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AGAUR

Memòria justificativa de recerca de les convocatòries BCC, BE, BP, CTP-AIRE, INEFC i PIV

La memòria justificativa consta de les dues parts que venen a continuació:
1.- Dades bàsiques i resums
2.- Memòria del treball (informe científic)

Tots els camps són obligatoris

1.- Dades bàsiques i resums

Nom de la convocatòria

BP

Llegenda per a les convocatòries:

BCC	Convocatòria de beques per a joves membres de comunitats catalanes a l'exterior
BE	Beques per a estades per a la recerca fora de Catalunya
BP	Convocatòria d'ajuts postdoctorals dins del programa Beatriu de Pinós
CTP-AIRE	Ajuts per accions de cooperació en el marc de la comunitat de treball dels Pirineus. Ajuts de mobilitat de personal investigador.
INEFC	Beques predoctorals i de col·laboració, dins de l'àmbit de l'educació física i l'esport i les ciències aplicades a l'esport
PIV	Beques de recerca per a professors i investigadors visitants a Catalunya

Títol del projecte: ha de sintetitzar la temàtica científica del vostre document.
Noninvasive functional and structural exploration of human subcortical structures with high resolution (7T) MRI and DTI

Dades de l'investigador o beneficiari

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Paraules clau: cal que esmenteu cinc conceptes que defineixin el contingut de la vostra memòria.
Ganglis Basals, Control Cognitiu, 7T-MRI, Ambigüitat, Error

Data de presentació de la justificació

13 de Setembre de 2012

Generalitat de Catalunya
Departament d'Economia
i Coneixement

Nom i cognoms i signatura
del/de la investigador/a

Vist i plau del/de la responsable de la
sol·licitud

Resum del projecte: cal adjuntar dos resums del document, l'un en anglès i l'altre en la llengua del document, on s'esmenti la durada de l'acció

Resum en la llengua del projecte (màxim 300 paraules)

El principal objectiu d'aquest projecte era estudiar en detall les estructures subcorticals, en concret, el rol dels ganglis basals en control cognitiu durant processament lingüístic i no-lingüístic. Per tal d'assolir una diferenciació minuciosa en els diferents nuclis dels ganglis basals s'utilitzà ressonància magnètica d'ultra-alt camp i alta resolució (7T-MRI). El còrtex prefrontal lateral i els ganglis basals treballant conjuntament per a mitjançar memòria de treball i la regulació "top-down" de la cognició. Aquest circuit regula l'equilibri entre respostes automàtiques i d'alt-ordre cognitiu. Es crearen tres condicions experimentals principals: frases/seqüències no-ambigües, no-gramatical i ambigües. Les frases/seqüències no-ambigües haurien de provocar una resposta automàtica, mentre les frases/seqüències ambigües i no-gramaticals produïren un conflicte amb la resposta automàtica, i per tant, requeririen una resposta de d'alt-ordre cognitiu. Dins del domini de la resposta de control, la ambigüitat i no-gramaticalitat representen dues dimensions diferents de la resolució de conflicte, mentre per una frase/seqüència temporalment ambigua existeix una interpretació correcte, aquest no és el cas per a les frases/seqüències no-gramaticals. A més, el disseny experimental incloïa una manipulació lingüística i no-lingüística, la qual posà a prova la hipòtesi que els efectes són de domini-general; així com una manipulació semàntica i sintàctica que avaluà les diferències entre el processament d'ambigüitat/error "intrínseca" vs. "estructural". Els resultats del primer experiment (sintax-lingüístic) mostraren un gradient rostroventral-caudodorsal de control cognitiu dins del nucli caudat, això és, les regions més rostrals sostenint els nivells més alts de processament cognitiu. El treball realitzat es dugué a terme entre el 1 de juliol de 2010 i el 30 de juny de 2012.

Resum en anglès (màxim 300 paraules)

The main goal of the project was to study in detail subcortical structures, namely, the role of the basal ganglia in cognitive control during linguistic and non-linguistic processing. In order to achieve a fine-grained functional differentiation in the different basal ganglia nuclei, ultra-high-field high resolution magnetic resonance imaging (7T-MRI) was used. The lateral prefrontal cortex and basal ganglia work together to mediate working memory and top-down regulation of cognition. This circuit regulates the balance between automatic and higher-order control responses. Three main conditions were tested: unambiguous, ungrammatical, and ambiguous sentences/sequences. Unambiguous sentences/sequences should elicit an automatic response, while ambiguous and ungrammatical sentences/sequences should conflict with an automatic response, and, hence, require a higher-order control response. Within the control response domain, ambiguity and ungrammaticality represent two different dimensions of conflict resolution, while for a temporarily ambiguous sentence/sequence a correct interpretation is available, that is not the case for ungrammatical sentences/sequences. The design included a linguistic and non-linguistic manipulation, which put to a test the hypothesis that the effects are domain-general; as well as a semantic and syntactic manipulation testing for differences in "intrinsic" vs. "structural" ambiguity/error processing. The results from the first experiment (syntactic-linguistic) showed a rostro-ventral-caudo-dorsal gradient of cognitive control within the head of the caudate nucleus, that is, the more rostral regions supporting higher levels of cognitive processing. This project was conducted from the 1st of July 2010 to the 30th of June 2012.

Resum en anglès (màxim 300 paraules) – continuació -.

2.- Memòria del treball (informe científic sense limitació de paraules). Pot incloure altres fitxers de qualsevol mena, no més grans de 10 MB cadascun d'ells.

The basal ganglia and thalamus interact with cortical regions through many parallel loops, which subserve and complement the functions of specific cortical regions they project to (Middleton and Stick, 2000), in order to create, to orchestrate, and to execute goal-directed behavior along with the motivation and cognition that drives them (Haber, 2003). Even though the role of the basal ganglia in human learning and cognition is well established (Seger, 2006, 2008) the basal ganglia have been relegated strictly to motor functions. However, in the last years this view has dramatically changed, establishing that basal ganglia and thalamus, through their interaction with the cortex are involved in a wide range of functions and have a major influence on sensorimotor, limbic, and cognitive information processing (Middleton and Stick, 2000, 2002). In short, the striatum receives inputs from different cortical areas and, throughout the thalamus, project principally to frontal lobe areas (prefrontal, premotor, and supplementary motor areas) (for review, see Haber, 2003; Utter and Basso, 2008). Ventral regions of the basal ganglia play a key role in reward and reinforcement (Schultz, 1997; Pessiglione et al., 2006). Cognitive functions such as procedural learning and working memory are assigned to the more central basal ganglia parts (Levy, et al., 1997; Jog et al., 1999). Finally, the dorso-lateral portion of the striatum is involved in motor control (Alexander et al., 1986).

The basal ganglia receive inputs from virtually the entire cerebral cortex. The anatomy of the basal ganglia and its well-position in the circuitry give these structures a crucial role in influencing many neural pathways and information processing systems. Due to this role, basal ganglia functions have remained elusive for a long time, and furthermore, it is likely that the many, varied and complex symptoms of basal ganglia dysfunction are due to the varied cortical inputs and basal ganglia influence on other neural regions. In general it has been suggested that the cortex employs the basal ganglia for additional processing of reward and cognition to modulate, gate, and control the information flow leading to the selection of an appropriate item, strategy or behavior, learning and decision making that leads to the development of goal-directed behavior and habit formation (Houk and Wise, 1995; Frank et al., 2001; Bar-Gad et al., 2003; Haber et al., 2006). The thalamus, on the other hand, regulates the allocation of resources and controls the information relayed to the cortex (Haber and Calzavara, 2009).

However, the basal ganglia and thalamus are structures difficult to image mainly because of their small size and decreased signal-to-noise ratio (SNR) in the BOLD contrast as compared to cortical regions. From a histological point of view, these structures are rich in iron, which causes T1-weighted magnetic resonance images to be insufficient for the segmentation of subcortical grey matter structures (see Helms et al., 2009 for a new method to improve segmentation). From a functional perspective, most investigations that have focused on cortical regions, using conventional field strengths, tend to neglect subcortical activation even when present in their results. This common pattern has jeopardized our understanding of basal ganglia and thalamic function. Some of the reasons may be a rather global understanding of subcortical functions, the difficulty in locating the exact activation due to low SNR and partial-volume effects, which hinder the dissociation between different subcortical structures and nuclei (with-in and between structures and subjects). In order to solve these problems, subcortical structures were studied using ultra-high-field high-resolution MRI (7T-MRI), which provides increased SNR and spatial resolution.

From a theoretical standpoint, this project aimed at disentangling subcortical function as well as to determine if these functions subserved a common scheme (domain-general) or respond to a domain-specific configuration. In order to achieve this goal, four experiments were proposed. These experiments were divided into a linguistic domain and its counterpart in the non-linguistic domain, both, as well, divided into syntax and semantics. Even though, the role of cortical structures in language processing has been well investigated for decades, the relative structural and functional contribution of subcortical structures to language processing is still a highly controversial topic. The role of the basal ganglia in language processing may or may not be language-specific. The basal ganglia are involved in categorization, learning, sequencing, timing, sequence and temporal chunking, and the extraction of regular patterns, based on this it has been proposed that syntactic processing is a form of hierarchical sequencing (Kotz et al., 2009). Furthermore, the semantic organization of the language system likely evolved at least in part to meet the need for categorization generated by the expansion of sensory information processing systems (Cangelosi and Parisi, 2004; Hauser, 2002; Lieberman, 2002). Therefore, we can think of language as a system governed by rules (syntax) and vocabulary that represents the categories of the world (semantics). These two systems work together to organize and to categorize our world, to generalize information, to acquire new information and to create new symbolic representations, and to express and to pass on information. In order to achieve the goals of the language system, an interplay between cortical and subcortical systems would be required (Ullman, 2006). As mentioned before, language processing is highly automated, in order to assure higher-order control (and therefore, subcortical structural involvement), the current experiments entailed different conditions where predictions were not fulfilled (errors) or created a conflict, which should be resolved in order to fulfill those expectancies (ambiguity).

Experiment 1: Syntactic ambiguity and error processing (linguistic)

The first experiment performed was a linguistic syntactic one. In this experiment, participants had to read and evaluate the grammaticality of syntactically unambiguous, ungrammatical, and ambiguous sentences.

As a first step sentence material was constructed. Once the experimental material had been tested, I proceeded to program the experiment (a pilot version and the experimental version) using the software Presentation. A behavioral pilot was performed with 16 native German speakers. This pilot demonstrated, as expected, that participants were slower and less accurate in judging the grammaticality of ambiguous sentences, followed by ungrammatical sentences, and unambiguous sentences. Following, this pilot study, the fMRI study started. As a matter of fact, this study was the first functional group study performed at the 7T scanner at the Institute. Due to this fact, several technical problems were encountered during scanning (mostly due to SAR (specific absorption rate) limit being exceeded). In consequence, 36 participants were scanned of which only 21 were part of the final sample.

The MRI behavioral performance showed in line with the pilot study that ambiguous sentences were responded to slower and less accurately than ungrammatical and unambiguous sentences and ungrammatical sentences than unambiguous ones (see Table 1).

Table 1. Behavioral performance

	UnA	UnG	A
RT (ms)	449 (08)	473 (103)	531 (128)
% correct	95% (4)	93% (5)	86% (8)

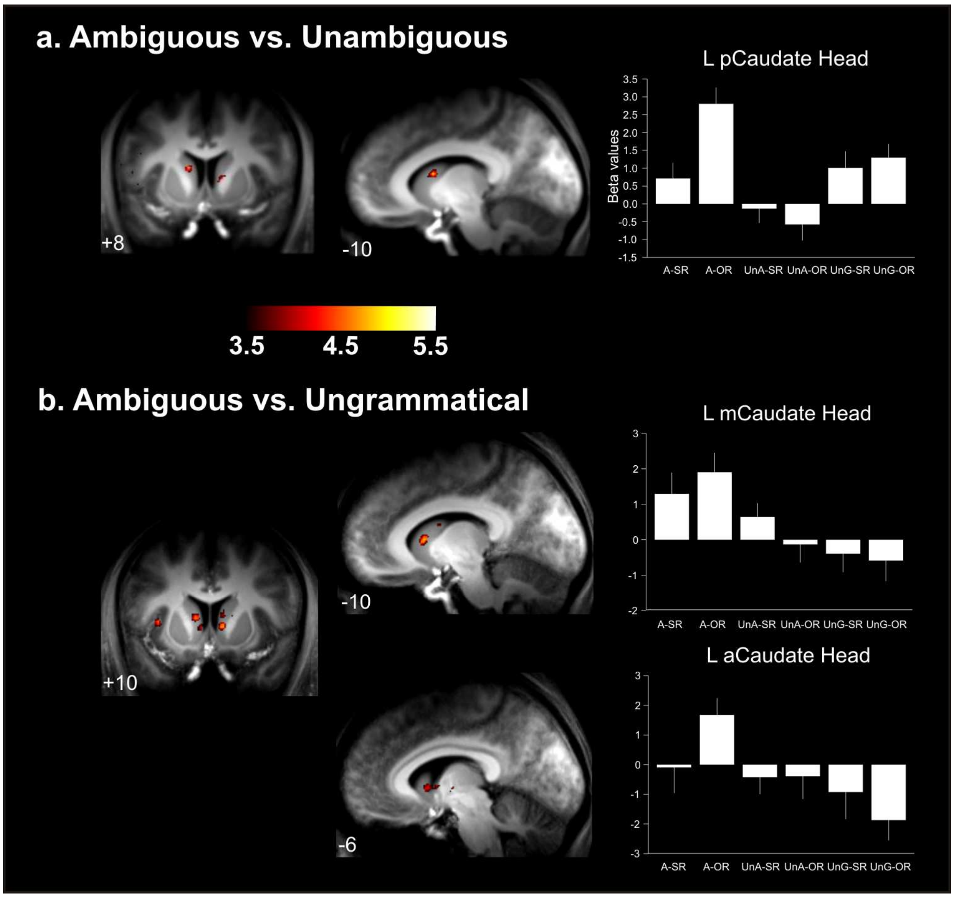
Notes: Reaction times (msec) and percentage of correct responses for the different sentence conditions. UnA: unambiguous; UnG: ungrammatical; A: ambiguous. Standard deviation in parentheses.

The fMRI results revealed a gradient of activation in the caudate nucleus, more specifically the head of the caudate nucleus (see Figure 1). Ambiguous and ungrammatical minus unambiguous sentences elicited larger activation in the postero-dorsal head of the caudate nucleus (see figure 1a right) and, dorsal and ventral prefrontal cortex (see Figure 2 top). In contrast, ambiguous minus ungrammatical sentences revealed larger activation in the left antero-ventral head of the caudate nucleus and anterior left prefrontal cortex (Figure 1b right, and Figure 2 bottom).

The data revealed three functionally different subregions within the head of the caudate nucleus to be related to cognitive control. They provide evidence of an anterior-posterior dimension in the associative caudate nucleus, with more anterior and ventral portions associated with higher-order cognitive processing. In the current study, participants read sentences that did not fulfill the expected sentence structure, hence creating a temporary conflict. To resolve this conflict, automatic passing processes have to be inhibited, and higher-order controlled processes have to be engaged. The experimental paradigm not only created a conflict, but also manipulated its resolution, by means of using ungrammaticality (error, no possible resolution) and temporary ambiguity (unexpected, resolution possible). The imaging results showed that more posterior and dorsal regions of the head of the caudate nucleus were active for both types of conflict situations. However, only ambiguity, the cognitively highest demanding condition, engaged the most anterior and ventral regions of the head of the caudate nucleus. These data demonstrate a clear differential involvement of subregions of the caudate nucleus in humans.

The anterior-posterior gradient in the head of the caudate nucleus fits well with the general topographical organization of the basal ganglia demonstrated in monkeys and humans, in which the anatomical and functional organization of the frontal cortex is reflected in the basal ganglia. In particular, it mimics the rostro-caudal gradient of the prefrontal cortex, whereby cognitive control is exerted from most anterior prefrontal to premotor regions. Thus more rostral (anterior) areas represent the highest level of executive control in frontal lobe hierarchy (Badre, 2008; Badre and D'Esposito, 2009; Christoff and Gabrieli, 2000; Koechlin et al., 2003; Petrides, 2005b; Petrides, 2005a). The results are in line with the proposed gradient in the prefrontal cortex, as different activations were observed ranging from dorso-lateral, ventro-lateral to anterior lateral prefrontal regions, as cognitive control in sentence processing and judgment increases. Crucially, however, they provide evidence for a similar gradient in the dorso-medial striatum. More posterior regions are engaged for both, processing of ambiguous and ungrammatical sentences, while in more anterior portions activation was found mainly for ambiguity processing.

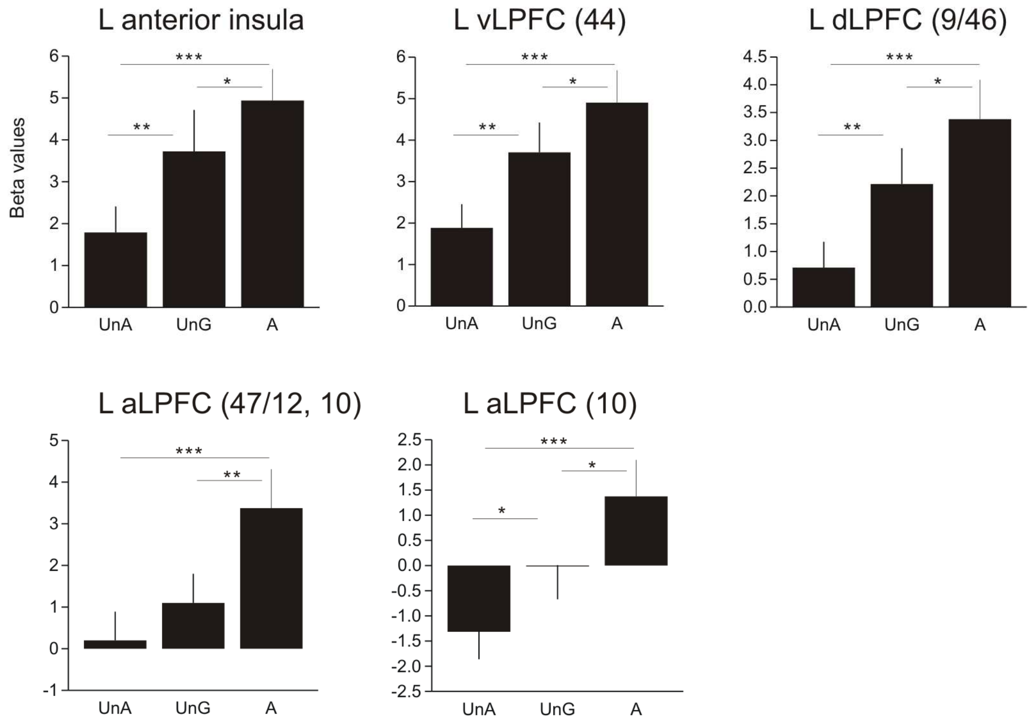
Figure 1. Functional imaging results for the different sentence conditions in the caudate nucleus.



Notes: (a) Left: Group-average comparisons between ambiguous and unambiguous sentences. Right: Group-average beta values for each condition in the posterior (p) head of the caudate nucleus (b) Left:

Group-average comparisons between ambiguous and ungrammatical sentences. Right: Group-average beta values for each condition in the middle (m) and anterior (a) head of the caudate nucleus.

Figure 2. Parameter estimate analysis in the different lateral prefrontal cortex regions for each condition.



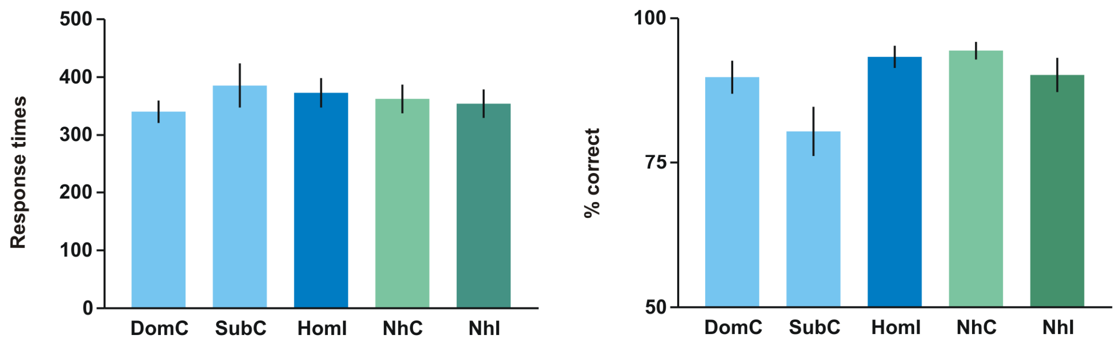
Notes: Group-average beta values for each condition in selected regions: left anterior insula, left ventrolateral prefrontal cortex (L vLPFC), left dorsolateral prefrontal cortex (dLPFC), left anterior lateral prefrontal cortex (L aLPFC). UnA: unambiguous; UnG: ungrammatical; A: ambiguous. Lines indicate paired *t*-test results in the pairwise comparisons (*p < 0.05; degrees of freedom: 20).

Experiment 2: Semantic ambiguity and error processing (linguistic)

In this experiment participants were required to read and judge the correctness of sentences. These sentences were semantically unambiguous, incorrect, or ambiguous. In this case, ambiguity occurred in form of homonyms; the last word of the sentence provided a biasing context, supporting either the most frequent, dominant, or a less frequent, subordinate interpretation of the homonym. A key difference between this form of semantic ambiguity and the syntactic ambiguity is that, in the semantic case the ambiguity is intrinsic to the word, while syntactic ambiguity was created by elements within the sentence (that is, the context).

First of all the sentence materials were created and tested. A behavioral pilot study (n = 16) confirmed that ambiguous sentences with a subordinate meaning interpretation were less accurately processed than the other sentence conditions; unfortunately this pattern was not as clear in the reaction times analysis (see Figure 3). After the behavioral pilot, the fMRI study began. In total 24 native German speakers were scanned in two sessions, in order to guarantee that each homonym appeared in its dominant and subordinate meaning. From the 24 participants, one did not perform the second session, and in consequence, was excluded from the final sample (n = 23). The behavioral results showed the same pattern as the pilot behavioral results (see Table 2).

Figure 3. Pilot behavioral results



Notes: DomC: dominant correct; SubC: subordinate correct; HomI: homonym incorrect; NhC: non-homonym correct; NhI: non-homonym incorrect.

Table 2. Behavioral performance (fMRI experiment)

	DomC	SubC	HomI	NhC	NhI
RT (ms)	401 (113)	423 (116)	430 (126)	396 (101)	422 (108)
% correct	90% (7)	71% (11)	92% (8)	95% (4)	92% (8)

Notes: Reaction times (msec) and percentage of correct responses for the different sentence conditions. DomC: dominant correct; SubC: subordinate correct; HomI: homonym incorrect; NhC: non-homonym correct; NhI: non-homonym incorrect. Standard deviation in parentheses.

The MRI analysis of these data was performed differently than in the previous experiment. Instead of a whole brain analysis, an anatomical region of interest analysis was performed. This way, the power 7T-MRI has to offer can be use at its full. To date, the analysis is ongoing due to being complex and laborious.

In this analysis, each basal ganglia nucleus is individually analyzed. For this purpose, the different structures are, automatically segmented using the software MIPAV. This automatic segmentation is not perfect and therefore needs to be manually adjusted; each striatum had to be delineated. For the segmentation of the globus pallidus and subthalamic nucleus another sequence had to be acquired and used. This is due to the poor differentiation of these nuclei in a standard anatomical

T1. Therefore, a FLASH 3-echo image was acquired, which enhance regions with high iron content, as it is the case of the globus pallidus and subthalamic nucleus. The next steps included slice timing correction and realignment of the EPI images (functional images) using SPM, and afterwards a manual co-registration of these images with the anatomical T1 image using landmarks. Furthermore, the FLASH and T1 images are manually co-registered using landmarks. In a next step, the basal ganglia are manually delineated in a (in-house) average anatomical image in SPM space. This new mask is used to co-register all participants' masks, and therefore, can be averaged across participants for all basal ganglia nuclei that will be used in SPM for statistical analysis.

Although, unfortunately, the provided grant has run out, the relevance and interest of this project lead to a 6-month contract with the Max Planck Institute in order to finish the data analysis and to carry out data collection of the non-linguistic experiments.

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