglione et al., 2007; Schmidt et al., 2012)

NEUROIMAGING CENTER GRONINGEN



Reward anticipation

- ventral striatum (NAcc)
- ventral pallidum
- thalamus
- insula
- middle temporal gyrus
- PCC

Effort computation

- ventral striatum (NAcc)
- ACC



Affective Forecasting task

(d'Argembeau et al., 2008)

NEUROIMAGING CENTER GRONINGEN



Affective Forecasting task

(d'Argembeau et al., 2008)

NEUROIMAGING CENTER GRONINGEN



- Positive future events & routine events
- Positive > negative
 - VMPFC
 - Caudate
 - middle/superior frontal
 - PCC
- Envisioning salient future events: VMPFC, PCC
(d'Argembeau et al., 2012)

Cognitive apathy (CA)

NEUROIMAGING CENTER GRONINGEN



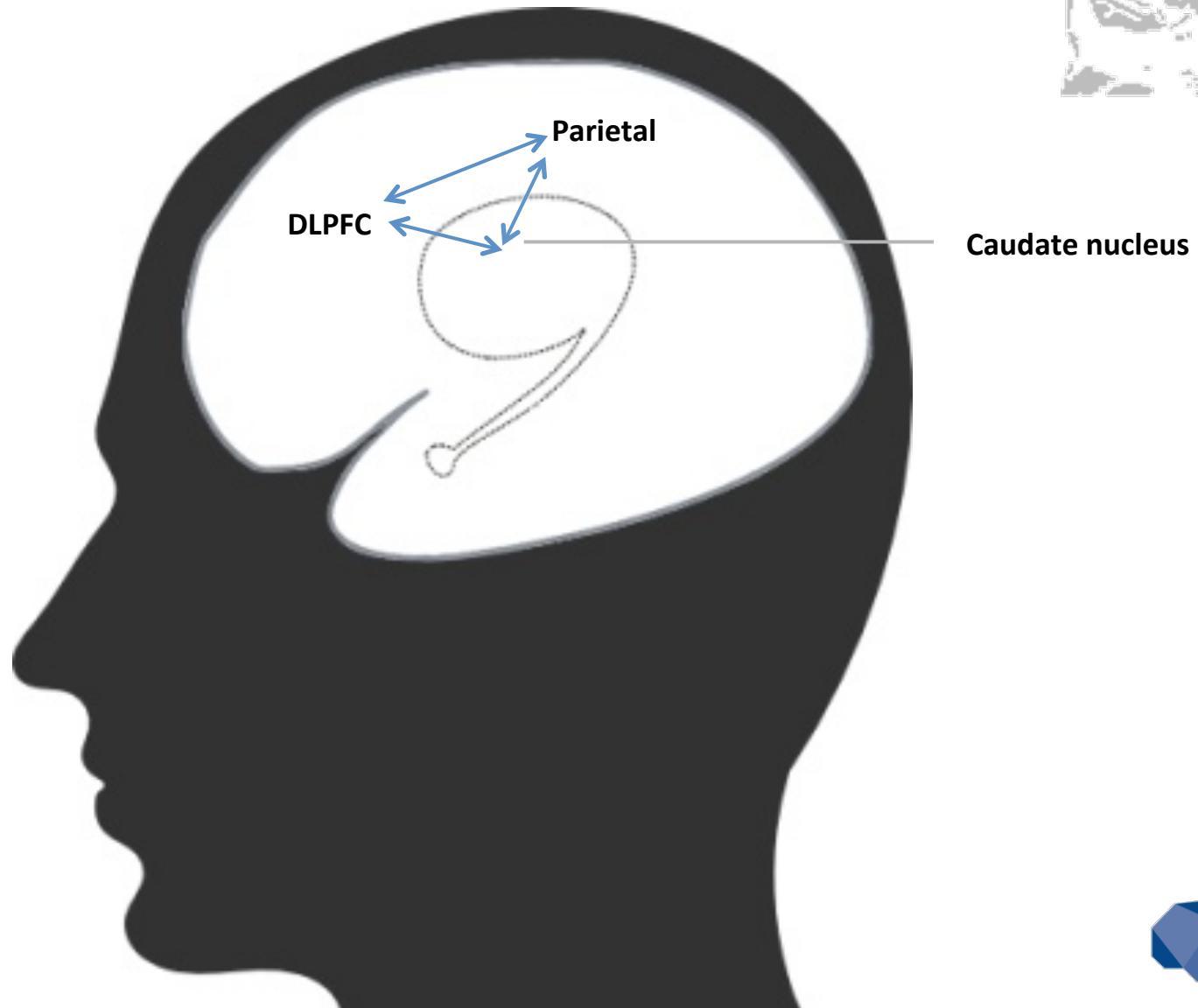
- Initiative
- Cognitive control

→ Difficulties initiating behaviour



Neural base of CA

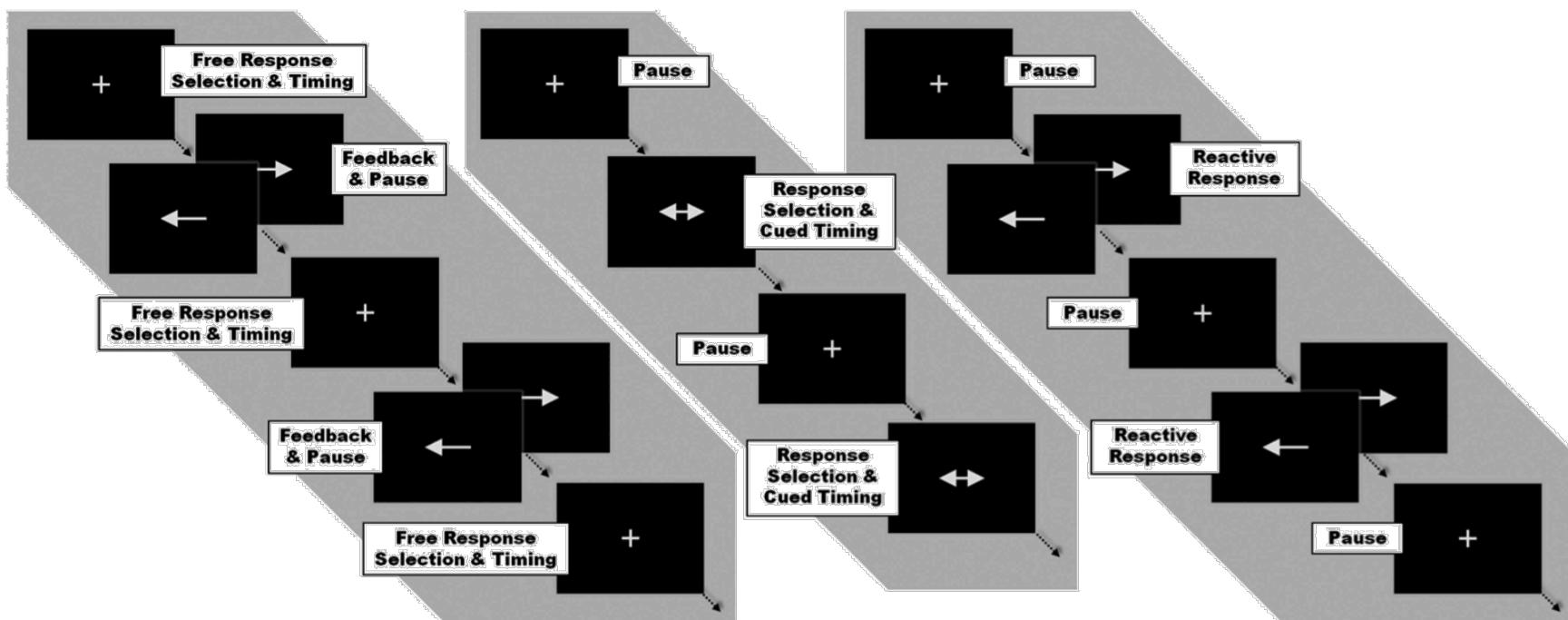
NEUROIMAGING CENTER GRONINGEN



Self Initiative task

(Hoffstaedter et al., 2012)

NEUROIMAGING CENTER GRONINGEN



umcg



apathy
study

Self Initiative task

(Hoffstaedter et al., 2012)

NEUROIMAGING CENTER GRONINGEN



- ‘What’ & ‘when’ (Haggard & Brass, 2008)
 - What
 - presupplementary motor area (SMA)
 - dorsal premotor cortex
 - When
 - superior SMA
 - Insula
 - BA 44
 - anterior putamen
 - globus pallidus
 - cerebellum

Go/No-Go task

(Wager et al., 2005)

NEUROIMAGING CENTER GRONINGEN



Go/No-Go task

(Wager et al., 2005)

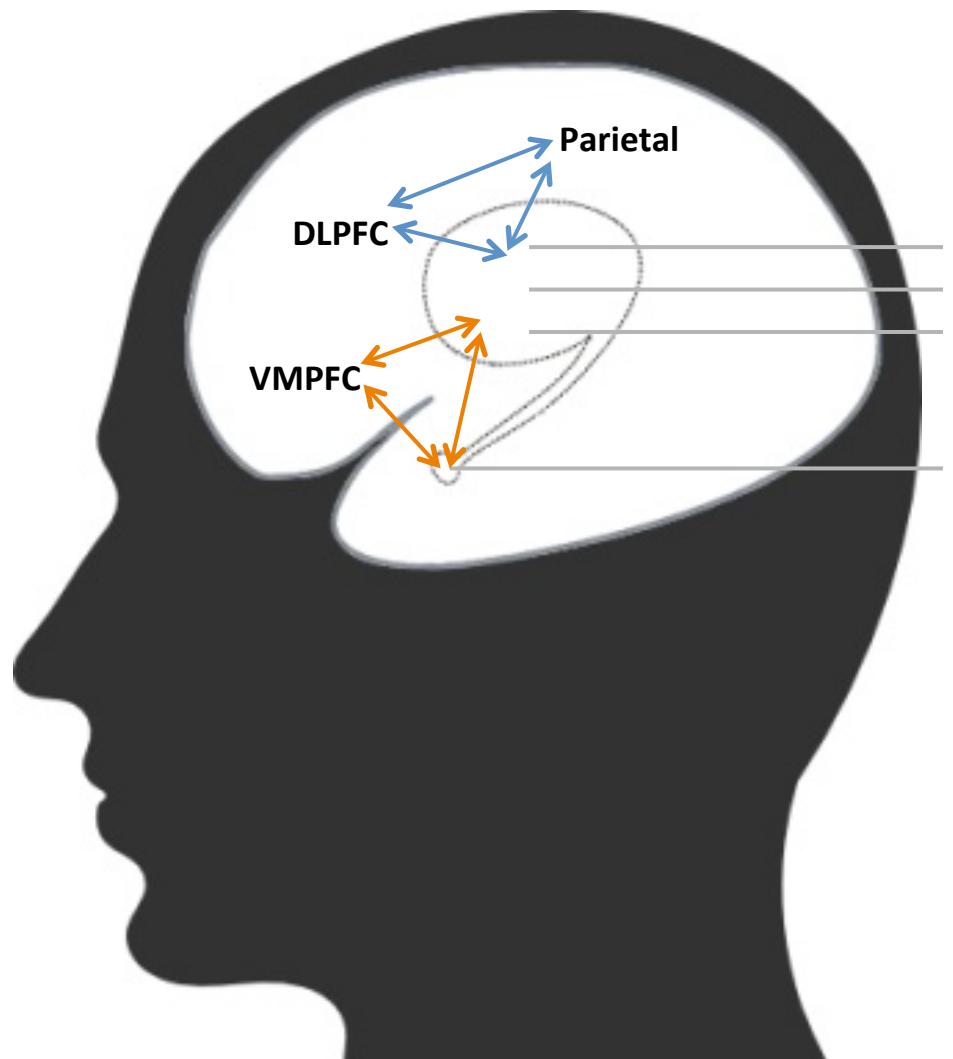
NEUROIMAGING CENTER GRONINGEN



- Response inhibition (No/Go>Go)
 - parietal (BA 7&40)
 - ant. prefrontal (BA 10)
 - DLPFC (BA 9&46)
 - Insula
 - ACC & PCC
 - putamen
 - thalamus

Hypotheses

NEUROIMAGING CENTER GRONINGEN



Caudate nucleus
Putamen
Globus pallidus

Amygdala

Hypotheses

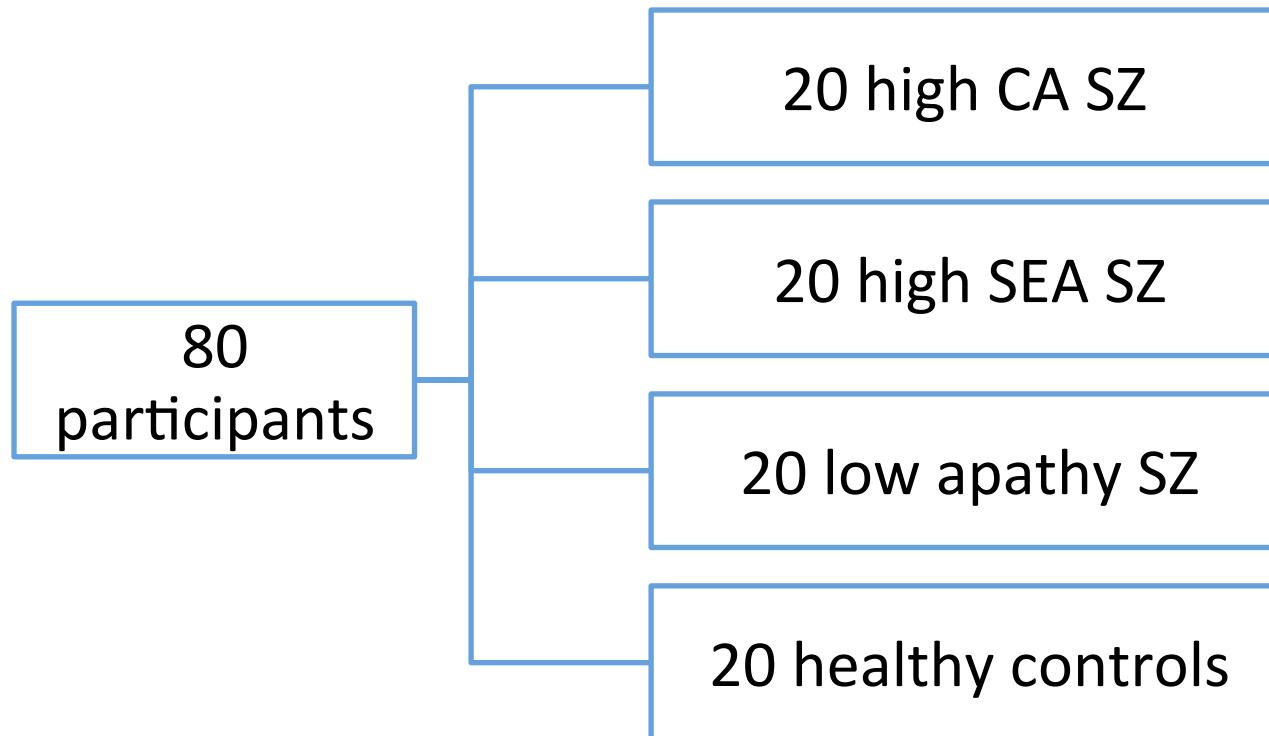
NEUROIMAGING CENTER GRONINGEN

- Altered (reduced) activation in patients
- Altered (reduced) connectivity of networks in patients



Participants

NEUROIMAGING CENTER GRONINGEN



Study design

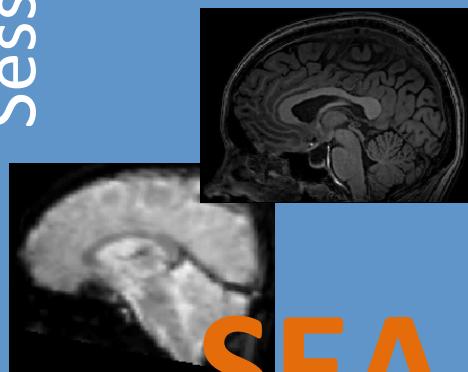
NEUROIMAGING CENTER GRONINGEN



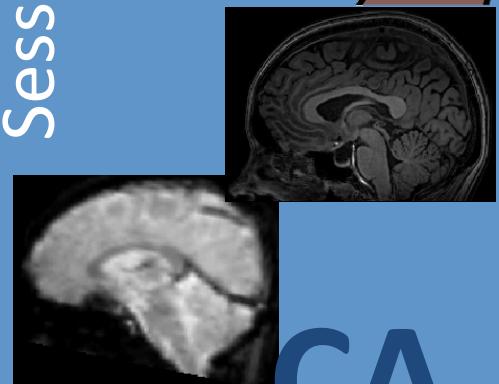
Session 1



Session 2



Session 3



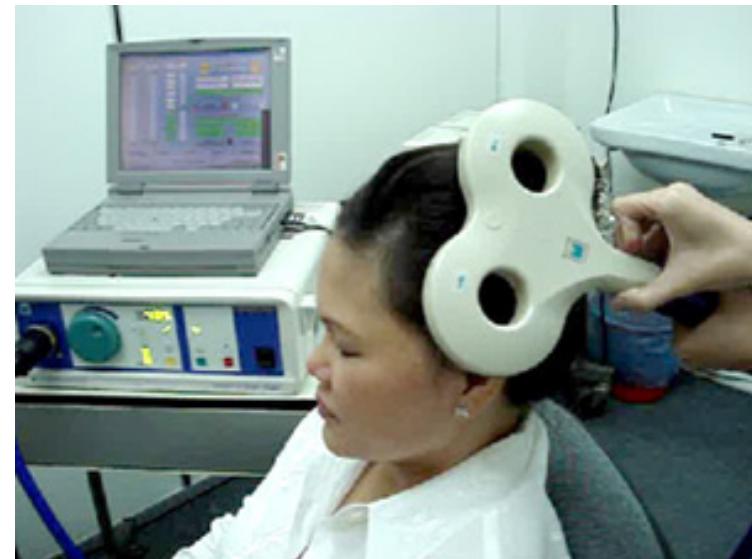
umcg



apathy
study

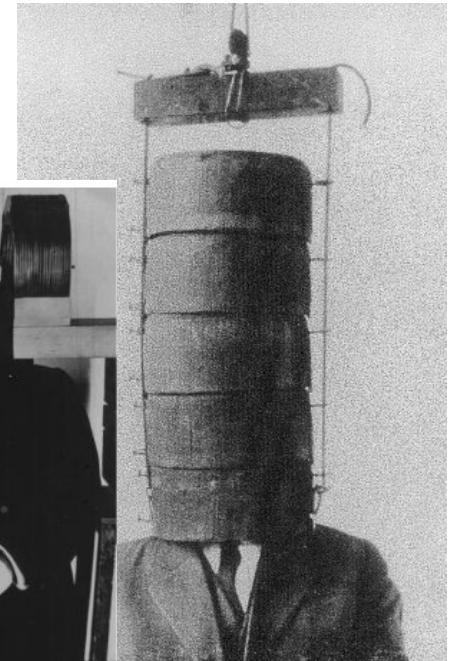
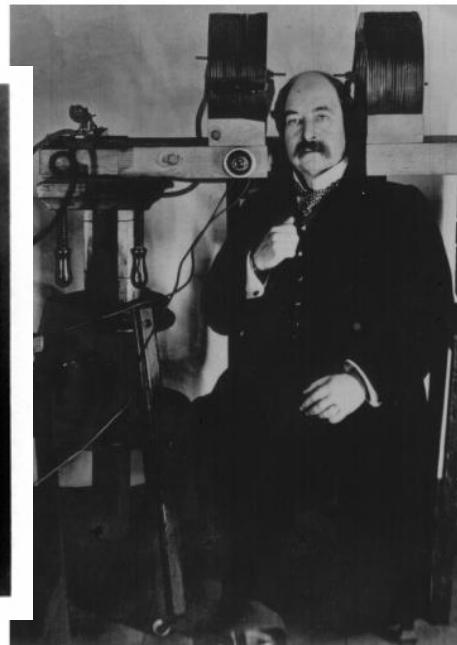
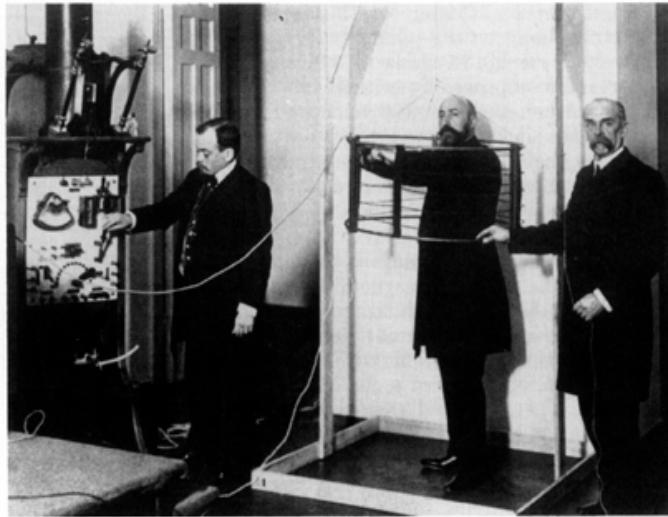


Innovative treatment: *transcranial magnetic stimulation (TMS)*



Neurostimulation avant la lettre...

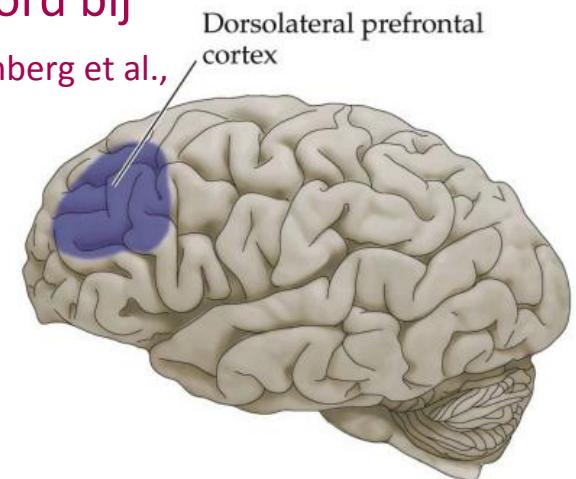
Zo dachten wetenschappers al aan het begin van de 20^{ste} eeuw. Zij experimenteerden met magnetische stimulatie van het brein (D'Arsonval; Magnussen & Stevens)



Negatieve symptomen en de hersenen



- Negatieve symptomen zijn in verband gebracht met een verminderde hersenactiviteit in de prefrontale cortex, met name de dorsolaterale prefrontale cortex (Siever and Davis, 2004; Tan et al., 2007)
- Daarnaast speelt de prefrontale cortex een belangrijke rol in de regulatie van dopaminerge neuronen in het middenhersenen. Deze regulatie is mogelijk verstoord bij mensen met schizofrenie (Laruelle et al., 2003; Meyer-Lindenberg et al., 2002)



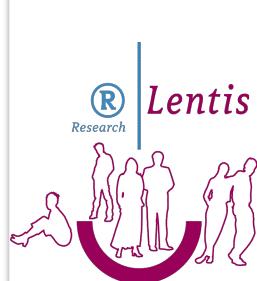
Dosering van de rTMS



- Frequentie in Hertz (pulsen per seconde)
- Duur van de behandeling
- Intensiteit van de magneetpuls
- Aantal magneetpulsjes



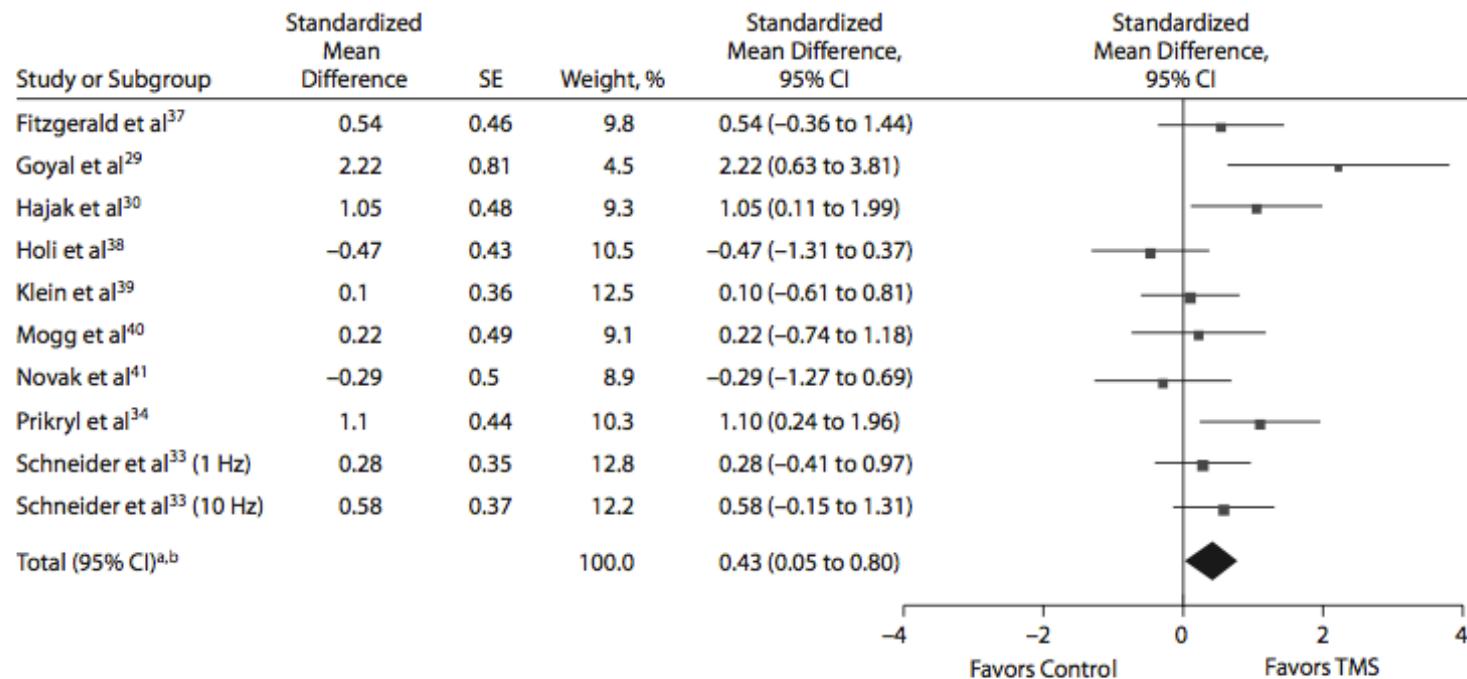
Zacht water	80ml	120ml	200ml
Gemiddeld water	120ml	160ml	240ml
Hard water	160ml	200ml	280ml



Repetitive Transcranial Magnetic Stimulation for Negative Symptoms of Schizophrenia: Review and Meta-Analysis

Jozarni J. Dlabač-de Lange, MD;
Rikus Knegtering, MD, PhD; and André Aleman, PhD

Figure 1. Meta-Analysis of Randomized Trials of Repetitive Transcranial Magnetic Stimulation for Negative Symptoms of Schizophrenia

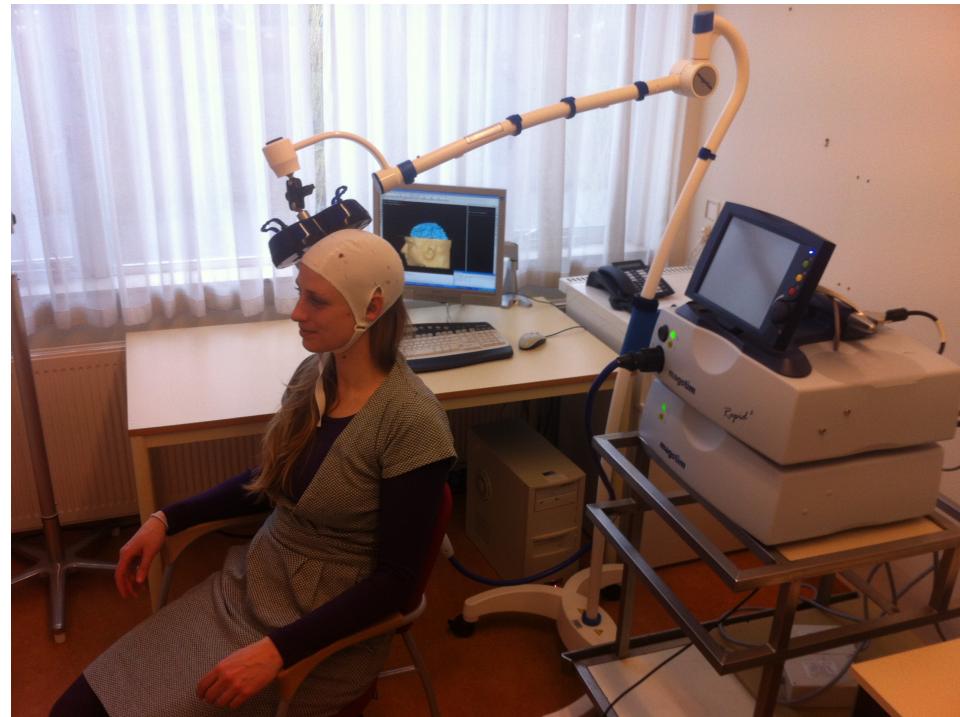


^aHeterogeneity: $\tau^2 = 0.17$; $\chi^2 = 16.69$, $P = .05$; $I^2 = 46\%$.

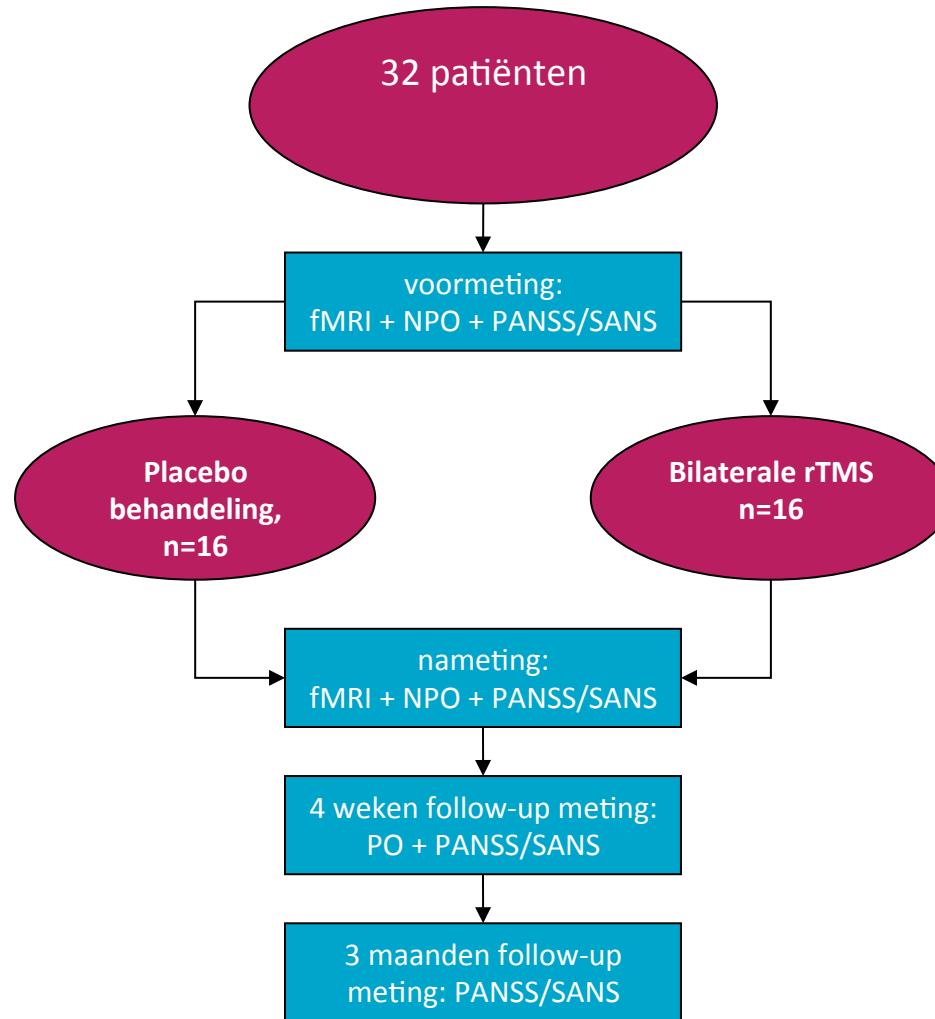
^bTest for overall effect: $Z = 2.23$, $P = .03$.

TRENSS: een RCT in Groningen

- 10 Hz
- 3 weken
- Bilaterale dorsolaterale prefrontale cortex (DLPFC)
- Tweemaal per dag
- Dubbelblind
- Placebo gecontroleerd



Het studiedesign



Het verloop



- Deelnemers geworven in Noord Nederland (UMCG, Lentis, GGz Drenthe en GGz Friesland)
- Behandelloccatie: UMCG en Lentis
- Er zijn 34 deelnemers geïncludeerd, waarvan 32 mensen het hele protocol hebben doorlopen
- Eerste deelnemer is in februari 2009 geïncludeerd, deelnemer 32 in februari 2013



Resultaten: Dlabac-de Lange et al. *Psychol Med* 2014

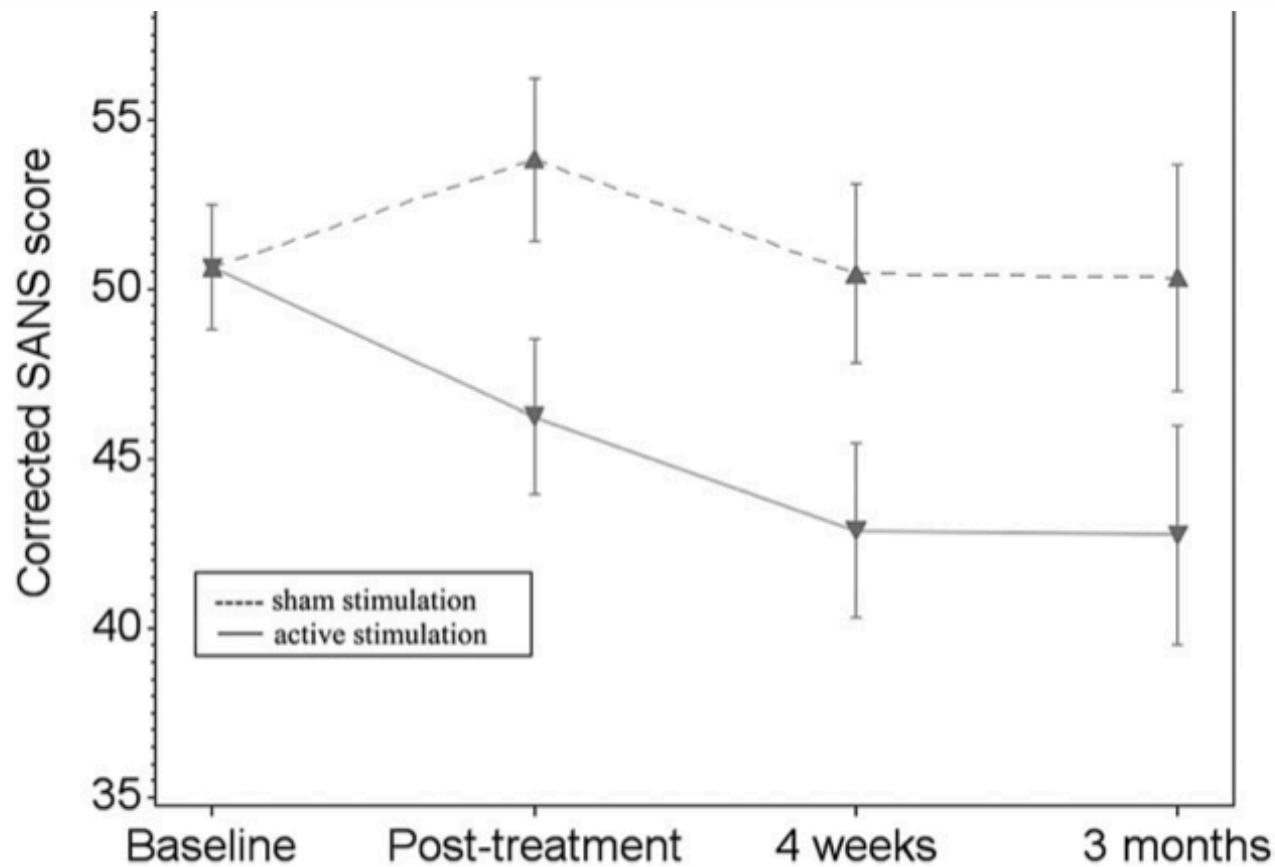


Fig. 1. Total Scale for the Assessment of Negative Symptoms (SANS) scores at baseline, post-treatment, 4 weeks and 3

Adverse events en bijwerkingen

Er hebben zich geen ernstige gebeurtenissen voorgedaan

Regelmatig genoemde bijwerkingen:

- Spiertrekkingen in het gezicht
- Lichte hoofdpijn



Treatment of social-emotional apathy?

- Behavioral activation therapy (BAT)
 - 40 patients in active group (2 months)
 - 40 patients in control group (cogn training and “small talk”)
- Effective in depression, activates reward systems of the brain (Dichter et al. 2008 *Biol Psychiat.*)

Objectives of current neuroimaging project in MCI:

- **Elucidate neural correlates of apathy in aMCI**
- **Discover structural and functional changes due to apathy & aMCI**
- Measures:
 - fMRI (oxygen use in the brain)
 - DWI (diffusion of water in brain tissue to assess white matter connectivity/integrity)
 - H MRS (spectroscopy technique using MR signal to detect abnormal levels of important molecules such as N-Acetyl Aspartate (NAA), Creatine and Phosphocreatine (Cr), myo-Inositol (ml), Glycerophosphocholine and phosphocholine (Cho), Glutamine and glutamate (Glu))
 - Cognitive and behavioural assessment using a battery of neuropsychological tests

Collaboration of Dept Neurol UMCG, Alzheimer Res (prof. De Deyn; F. Reesink, prof. Kremer) with Neuroimaging Center Groningen (Prof. Aleman, S. Tumati, Dr S. Martens)

Thank you for your attention!

Acknowledgments:

Edith Liemburg

Rikus Knegtering

Claire Kos

Nicky Klaassen

Leonie Bais

Leonie van Asperen

Esther Opmeer

Marie-José van Tol

Branislava Curcic-Blake

Jozarni Dlabac-de Lange

Richard Bruggeman

Lex Wunderink

Johan Arends

Annerieke de Vos

Marieke Pijnenborg





Questions?

