

# The role of anterior cingulated cortex (ACC) in Anosognosia: a transcranial magnetic stimulation (TMS) study .

Gallart-Palau X<sup>1,2,3</sup>, Muñoz Marrón E<sup>2,3,4</sup>. (2011) – IN3 Research Institute at UOC

1. UOC (Open University of Catalonia), Bachelor of Arts in Psychology, final degree project.
2. Cognitive Neuroscience and Information Technology Research Group, (CNIT).
3. Internet Interdisciplinary Research Institute (IN3) · Cognitive Neurolab
4. UOC (Open University of Catalonia), Biopsychology Dep. Practicum Supervisor, (CNIT) co-director.

## **1. Introduction**

### **1.1 Anosognosia in neurological and psychiatric disorders**

It's in Alzheimer disease (AD), other degenerative conditions and schizophrenia where anosognosia is more severe and devastating as a symptom (Amanzio & Torta, 2009). Anyway anosognosia encloses a wide range of cognitive processes impaired before its apparition: language, perception, memory, control of action and executive functioning. In addition, anosognosia can be present in other neuropsychological disorders like hemiplegia or aphasia. Different terms like "reduced awareness" or "lack of insight" have been used along time instead of anosognosia (Lopez et al., 1994). It happens sometimes to complement this as a concept and sometimes to substitute its theoretical implications. Anyway, we consider that anosognosia nowadays, despite its past like a concept [when was considered for some experts a defensive mechanism that protected patients from disease (Weinstein & Kahl, 1955)] includes all metacognitive implications of a person who is not aware about his own conductual impairments, or at least shows a lack of introspective capacities to evaluate his own behavior.

In patients with AD, especially when they are in the early stages of disease, anosognosia appears mainly on new, unexpected and difficult cognitive tasks (Sebastian et al., 2006). For this reason, many experts have highlighted its capacity to predict this pathology, and its relationship with executive system and with dysexecutive syndrome (Baddeley, 1986). On the other hand, this relationship have opened a new and wide way to explore cognitive implications of anosognosia using neuroimaging approaches like functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) in patients and healthy controls subjects. The most used paradigm in neuroimaging studies are tasks requiring inhibition of responses, where diverse adaptations of Stroop test have had maximum leadership (Kashiwa et al., 2005). Several studies have concluded that in schizophrenia at least 50% of patients present anosognosia (e.g. Amador et al., 1994; Lele et al., 1998; Niznikiewicz et al., 2003). All this works support nowadays general conception of anosognosia, which have been stepping out its psychoanalytic implications whom have declared this symptom as "lack of insight", currently authors consider the weight of neurological implications in this critical symptom. In schizophrenia there is a remarkable study conducted by Young and colleagues in 1998, in which they have demonstrated strong correlations between frontal hypoactivity and anosognosia using tests like WCST (Wisconsin Cards Sorting Test).

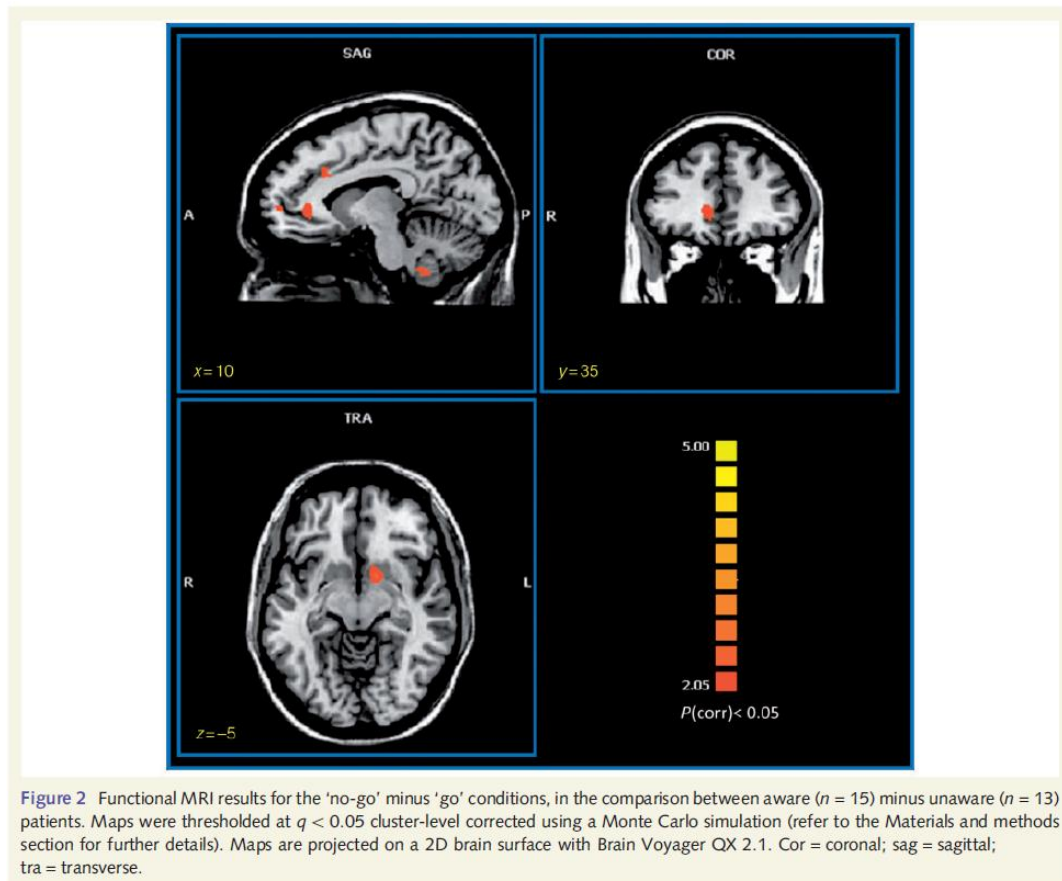
### **1.2 Clinic and economic implications of anosognosia**

Despite other typical symptoms of neurological and psychiatric disorders mentioned above, anosognosia has been kept for long time as a controversial concept, since it is an

unclear aspect of brain functioning. Meanwhile lots of patients remain misfits for their families and society, and unconscious about their poor cognitive abilities (Lorenzo & Tamietto, 2006). Many scientists, like physicians and psychologists argued that control of anosognosia by patients is crucial to start its own adaptative recovery in schizophrenia and a prospective sign to slower demential progress in AD on its early stages (e.g. Krabbendam et al., 1999). For this reason, control of anosognosia becomes a crucial objective in many patients during first months of neuropsychological treatment. On the other hand, foundations like World Health Organization (WHO) or Alzheimer's Disease International (ADI) have described an economic impact of AD and other dementias, which ascends nowadays to 604 billions of dollars over the world (Alzheimer's Disease International Symposia, 2011). This amount is growing in conjunction with life expectancy in developed countries. We should highlight that make slower the dementia course is an essential pending subject because as fast as dementia degenerates the patients freedom and quality of life decay, while caregivers attentions grow up.

### **1.3 Neuroanatomical data of anosognosia**

Several researches have reported a crucial role of anterior cingulate cortex (ACC) in anosognosia (e.g. Devinsky et al., 1995). Despite the association between ACC and anosognosia is not clear yet due to the limitation of neuroimaging techniques to explore causal relations, this cortical region seems to monitoring in real time behavior on affective and executive functions in normal subjects. Amanzio and co-workers (2011) have conducted an experiment to explore the role of ACC in Alzheimer's disease patients and healthy controls using a specific executive task consistent in a classical *inhibition response* used in several studies and classified as an ACC sensitive task (e.g. Amanzio et al. 2011; Braver et al. 2011). Amanzio and co-workers (2011) composed two groups of patients; based on their previous neuropsychological explorations: *Aware* and *Unaware* groups. Each trial presented to such group of subjects was composed of 83% proportion randomized of "go answer" stimuli while other 17% were "non go answer" stimuli. In figure 1 we reproduce their remarkable fMRI results.



**Figure 1.** Extracted from Amanzio-, Torta , Sacco , et al. (2011).

As we can see on different fMRI slices; prefrontal cortex, ACC, temporal gyrus, putamen, and some areas of cerebellum were hypoactivate during task in unaware patients while *inhibition task* performance was statistically significant worst on *unaware* group. These results were interpreted by authors as a lack of cognitive flexibility showed by unaware AD patients, which makes impossible to follow a task which requires cognitive flexibility, Furthermore; this trait seems absolutely related with unawareness in AD (Amanzio et al. 2011).

On the other hand some experiments have been conducted using neuroimaging techniques to determine if ACC is implicated in Stroop task. However Hayward, Goodwin and Harmer, in 2004, have demonstrated using transcranial magnetic stimulation (TMS) that when ACC is disrupted; the Stroop effect disappears while reaction time of subjects tends to time showed in non Stroop trials. This results are incongruent with theories that defend facilitation effect of ACC on the Stroop task (Bush et al., 1998) while highlights a "possible" metacognitive processing role of this cortical area.

#### **1.4 TMS. Aim of our research and new therapeutic approaches for anosognosia**

Transcranial Magnetic Stimulation (TMS) is a safe and non-invasive brain stimulation technique which can be used to disrupt neural activity within a relatively localized cortical area (Walsh & Rushworth, 1999; Hallett, 2000; Jahanshahi& Rothwell, 2000) that allows neuroscientists to research with virtual impaired patients (Hallett M., 2000). Although use of TMS to disrupt or stimulate deep brain areas, as ACC, have been

controversial, nowadays there are remarkable experiments with successful results combining neuroimaging with TMS to explain its action over ACC (Hayward et al., 2007).

To our knowledge this is the first study that tries to establish causal relationship between ACC and anosognosia based on a conductual task while measuring subjective perception of behavior. No other experiments are conducted so far to that aim using TMS.

Thus, new approaches studying different roles of ACC on anosognosia with combination of neuroimaging techniques and TMS in patients and healthy controls could be conducted after our research. Furthermore, our results could have clinical implications, for example, they could draw a new horizon for TMS and other magnetic or portable electrical stimulation techniques to stimulate ACC on clinical patients with anosognosia and improve their quality of life.

## **2. Material and methods**

### **2.1 Participants**

Twenty-four right-handed healthy volunteers screened based on Handedness Inventory (Olfield, 1971) -between 18 and 30 years old (undergraduate students most of them) will be included in the study in three different groups (one experimental and two control groups). Control groups and experimental group assignation will be conducted randomly for all accepted subjects, and they will sign a consent form previous to test. All experimental subjects will pass a previous screening for psychiatric disorders using the Spanish adaptation by Santamaria (2010) of Minnesota Multiphase Personality Inventory *MMPI 2-RF* and another screening for neurologic disorders using Behavioural Assessment of the Dysexecutive Syndrome *BADS* (Norris & Tate, 2000). If some subjects, considering that majority of them are undergraduates find hard test by language or its cultural implications noting that it has no Spanish adaptation we will use *Anillas Test* in its Spanish edition (Portellano & Martínez-Arias, *in press*). Furthermore subjects will be assessed about their judging magnitudes capacity using *ad hoc* task consisting in estimation of “celebrities ages” or weight of “quotidian objects” to control their subjective estimation capacity, subjects with bias of more than 30% to the right magnitude will be excluded of our experiment.

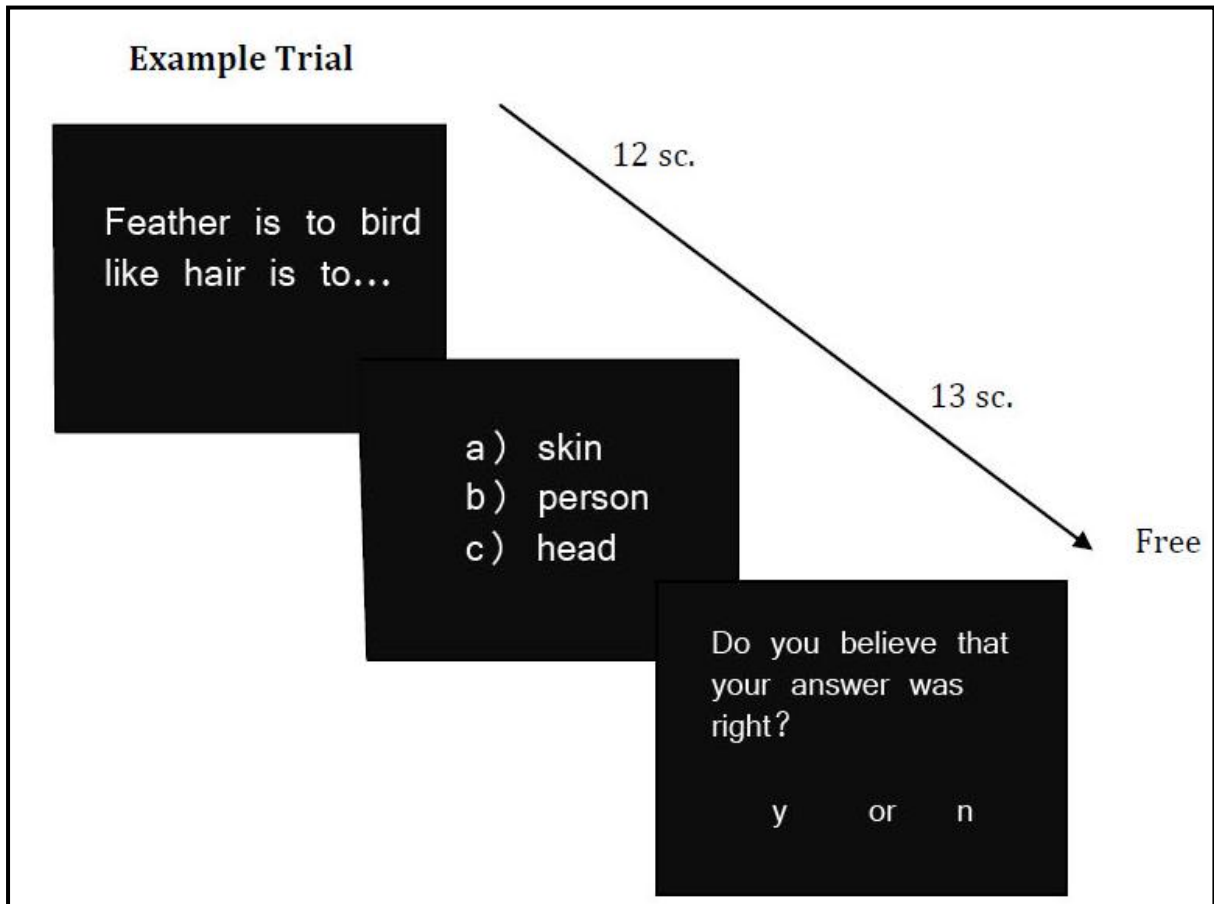
Only non pathologic profiles will be accepted in our study, giving special interest to psychotic and executive functioning results. All subjects will receive further explanations and will practice some practical trials to familiarize with experimental setting. Subjects unable to follow the experiment before or during test period will be excluded of our analysis and results.

### **2.2 Design and procedures**

#### **2.2.1 Cognitive task**

Cognitive task will consist in 20 + 20 different trials with syllogisms extracted from 16 Personality Factors (Aluja & Blanch 2002) and Wechsler Adult Intelligence Scale (Spanish adaptation by TEA of 1996) answer and subjective judging slices will compose each trial. Stimulus will be showed trough E-Prime (Psychology Software Tools, Inc.) on a Dell computer monitor model CRT 15 inch. Syllogisms will be presented for a controlled exposure time of 12 seconds. After the syllogism slice screen will refresh and will appear a new slice containing multiple choice answer for a controlled exposure time of 13 seconds. After the answer slice, screen will refresh and will appear a new slice asking subject if he believes his/her answer was correct or incorrect for free exposure time.

All answers given by subjects on second and third slice each trial will be recorded to be analyzed. Figure 2 shows an example of one trial used on our cognitive task.



**Figure 2.** Based on a previous work (Norton, Gallart-Palau, Chen, & Cronin-Golomb. 2011).

### **2.2.2 TMS protocol**

We will use in our research a TMS inductor Magstim Rapid 2 attached to a double-cone coil rather than figure-of-eight coil despite that the more common used in general research is figure-of-eight coil. Double-cone coil is the most used to research in experiments aimed to stimulation/inhibition of deep brain areas (Machii et al., 1999); (Hayward G. et al., 2007).

The experimental and control groups will be composed by 8 subjects each.

TMS stimulation to experimental group, will be applied over medial parietal cortex adapted to each subject using *Brainsight Neuronavigator* (Rogue Research, Inc.). An offline TMS paradigm will be applied, in which TMS stimulation will start after the first part of the task (20 trials). After 10 minutes of TMS the subjects will completed the second part of the task (20 trials).

Following Hayward and co-workers (2007) we will use short trains of 4 pulses each with an intensity of 100% of motor threshold and a frequency of 1Hz. The maximum number of trains delivered will be 20 per minute.

TMS stimulation to control group, will be applied over the brain vertex in the same conditions and protocol as in experimental group. Subjects of the second control group, will not be stimulated with TMS and just will perform the same cognitive task (40 trials in 2 blocks of 20).

### **3. Hypothesis and statistical analysis\***

We hypothesize that experimental group will show after TMS stimulation a statistically significant positive or “y” answers in comparison to the control groups.

We will pay special attention to analyze data on number of “y” or “n” answers on subjective judgment of syllogisms, and furthermore our analysis will be remarkable focused over all data collected about right/erroneous answers on syllogisms task depending on normal status or TMS inhibition.

We will try to conduct different parametric tests (ANOVA) between groups and levels of independent variables. Otherwise, if data induces to non parametric tests we will conduct that analysis over data results.

*\* Authors declare no conflict of interests with other research groups or institutions.*

### **Acknowledgments**

Mr. Gallart would give specially thanks to PhD and Neuropsychology professor Elena Muñoz Marrón for her affect and her master support along all this project creation. Also, thanks for his acceptance and support to PhD. and Psychobiology professor Diego Redolar Ripoll as a co-director of CNIT group at IN3.

Thanks to Daniel J. Norton, graduate researcher in Vision & Cognition Laboratory at Boston University (BU) for his outstanding scientific stare-point and his friendship.

Thanks to Alice Cronin Golomb, PhD. Director of Vision and Cognition Laboratory and Neuroscience professor at BU. Without her support and confidence probably my life never had been aspired to achieve the expectations that I’ve available at this moment.

Thanks to my loved Aida Serra Maqueda for her awesome imprint in almost everything that I am and what I do.

### **References**

- Aluja A. & Blanch A. (2002). Análisis descriptivo y comparativo del 16-PF 5 en muestras americana y española. *Boletín de Psicología*, 74, 27-38.
- Amador XF, Flaum M, Andreasen NC, Strauss DH, Yale SA, Clark SC & Gorman JM. (1994). Awareness of illness in schizophrenia and schizoaffective and mood disorders. *Arch. Gen. Psychiatry*, 51, 826–836.
- Amanzio M. & Torta DM. (2009) Unawareness of deficits in Alzheimer’s disease through a bio-psycho-social perspective. In: *Metacognition: New Research development. Columbus F.* Ed. Nova Science Publishers, Hauppauge, New York: pp 240-253
- Amanzio M., Torta D., Sacco K., Cauda F., D’Agata F., Duca S., Leotta D., Palermo S. & Geminiani G. (2011). Unawareness of deficits in Alzheimer’s disease: role of the cingulate cortex. *Brain*, 134, 1061-1076.
- Baddeley AD. (1986). *Working memory*. Oxford: Clarendon Press.
- Bush, G., Whalen, P.J., Rosen, B.R., Jenike, M.A., McInerney, S.C. & Rauch, S.L. (1998) The counting Stroop: an interference task specialized for functional neuroimaging – validation study with functional MRI. *Hum. Brain Mapp.*, 6, 270–282.

- Devinsky O., Morrell M.J. & Vogt B.A. (1995). Contributions of anterior cingulate cortex to behavior. *Brain*, 118, 279–306.
- Hallett M. (2000). Transcranial magnetic stimulation and the human brain. *Nature*, 406,(6792), 147-50
- Hayward, G., Goodwin, G.M. & Harmer, C.J. (2004). The role of the anterior cingulate cortex in the counting Stroop task. *Exp. Brain Res.*, 154, 355–358.
- Hayward G., Mehta M. A., Harmer C. Spinks T.J., Grasby P.M. & Goodwin G.M. (2007). Exploring the physiological effects of double-cone coil TMS over the medial frontal cortex on the anterior cingulate cortex: an H<sub>2</sub> <sup>15</sup>O PET study. *Europ. Journal of Neuroscience*, 25, 2224-33
- Jahanshahi M & Rothwell J. (2000). Transcranial magnetic stimulation studies of cognition: an emerging field. *Exp. Brain. Res.*, 131, (1), 1-9
- Kashiwa Y, Kitabayashi Y, Narumoto J, Nakamura K, Ueda H. & Fukui K. (2005). Anosognosia in Alzheimer's disease: association with patient characteristics, psychiatric symptoms and cognitive deficits. *Psychiatry Clin Neurosci*, 59, 697–704.
- Krabbendam L., de Vugt M.E., Derix M.M. & Jolles J. (1999). The behavioral assessment of the dysexecutive syndrome as a tool to assess executive functions in schizophrenia. *Clin Neuropsychol*, 13, 370–5.
- Lele M.V. & Joglekar A.S. (1998). Poor insight in schizophrenia: neurocognitive basis. *J. Postgrad. Med.*, 44, 50–55.
- Lopez OL, Becker JT, Somsak D, Dew MA & DeKosky ST. (1994). Awareness of cognitive deficits and anosognosia in probable Alzheimer's disease. *Europe Neurology*, 34, 277–82.
- Lorenzo P. & Tamietto M. (2006). Unawareness in schizophrenia: Neuropsychological and neuroanatomical findings. *Psychiatry and Clinical Neurosciences*, 60, 531-537.
- Machii K., Ugawa Y., Terao Y., Hanajima R., Furubayashi T., Mochizuki H., Shiio Y., Enomoto H., Uesugi H., Kuzuhara S. & Kanazawa, I. (1999) Input–output organization of the foot motor area in humans. *Clin. Neurophysiol.*, 110, 1315–20
- Niznikiewicz M.A., Kubicki M. & Shenton M.E. (2003). Recent structural and functional imaging findings in schizophrenia. *Curr. Opin Psychiatry*, 16, 123–147.
- Norris G. & Tate R.L. (2000). The behavioural assessment of the dysexecutive syndrome (BADS): Ecological, concurrent and construct validity. *Neuropsychological Rehabilitation*, 10 (1), 33-45.
- Norton D., Gallart-Palau X., Chen Y. & Cronin-Golomb A. (2011). Opposite central and peripheral perceptual biases of short and long lines: compensation by attention?. *Perception*. In Press.
- Oldfield, R.C. (1971). The assessment and analysis of handedness: the Edinburgh 670 inventory. *Neuropsychologia* 9, 97–113.
- Portellano J.A., Martínez-Arias R. (2011). *Test de las Anillas*. TEA Ediciones. In Press.
- Santamaria Fernández P. (2009). *Minnesota Multiphasic Personality Inventory*. Madrid:TEA Ediciones
- Sebastian MV, Menor J & Elosua MR. (2006). Attentional dysfunction of the central executive in AD: evidence from dual task and perseveration errors. *Cortex*, 42, 1015–20.

- Walsh V. & Rushworth M. (1999). A primer of magnetic stimulation as a tool for neuropsychology. *Neuropsychologia*, 37,(2), 125-35
- Weinstein E.A. & Kahn R.L. (1955). *Denial of Illness: symbolic and Physiological Aspects*. Charles C. Thomas: Springfield.
- Young D.A., Zakzanis K.K., Bailey C., Davila R., Griese J., Sartory G. & Thom A. (1998). Further parameters of insight and neuropsychological deficit in schizophrenia and other chronic mental disease. *J. Nerv. Ment. Dis.*, 186, 44-50