Brain Imaging and Behavior (2019) 13:651–659
https://doi.org/10.1007/s11682-018-9891-3

ORIGINAL RESEARCH

Inhibition impairment in frontotemporal dementia, amyotrophic lateral sclerosis, and Alzheimer's disease: clinical assessment and metabolic correlates

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Published online: 10 May 2018
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Abstract

The ability to reject an automatic tendency, i.e. inhibition, has been linked to the prefrontal cortex, but its neural underpinnings are still controversial. Neurodegenerative diseases represent an interesting model to explore this issue, given its frequent impairment in these disorders. We investigated the inhibitory impairment and its neural basis using four different tests, which evaluate the presence of inhibitory dysfunction (Stroop test, Hayling test, and two graphical perseveration tests), and assessed their correlation with brain metabolism using ^{18}F-fluorodeoxyglucose positron emission tomography in a group of 76 participants with behavioral variant frontotemporal dementia (bvFTD), Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS) and healthy controls (HC). Inhibition impairment was more frequent in bvFTD and AD, than ALS and HC. AD and bvFTD only differed in the strategy used in Hayling test, and the frequency of impairment in graphical perseveration tests. Correlation between inhibition tests was moderate. The Stroop test correlated with several regions of the frontal and parietal lobes, mainly on the left side. Hayling test correlated with almost all regions of the frontal lobe and, especially, with the orbitofrontal cortex. Some differences in the impaired regions in each disease were found. Inhibition ability was mainly impaired in bvFTD and AD, and it correlated with the bilateral frontal lobe metabolism. There were certain particularities according to the specific task and patients evaluated. These dissimilarities may support the concept of inhibition as a multidimensional construct, with the involvement of common and divergent neural mechanisms.

Keywords Inhibition · Executive functioning · Frontotemporal dementia · Alzheimer's disease · Amyotrophic lateral sclerosis · Hayling test

Introduction

Inhibition has been defined as the ability to reject an automatic behavior in a given situation (Thierry et al. 1994). It is an important cognitive ability comprised within the executive functioning and, thus, it is associated to alterations in the prefrontal cortex (Bari and Robbins 2013). Some authors have advocated a multidimensional view of inhibition, which could be further classified in several subtypes, such as motor inhibition, cognitive inhibition, interference control, motivational inhibition, and automatic inhibition of attention (Goldstein and Naglieri 2014; Bayard et al. 2017). Furthermore, the ability of inhibiting results from several processes, including the suppression of a prepotent response, the resistance to environmental interference and the resistance to proactive interference (Bayard et al. 2017). Taking this into account, we may hypothesize the potential existence of different neural mechanisms and networks involved in inhibition.

In recent years, several studies have focused on the presumed relationship of inhibition with the prefrontal cortex (Robinson et al. 2015, 2016). In this regard, some investigations have linked inhibition to right inferior frontal cortex

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11682-018-9891-3) contains supplementary material, which is available to authorized users.

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dysfunction using a stop-signal task and a task-set switching (Aron et al. 2003, 2014), while others have pointed out to the left superior medial frontal cortex using a go/no-go task (Picton et al. 2007).

Very recently, in an interesting study using the Hayling test and the Stroop Color-Word Test in a large group of patients with lateralized frontal lesions (tumors, strokes, etc.), Hayling test was associated to right prefrontal cortex damage, while the Stroop task was linked to left prefrontal lesions (Cipolotti et al. 2016). These findings suggest that inhibition may comprise different forms with different neural underpinnings.

In the specific setting of neurodegenerative diseases, impairment of inhibitory ability is frequent; in fact, it often manifests as disinhibition. This is an important symptom in terms of clinical diagnosis, generally favoring the diagnosis of frontal-lobe dementias. Besides, perseverative actions and errors often arise as a consequence of inhibitory problems and, overall, these symptoms produce a frequent impact and burden on patients and their caregivers (Shim et al. 2016). Therefore, neurodegenerative diseases represent an interesting model to study the complex relationship between brain and behavior, because brain damage tends to impair further brain regions than in the other traditional etiologies included in lesion studies, such as tumors or strokes (Matías-Guiu et al. 2017a).

Inhibition may be assessed using several cognitive tests, for instance, the Stroop Color Word Interference Test, the Hayling Sentence Completion Test, and some specific tasks searching for perseverative behaviors, such as Go/no-go, tapping tests, antisaccade task or copy of graphic alternating patterns (Friedman and Miyake 2004). Although alternative versions have been suggested, the Stroop Color Word Interference test is generally arranged in three parts. In the first two, the patient has a routine-based task consisting of reading three words (*blue*, *red*, and *green*) and naming three colors (blue, red, and green). In the last part, a list with incongruent color-word is showed (e.g. the word "red" is printed in green) and the patient is asked to name the color in which the word is written, instead of reading the word itself. Thus, in this third part, the patient has to inhibit a prepotent response (reading) and, instead of this, name the color.

In the case of the Hayling test, sentences in which the last word has been omitted (Burgess and Shallice 1996) are used. Specifically, the test comprises two tasks: in the first one (part A), the patient must complete a sentence with a word, which is clearly suggested by the meaning of the first part of the sentence (e.g.: "Cows produce… *milk*"). In the second part (part B), the patient has to produce a word that should have no relation whatsoever with the sentence (e.g. "Cows produce… *sky*"). The first part will measure initiation and serve as control to the second part, which indicates the ability to inhibit a prepotent and overlearned response (Volle et al. 2012; Pérez-Pérez et al. 2016).

To our knowledge, few studies have been conducted in the setting of neurodegenerative diseases that specifically investigate the neural correlates of inhibitory impairment. In fact, the Stroop test has been more linked to the left middle frontal gyrus in mild Alzheimer's Disease (AD) (Bracco et al. 2007), to middle frontal gyrus, inferior parietal lobule and middle temporal gyrus in other study in AD (Yun et al. 2011), and to the left inferior frontal junction and posterior superior and middle frontal gyrus (Brodmann areas 8/9) in a cohort of patients with AD and behavioral variant Frontotemporal Dementia (bvFTD) (Schroeter et al. 2012). The Hayling test, on its side, has been correlated in one study with atrophy in bilateral temporal poles, medial prefrontal and orbitofrontal cortex in bvFTD (Hornberger et al. 2011). The association between performance in the Hayling test and orbitofrontal dysfunction may be especially relevant, because most of neuropsychological tests evaluating executive functioning have been associated to dorsolateral prefrontal cortex function; but in bvFTD, impairment of orbitofrontal cortex occurs earlier than the dorsolateral dysfunction (Fernández-Matarrubia et al. 2014). In AD, on its side, marked inhibition deficits in the second part of the Hayling test are found, but, as far as we are concerned, the underlying neural basis of this have not been studied according to our knowledge (Belleville et al. 2006; Nash et al. 2007; Martyr et al. 2017).

The aim of our study was to investigate the inhibitory impairment and its neural basis using different cognitive tasks evaluating inhibitory dysfunction (Stroop test, Hayling test, and two graphical perseveration tests) and assessing their correlation with brain metabolism evaluated by ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET). To do so, we studied a cohort of patients with bvFTD, AD, and amyotrophic lateral sclerosis (ALS), which are the main neurodegenerative diseases in which inhibition dysfunction have been emphasized.

Methods

Participants

This study included 76 participants: 19 patients with bvFTD, 19 with ALS without dementia, 19 with AD, and 19 healthy controls (HC). All patients fulfilled current diagnostic criteria for their specific diseases (McKhann et al. 2011; Brooks et al. 2000; Rascovsky et al. 2011), they were corroborated by findings in FDG-PET, and had, at least, 1 year of follow-up. Patients with language disorders were not included. The time interval between neuropsychological assessment and FDG-PET was inferior to 2 months.

Healthy controls were recruited among healthy volunteers and spouses of patients.

Baseline neuropsychological assessment

Cognitive assessment was performed using a common protocol, which included the following tests: Mini-Mental State Examination (MMSE); digit span forward and backward; Corsi's cubs forward and backward; Boston Naming Test; Trail Making Test A and B; Symbol Digit Modalities Test; Free and Cued Selective Reminding Test; Rey-Osterrieth Complex Figure test (copy and memory at 3 and 30 min); verbal fluency (animals and words beginning with "p" in 1 min), and Visual Object and Space Perception Battery (subtests object decision, progressive silhouettes, position discrimination, and number location).

Experimental tasks

Hayling test was administered using the version previously developed and validated in our setting (Pérez-Pérez et al. 2016). This version was built by selecting 30 sentences with a very homogeneous and automated response in a group of 50 healthy controls (Pérez-Pérez et al. 2016). Two variables were obtained: time (response latency) and scoring (adjustment of the response) to each part. In part B, responses were classified as follows: a) Type 1, when the patient provided a word that appropriately completed the sentence (3 points); b) Type 2, when the patient answered with a word semantically related or opposite (2 points); c) Type 3, when the response was not related to the context of the sentence (0 points), which was indeed the aim of the test. A higher scoring in part B suggests that patient is not able to suppress an automatic response and, thus, means an inhibitory impairment. According to the patient' strategy to answer, type 2 responses were subclassified as O (opposite); SA (semantically related); SB (semantically related, but this relationship is milder); SC (the word fits at the end of the sentence, but the meaning is ridiculous or obscene). Regarding type 3, responses were subclassified as: N (non-related to the context of the sentence), NR (word non-related but present in the room); NL (non-related with the sentence but semantically related to the last response); NB (non-related but both conditions NR and NL are met). A further explanation about scoring and strategies is provided at Pérez-Pérez et al. (2016).

In addition, Golden's version of the Stroop Color Word Interference Test (Golden 1978; Peña-Casanova et al. 2009) was used. In this assessment, the patient is given a first page with the words "red", "green" or "blue" written 100 times printed in black ink (part A); a second page with 100 rows of ""XXX" printed in color (red, green, and blue) (part B); and a third page with 100 words reading the prior three colors (red, green or blue") printed in these same three colors, but with an incongruence between the written word and the color in which it is printed (part C). The score of each part consisted of the number of items accomplished in 45 s. An interference index was calculated according to the following formula: Interference = C – (A x B)/(A + B).

Graphic perseveration was assessed using two copy tasks: four double loops and a line with alternating peaks and plateaus.

^{18}F-FDG-pet

All participants were studied using ^{18}F-FDG-PET. Images were acquired in a PET-CT Siemens Biograph True Point platform and carried out according to the current European guidelines for brain PET imaging (Varrone et al. 2009). Mean dose of ^{18}F-FDG was 185 MBq, and the studies were performed after fasting at least 6 h and checking for capillary glucose below 150 mg/dL. Static PET was acquired in sinogram mode, during 10 min in a single bed position and after 30 min of the administration of ^{18}F-FDG. CT parameters were 130/40/1 (kVp/effective mAs/rotation time); slice thickness 3 mm; reconstruction interval 1.5 mm; and pitch 0.75. True X method with 2 iterations and 21 subsets was employed for an iterative three-dimensional image reconstruction.

Image preprocessing and analysis

Statistical Parametric Mapping version 8 (SPM 8, The Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College of London) was used for preprocessing and analysis of images. Specifically, images were realigned and normalized to the Montreal Neurological Institute space using a specific FDG-PET template for dementia (Della Rosa et al. 2014). Then, images were smoothed with a Full width at half maximum of 12 mm.

A region of interest (ROI) analysis of brain metabolism restricted to the frontal lobe was performed, using the Anatomic Automatic Labeling atlas and the software Marsbar version 0.44 (Tzourio-Mazoyer et al. 2002).

Furthermore, a voxel-based brain mapping analysis was performed in order to study the correlation between the experimental tasks and any brain region. A multiple regression analysis was used to calculate the correlation between Hayling test (part B), Stroop scores and whole brain metabolism, using age, years of education, diagnostic group (bvFTD, AD, ALS, and HC), and MMSE as covariates. We used part B of Hayling test, which is the score associated to inhibition. In the case of the correlation with Hayling test time part B, the time spent in part A was also entered as covariate. In the case of Stroop part C, parts A and B were also added as covariates to the statistical model. All these covariates were entered in the model in order to avoid potential factors influencing (age, level of education, degree of global cognitive impairment, etc.) in the test results beyond inhibition impairment.

We included the global metabolism as a nuisance covariate in the general linear model. We preferred this method instead

of scaling to a reference region, such as cerebellum or pons, due to the potential alterations of cerebellar and pontine metabolism in ALS (Matías-Guiu et al. 2016). A false-discovery rate corrected p-value <0.05 was used to correct for ROI analysis. For multiple regression analysis, an uncorrected p-value <0.001 was considered statistically significant, with an extent threshold k = 50 voxels.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 20.0. Data are shown as mean ± standard deviation or absolute frequencies (percentage). Kruskall-Wallis test and the post-hoc Dunn-Bonferroni method were used to compare quantitative variables between groups, and Fisher's test was performed to compare qualitative variables. Median test was preferred instead of Kruskall-Wallis test for comparison of the types of strategies used in Hayling B due to differences in variance. Pearson correlations were estimated between inhibition tests. Partial correlations were calculated between tasks and brain metabolism in the frontal lobe, controlling for age, years of education, and MMSE.

Results

Demographic and general cognitive testing

Demographics and main cognitive testing results are presented in Table 1. There were no significant differences between HC and each disease group, except for the variable years of education, which was lower in bvFTD in comparison to HC.

Inhibition test results

The complete set of results for inhibition tests are presented in Table 2. There were significant differences between groups in the times for parts A and B from the Hayling. In fact, pairwise comparisons showed that mean time of Hayling part A was higher in bvFTD, with significant differences in comparison to AD and HC. The score for part B, on its side, was significantly higher in bvFTD and AD, in comparison to HC and ALS, but there were no significant differences between bvFTD and AD. Similar results were observed in the score Hayling B/A. In contrast, there were no significant differences between groups in the score for part A and the time for part B. However, differences in the type of responses and strategies used in Hayling part B were different between groups. Specifically, type 1 responses were more frequent in bvFTD in comparison to AD and the other groups, while type 2 responses were more frequent in AD than bvFTD (Table 2).

There were significant differences between groups in the three parts of the Stroop test, but not in the Interference Score. In parts A and B, mean score of bvFTD and AD was significantly higher than HC. In part C, the score was higher in bvFTD and AD, in comparison to ALS and HC. In contrast, there were no significant differences between bvFTD and AD in any score.

Regarding graphic perseveration, frequency of perseveration in alternating lines and loops was higher in bvFTD and AD, in comparison to ALS and HC. Besides, presence of graphic perseveration in both tasks was more frequent in bvFTD than in the other diagnoses, including AD.

Table 1 Demographic and main cognitive testing results

	bvFTD	AD	ALS	HC	Statistic value (p-value)
Age	71.05 ± 7.72[b]	72.16 ± 8.48[d]	57.89 ± 9.74	64.89 ± 8.81	22.55 **(0.000)**
Women n (%)	10 (52.6%)	12 (63.2%)	11 (57.9%)	10 (52.6%)	0.589 (0.899)
Years of education	8.21 ± 10.74[c]	10.74 ± 5.70	12.74 ± 5.13	13.89 ± 4.01	11.68 **(0.009)**
MMSE	24.00 ± 4.79[b,c]	24.26 ± 4.33[d,e]	28.00 ± 1.63	29.16 ± 1.21	32.24 **(0.000)**
Digit forward	5.26 ± 1.32[b]	5.47 ± 1.17	6.50 ± 1.42	6.00 ± 1.36	9.15 **(0.027)**
Digit backward	3.21 ± 1.47	3.59 ± 1.00	4.22 ± 1.39	4.12 ± 0.60	7.64 (0.054)
Trail Making Test A	88.89 ± 55.85[c]	87.25 ± 42.80[d,e]	51.31 ± 25.22	40.41 ± 17.19	21.67 **(0.000)**
Trail Making Test B	283.63 ± 171.36[c]	246.40 ± 187.74[d,e]	142.06 ± 96.49	93.29 ± 42.19	23.36 **(0.000)**
ROCF (copy)	20.97 ± 10.30[b,c]	23.50 ± 7.32[d,e]	30.50 ± 5.10	31.14 ± 3.40	18.13 **(0.000)**
FCSRT total delayed recall	5.00 ± 4.61[b,c]	4.59 ± 4.03[d,e]	14.11 ± 2.58	13.38 ± 2.63	42.31 **(0.000)**
ToL (correct moves)	1.62 ± 1.62[b,c]	1.94 ± 1.88[d,e]	5.07 ± 2.21	5.06 ± 2.56	24.73 **(0.000)**
VOSP discrimination of position	18.84 ± 1.83[c]	17.59 ± 2.45[e]	19.39 ± 1.14	19.65 ± 0.60	17.15 **(0.000)**

Statistically significant p-values are shown in bold

Statistically significant differences in post-hoc analysis: [a] bvFTD vs AD; [b] bvFTD vs ALS; [c] bvFTD vs HC; [d] AD vs ALS; [e] AD vs HC. [f] ALS vs HC

Abbreviations: *ROCF* Rey-Osterrieth Complex Figure, *FCSRT* Free and Cued Selective Reminding Test, *ToL* Tower of London, *VOSP* Visual and Object Perception Battery

Table 2 Inhibition tests. Comparison between groups

	bvFTD	AD	ALS	HC	X^2 (*p*-value)
Hayling A score	0.84 ± 1.25	0.16 ± 0.50	0.79 ± 2.74	0.21 ± 0.53	5.32 (0.150)
Hayling A time	17.45 ± 10.05[a,c]	10.59 ± 2.50	11.16 ± 3.31	9.29 ± 1.95	17.40 **(0.001)**
Hayling B score	22.68 ± 12.83[b,c]	18.11 ± 9.72[d,e]	7.68 ± 3.59	7.32 ± 6.55	27.12 **(0.000)**
Hayling B time	48.75 ± 17.03	49.01 ± 19.2	48.53 ± 39.09	39.96 ± 27.52	4.84 (0.183)
Hayling B/A score	2.98 ± 1.07[b,c]	2.77 ± 0.98[d,e]	1.69 ± 0.65	1.70 ± 0.38	26.90 **(0.000)**
Hayling B/A time	3.54 ± 2.06	5.08 ± 2.75	4.17 ± 2.35	4.13 ± 2.42	3.80 (0.284)
Type 3 responses (Hayling B)	2.84 ± 3.40[c]	3.05 ± 4.09[e]	7.66 ± 5.60	8.41 ± 3.20	29.93 **(0.000)**
Type 2 responses (Hayling B)	6.73 ± 3.58[a]	10.05 ± 3.63[e]	7.05 ± 6.29	6.29 ± 3.17	12.03 **(0.007)**
Type 1 responses (Hayling B)	5.36 ± 5.16[a,b,c]	1.94 ± 2.30[d,e]	0.27 ± 0.75	0.17 ± 0.52	18.37 **(0.000)**
Stroop A	64.95 ± 26.11[c]	75.35 ± 19.68[e]	87.25 ± 22.43	96.68 ± 22.00	15.48 **(0.001)**
Stroop B	41.06 ± 17.58[c]	45.06 ± 11.51[e]	55.38 ± 13.17	58.63 ± 11.81	15.76 **(0.001)**
Stroop C	18.44 ± 11.47[b,c]	20.35 ± 8.05[d,e]	31.13 ± 11.09	31.89 ± 9.33	19.83 **(0.000)**
Interference index	−6.53 ± 9.80	−7.59 ± 7.13	−2.65 ± 7.31	−4.15 ± 4.70	4.14 (0.246)
Graphic perseveration (loops)	7 (36.8%)[b,c]	2 (10.5%)[d,e]	0 (0%)	0 (0%)	16.18 **(0.001)**
Graphic perseveration (alternating line)	7 (36.8%)[b,c]	6 (31.6%)[d,e]	0 (0%)	0 (0%)	15.49 **(0.001)**
Graphic perseveration in both tasks	6 (31.6%)[a,b,c]	1 (5.3%)	0 (0%)	0 (0%)	15.29 **(0.002)**

Statistically significant *p*-values are shown in bold

Statistically significant differences in post-hoc analysis: [a] bvFTD vs AD; [b] bvFTD vs ALS; [c] bvFTD vs HC; [d] AD vs ALS; [e] AD vs HC. [f] ALS vs HC

Correlations between inhibition tasks and with other cognitive tests

Correlation between Hayling B (score) and Stroop C was moderate ($r = -0.596$, $p < 0.001$). There was no correlation between score and time in Hayling B ($r = -0.048$, $p = 0.681$), and between Hayling B (time) and Stroop C ($r = -0.226$, $p = 0.060$). Correlations between graphic perseveration and Hayling B ($r = 0.520$, $p < 0.001$) and Stroop C ($r = -0.519$, $p = <0.001$) were also moderate.

Correlation between inhibition tests and frontal lobe metabolism: ROI analysis

In the whole sample, Hayling test (part B) was negatively correlated with all regions of frontal lobe, except bilateral supplementary motor area, right superior frontal gyrus and right olfactory gyrus. Correlations were higher with the orbital part of left middle and left superior frontal gyri, and right medial frontal gyrus. In bvFTD, it was negatively correlated with anterior cingulate, superior, middle, medial and inferior frontal gyri, and rectus and olfactory gyri, especially on the left hemisphere. Correlations were higher in orbital parts of bilateral middle and medial frontal gyri. In AD, the test was negatively correlated with the metabolism of the inferior frontal (orbital and triangular part), middle frontal (orbital part), and rectus gyri on the left hemisphere, and with the orbital part of medial and middle frontal gyri on the right side. In ALS, Hayling part B was correlated with inferior frontal (opercular part), middle frontal, medial frontal, orbital part of superior frontal and rectus gyri on the left hemisphere, and inferior frontal (triangular part), middle and superior frontal gyri on the right side.

Regarding Stroop test, part C was positively correlated with left inferior frontal (opercular and triangular parts), bilateral middle frontal, bilateral superior frontal, and bilateral medial frontal gyri, and bilateral supplementary motor area. In bvFTD, the test was correlated with metabolism in left inferior frontal (opercular part), left middle frontal, and left superior frontal gyri and right supplementary motor area. In contrast, none region of the frontal lobe was correlated with Stroop C performance in AD. In ALS, Stroop C was correlated with bilateral middle frontal, bilateral superior frontal, and bilateral medial frontal gyri. All correlations between tests and frontal lobe metabolism are shown in Table S1 from Supplementary Material.

Voxel-based brain mapping analysis

Hayling score part B was negatively correlated with the metabolism of left frontal lobe, comprising superior, middle and inferior frontal gyri, medial and orbital gyrus, and anterior cingulate. It correlated also with the right frontal lobe, particularly with orbital gyrus, and superior, middle and inferior frontal gyri, as well as the left parahippocampal and inferior temporal gyri. Regarding the time of the part B, it was negatively correlated with the metabolism of right precentral, middle and superior frontal gyri, as well as the left and righ inferior parietal lobule (Fig. 1, Table S2 Supplementary Material).

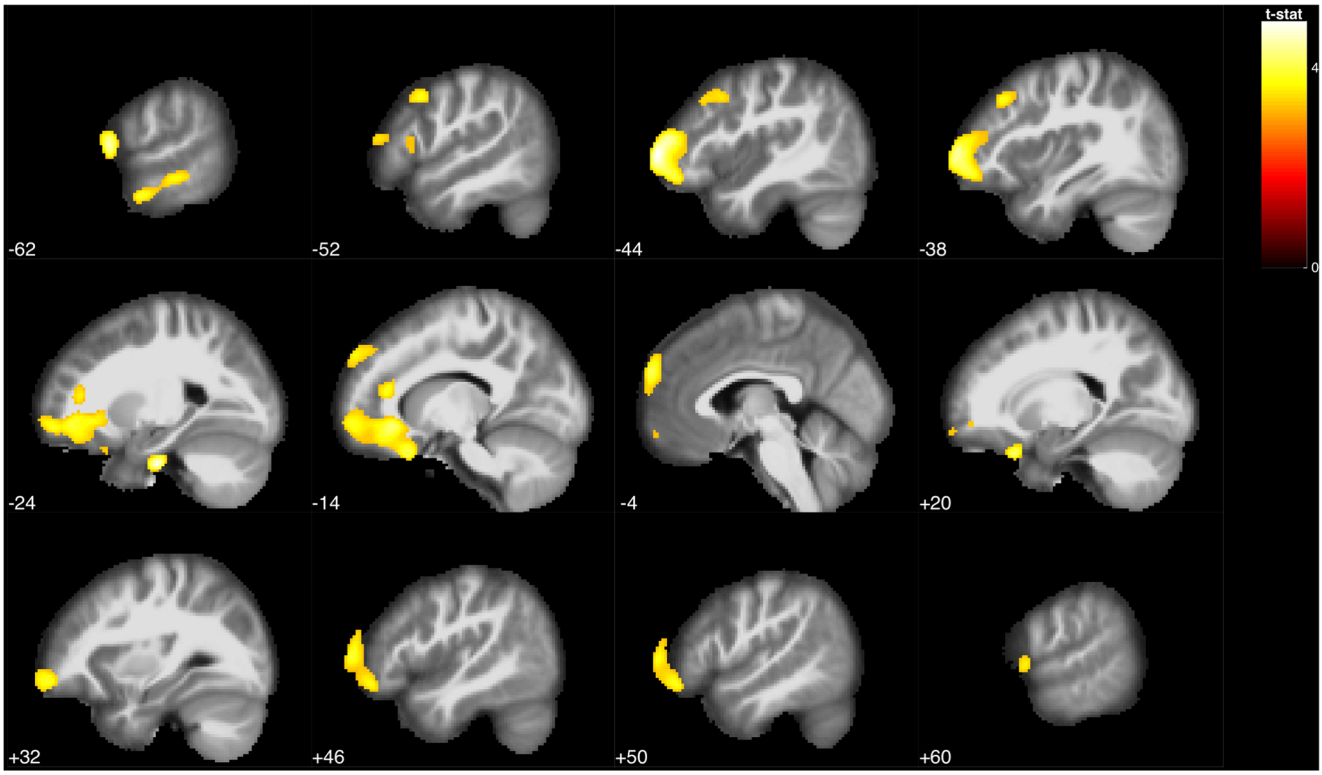

Fig. 1 Voxel-based brain mapping analysis showing correlation between Hayling test (part B) and brain metabolism, using age, years of education, diagnostic group, and MMSE as covariates (uncorrected p-value <0.001, k = 50). Labels in *x* axis are shown (negative values: left hemisphere; positive values: right hemisphere)

Stroop test part C was positively correlated with several regions of the frontal and parietal lobes, mainly on the left sided. Specifically, it was correlated with left precentral, middle and inferior frontal gyri, as well as left precuneus, left postcentral gyrus, and left and right inferior parietal lobule (Fig. 2, Table S2 Supplementary Material).

Discussion

In this study, we evaluated inhibition in a cohort of patients with bvFTD, AD and ALS using three different tasks. Inhibition impairment was more frequent in bvFTD and AD, and the relationship between inhibition and brain metabolism was investigated using a ROI approach of the frontal lobe, as well as a voxel-based analysis including the whole brain.

Inhibition alterations were mainly present in bvFTD and AD, but not in ALS and HC. Interestingly, there were no significant differences in inhibition scores of Hayling and Stroop tests between bvFTD and AD. In contrast, graphic perseveration in both alternating lines and loops was present in 31.6% of patients with bvFTD, but only in 5.3% of AD. This confirms previous findings showing a poor level of discrimination between bvFTD and AD using Stroop test (Collette et al. 2007), but contrasts with studies by Hornberger et al. (2010, 2011), showing Hayling test could discriminate bvFTD and AD in 79.2% of cases (Hornberger et al. 2010). Intriguingly, although there were no differences in Hayling scores between bvFTD and AD, strategies used in bvFTD and AD were different. In this regard, bvFTD showed a higher frequency of type 1 responses, while AD resorted more frequently to type 2 responses. This suggests a failure in suppressing the correct response in bvFTD, which supports a true failure in inhibition. Conversely, in AD, the impairment in Hayling test seems to be more related to difficulties in generating an adequate strategy to produce an alternative response to the correct word that completes the sentence. In fact, in AD, type 1 responses suggestive of a failure of inhibition were also present more frequently than in ALS and HC, but were not as important as in bvFTD. Besides, slowness in initiation capacity was also observed in Hayling test part A in the group with bvFTD.

Correlation between tasks evaluating inhibition was moderate, but not complete, suggesting that each task does not exactly measure the same cognitive processes. In this regard, although Stroop and Hayling were mainly correlated with brain metabolism in the frontal lobe, there were some differences in the specific regions involved. For instance, Stroop was mainly correlated with superior, middle and inferior

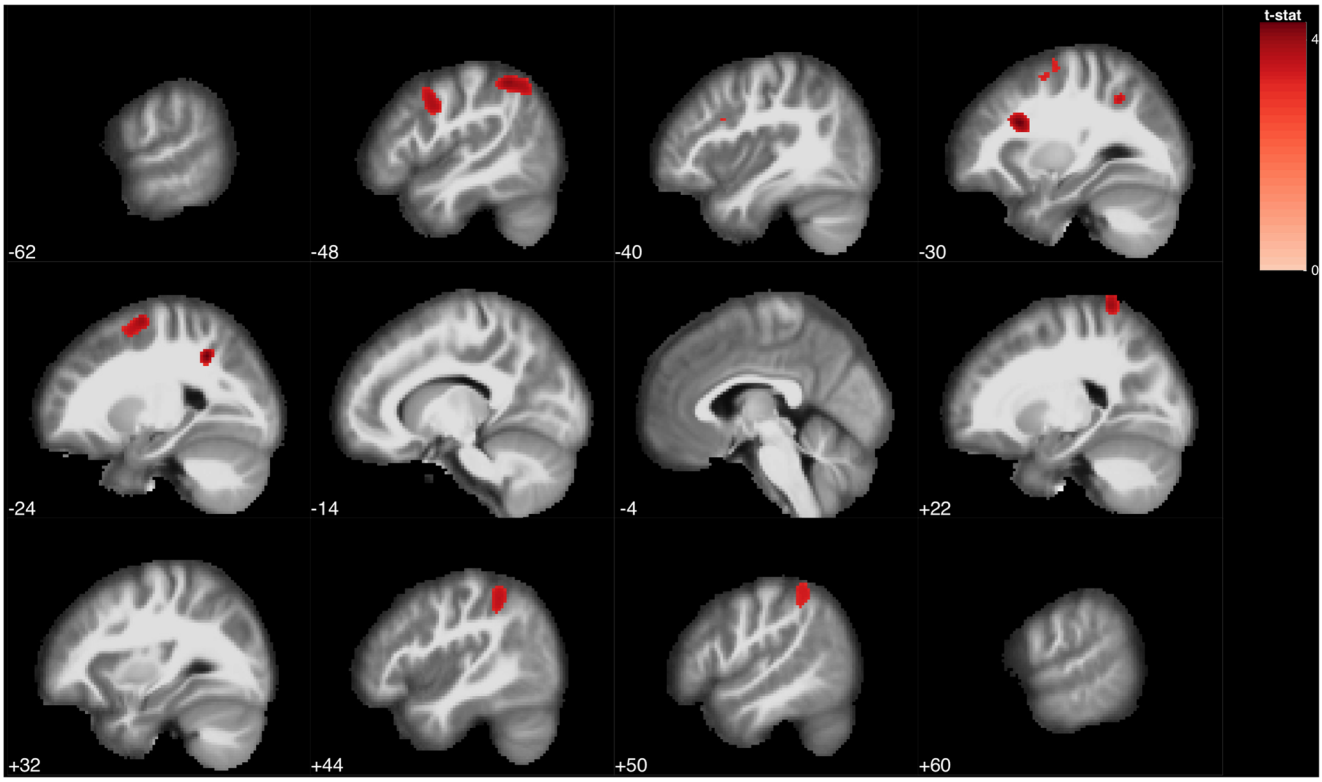

Fig. 2 Voxel-based brain mapping analysis showing correlation between Stroop (part C) and brain metabolism, using age, years of education, diagnostic group, MMSE, Stroop part A and Stroop part B as covariates (uncorrected p-value <0.001, k = 50). Labels in *x* axis are shown (negative values: left hemisphere; positive values: right hemisphere)

frontal gyri, while Hayling test was correlated with orbital parts of those gyri and rectus gyrus. This may suggest that Stroop was more related to those regions associated to dorsolateral prefrontal cortex, and Hayling more associated to orbitofrontal dysfunction.

Concerning the previously suggested association between Hayling and Stroop tasks with the left or right hemisphere, respectively (Cipolotti et al. 2016), our study showed that Stroop was mainly correlated with the left hemisphere. However, Hayling task was not lateralized to a specific hemisphere, but it was rather associated to brain metabolism in both sides. This is in agreement with a previous study correlating Hayling test with bilateral medial frontal gyri atrophy in Parkinson's disease and frontotemporal dementia (O'Callaghan et al. 2013).

Another interesting issue is the possibility that regions associated to the performance of each test could be different in each disease. In this regard, Stroop test was correlated with several regions of the frontal lobe in bvFTD and ALS, but we did not find a significant correlation in the group with AD. In voxel-based analysis, Stroop C was correlated also to the parietal lobe, even controlling by parts A and B. This may be partly explained because Stroop test implies reading and naming, but also because these regions have been involved in attention and executive processes through fronto-parietal connections, and parietal cortex dysfunction may be more explicative than frontal lobe damage of executive dysfunction in AD (Matías-Guiu et al. 2017b; Bettcher et al. 2016). Besides, Stroop test measures other executive processes beyond inhibition, such as selective attention, flexibility and information processing speed (Peña-Casanova et al. 2009). Otherwise, Hayling test (part B) was mainly associated to orbitofrontal cortex in bvFTD, ALS, and AD, suggesting that this test could be a relatively sensitive marker of orbitofrontal cortex function in neurodegenerative disorders, although part B was also correlated to other regions linked to dorsolateral prefrontal cortex.

In this regard, Hayling test was correlated with other regions of the frontal lobe, including the right inferior frontal cortex. This region has been proposed as having a critical role in inhibition, by stopping actions (Aron et al. 2014), based on several experiments using functional MRI or transcranial magnetic stimulation. In our study, brain metabolism of this region was significantly correlated with Hayling test in the whole sample and in the bvFTD group, but not in AD. In contrast, Stroop test was not significantly correlated. On one hand, the correlation with wide regions of frontal lobe supports a more general view of inhibition not exclusively dependent of specific brain regions, such as right inferior frontal or the orbitofrontal cortex. But, on the other hand, it opens the

possibility, as we suggested above, that some inhibition tasks are also examining other cognitive functions beyond inhibition, especially in some groups of patients such as AD, where other type of errors were more frequently detected.

Our study has some limitations. The cross-sectional design did not allow the assessment of inhibition impairment along the course of diseases, which may be of interest, and provide a better understanding of the usefulness of these tasks in the differential diagnosis. We decided not to calculate the correlations in patients between graphic perseveration and brain metabolism, because groups with and without perseveration were very unequally sized. Future studies will be necessary to understand the neural basis of graphic perseveration. However, the higher frequency in bvFTD (particularly when patients perseverate at both tasks) and the correlation with other inhibition tests, may suggest similar underpinnings. Furthermore, we had to use uncorrected p-value <0.001 as statistical threshold, which is a less strict correction for multiple comparison problems than other procedures such as family-wise error. We chose that threshold because of the sample size of our study and the need to add several covariates for controlling for other factors that may influence in the performance of tasks measuring inhibition (age, level of education, control tasks, etc.). On the other hand, ALS patients included in this study were in an early stage of the disease, in order to be able to perform the several cognitive tasks included in the research protocol. This could have selected a group of ALS patients with a low frequency of inhibition impairment. For this reason, a specific study of inhibition in ALS including different clinical stages should be necessary to better understand the neural basis of inhibition in this disease.

In conclusion, our study contributes to the knowledge suggesting that AD and bvFTD may both impair some specific functions, but the underlying neural mechanisms may not be exactly shared (Dermody et al. 2016; Fernández-Matarrubia et al. 2017). Inhibition ability was impaired in both entities, as we observed using different tasks. Some clinical differences could be detected, which may be clinically relevant, such as the specific strategy used in Hayling test. The dissimilarities observed between tests evaluating inhibition functioning and their neural correlates support the concept of inhibition as a multidimensional construct, with common and divergent neural mechanisms involved. Overall, this promotes the need for a comprehensive assessment of each cognitive function with several tools, in order to search for specific differences that could help to disentail the precise neural mechanisms, and could be valuable for the differential diagnosis between neurodegenerative diseases.

Compliance with ethical standards

Conflict of interest The authors declare than they have no conflict of interest.

Research involving human participants All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

Inform consent Informed consent was obtained from all individual participants included in the study.

References

Aron, A. R., Fletcher, P. C., Bullmore, E. T., Sahakian, B. J., & Robbins, T. W. (2003). Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. *Nature Neuroscience, 6*(2), 115–116.

Aron, A. R., Robbins, T. W., & Poldrack, R. A. (2014). Inhibition and the right inferior frontal cortex: one decade on. *Trends in Cognitive Sciences, 18*(4), 177–185. https://doi.org/10.1016/j.tics.2013.12.003.

Bari, A., & Robbins, T. W. (2013). Inhibition and impulsitivy: behavioral and neural basis of response control. *Progress in Neurobiology, 108*, 44–79. https://doi.org/10.1016/j.pneurobio.2013.06.005.

Bayard, S., Gély-Nargeot, M.C., Raffard, S., Guerdoux-Ninot, E., Kamara, E., Gros-Balthazard, F., … Moroni, C.; Collège des Psychologues Cliniciens specializes en Neuropsychologie du Languedoc Rousillon (CPCN-Languedoc Rousillon). (2017). French version of the Hayling Sentence Completion Test, Part I: normative data and guidelines for error scoring. *Archives of Clinical Neuropsychology, 7*, 1–7. https://doi.org/10.1093/arclin/acx010.

Belleville, S., Rouleau, N., & Van der Linden, M. (2006). Use of the Hayling task to measure inhibition of prepotent responses in normal aging and Alzheimer's disease. *Brain and Cognition, 62*(2), 113–119.

Bettcher, B.M., Mungas, D., Patel, N., Elofson, J., Dutt, S., Wynn, M., … Kramer, J.H. (2016). Neuroanatomical substrates of executive functions: Beyond prefrontal structures. *Neuropsychologia, 85*, 100–109. https://doi.org/10.1016/j.neuropsychologia.2016.03.001.

Bracco, L., Bessi, V., Piccini, C., Mosconi, L., Pupi, A., & Sorbi, S. (2007). Metabolic correlates of executive dysfunction. Different patterns in mild and very mild Alzheimer's disease. *Journal of Neurology, 254*, 1052–1065.

Brooks, B. R., Miller, R. G., Swash, M., Munsat, T. L., & World Federation of Neurology Research Group on Motor Neuron Diseases. (2000). El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders, 1*(5), 293–299.

Burgess, P., & Shallice, T. (1996). Response supression, initiation and strategi use following frontal lobe lesions. *Neuropsychologia, 34*(4), 263–272.

Cipolotti, L., Spanò, B., Healy, C., Tudor-Sfetea, C., Chan, E., White, M., … Bozzali, M. (2016). Inhibition processes are dissociable and lateralized in human prefrontal cortex. *Neuropsychologia, 93*(Pt A), 1–12. https://doi.org/10.1016/j.neuropsychologia.2016.09.018.

Collette, F., Amieva, H., Adam, S., Hogge, M., Van der Linden, M., Fabrigoule, C., & Salmon, E. (2007). Comparison of inhibitory functioning in mild Alzheimer's disease and frontotemporal dementia. *Cortex, 43*(7), 866–874.

Della Rosa, P.A., Cerami, C., Gallivanone, F., Prestia, A., Caroli, A., Castiglioni, I., … Perani, D.; EADC-PET Consortium. (2014). A standardized [^{18}F]-FDG-PET template for spatial normalization in statistical parametric mapping of dementia. *Neuroinformatics, 12*(4), 575–593. https://doi.org/10.1007/s12021-014-9235-4.

Dermody, N., Hornberger, M., Piguet, O., Hodges, J. R., & Irish, M. (2016). Prospective memory impairments in Alzheimer's disease

and behavioral variant frontotemporal dementia: clinical and neural correlates. *Journal of Alzheimer's Disease, 50*(2), 425–441. https://doi.org/10.3233/JAD-150871.

Fernández-Matarrubia, M., Matías-Guiu, J. A., Moreno-Ramos, T., & Matías-Guiu, J. (2014). Behavioral variant frontotemporal dementia: clinical and therapeutic approaches. *Neurología, 29*(8), 464–472. https://doi.org/10.1016/j.nrl.2013.03.001.

Fernández-Matarrubia, M., Matías-Guiu, J. A., Cabrera-Martín, M. N., Moreno-Ramos, T., Valles-Salgado, M., Carreras, J. L., & Matías-Guiu, J. (2017). Different apathy clinical profile and neural correlates in behavioral variant frontotemporal dementia and Alzheimer's disease. *International Journal of Geriatric Psychiatry, 33*, 141–150. https://doi.org/10.1002/gps.4695.

Friedman, N. P., & Miyake, A. (2004). The relations among inhibition and interference control functions: a latent-variable analysis. *Journal of Experimental Psychology. General, 133*(1), 101–135.

Golden, C. J. (1978). *Stroop color and word test. A manual for clinical and experimental uses*. Chicago: Stoelting.

Goldstein, S., & Naglieri, J. A. (2014). *Handbook of executive functioning*. New York: Springer-Verlag.

Hornberger, M., Savage, S., Hsieh, S., Mioshi, E., Piguet, O., & Hodges, J. R. (2010). Orbitofrontal dysfunction discriminates behavioral variant frontotemporal dementia from Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders, 30*(6), 547–552. https://doi.org/10.1159/000321670.

Hornberger, M., Geng, J., & Hodges, J. R. (2011). Convergent grey and white matter evidence of orbitofrontal cortex changes related to disinhibition in behavioral variant frontotemporal dementia. *Brain, 134*(Pt 9), 2502–2512. https://doi.org/10.1093/brain/awr173.

Martyr, A., Boycheva, E., & Kudlicka, A. (2017). Assessing inhibitory control in early-stage Alzheimer's and Parkinson's disease using the Hayling sentence completion test. *Journal of Neuropsychology*. https://doi.org/10.1111/jnp.12129.

Matías-Guiu, J. A., Pytel, V., Cabrera-Martín, M. N., Galán, L., Valles-Salgado, M., Guerrero, A., Moreno-Ramos, T., Matías-Guiu, J., & Carreras, J. L. (2016). Amyloid- and FDG-PET imaging in amyotrophic lateral sclerosis. *European Journal of Nuclear Medicine and Molecular Imaging, 43*(11), 2050–2060. https://doi.org/10.1007/s00259-016-3434-1.

Matías-Guiu, J. A., Cuetos, F., Cabrera-Martín, M. N., Valles-Salgado, M., Moreno-Ramos, T., Carreras, J. L., & Matías-Guiu, J. (2017a). Reading difficulties in primary progressive aphasia in a regular language-speaking cohort of patients. *Neuropsychologia, 101*, 132–140. https://doi.org/10.1016/j.neuropsychologia.2017.05.018.

Matías-Guiu, J. A., Cabrera-Martín, M. N., Valles-Salgado, M., Pérez-Pérez, A., Rognoni, T., Moreno-Ramos, T., et al. (2017b). Neural basis of cognitive assessment in Alzheimer disease, amnestic mild cognitive impairment, and subjective memory complaints. *The American Journal of Geriatric Psychiatry, 25*(7), 730–740. https://doi.org/10.1016/j.jagp.2017.02.002.

McKhann, G.M., Knopman, D.S., Chertkow, H., Hyman, B.T., Jack, C.R. Jr, Kawas, C.H., … Phelps, C.H. (2011). The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association Workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement, 7*(3), 263–269. https://doi.org/10.1016/j.jalz.2011.03.005.

Nash, S., Henry, J. D., McDonald, S., Martin, I., Brodaty, H., & Peek-O'Leary, M. A. (2007). Cognitive disinhibition and socioemotional functioning in Alzheimer's disease. *Journal of the International Neuropsychological Society, 13*(6), 1060–1064.

O'Callaghan, C., Naismith, S. L., Hodges, J. R., Lewis, S. J. G., & Hornberger, M. (2013). Fronto-striatal atrophy correlates of inhibitory dysfunction in Parkinson's disease versus behavioral variant frontotemporal dementia. *Cortex, 49*(7), 1833–1843. https://doi.org/10.1016/j.cortex.2012.12.003.

Peña-Casanova, J., Quiñones-Úbeda, S., Gramunt-Fombuena, N., Quintana, N., Aguilar, M., Molinuevo, J.L., … Blesa, R.; NEURONORMA Study Team. (2009). Spanish Multicenter Normative Studies (NEURONORMA Project): norms for the Stroop color-word interference test and the Tower of London-Drexel. *Archives of Clinical Neuropsychology, 24*(4), 413–429. https://doi.org/10.1093/arclin/acp043.

Pérez-Pérez, A., Matías-Guiu, J.A., Cáceres-Guillén, I., Rognoni, T., Valles-Salgado, M., Fernández-Matarrubia, M., … Matías-Guiu, J. (2016). The Hayling test: development and normalization of the Spanish version. *Archives of Clinical Neuropsychology, 31*(5), 411–419. https://doi.org/10.1093/arclin/acw027.

Picton, T. W., Stuss, D. T., Alexander, M. P., Shallice, T., Binns, M. A., & Gillingham, S. (2007). Effects of focal frontal lesions on response inhibition. *Cerebral Cortex, 17*(4), 826–838.

Rascovsky, K., Hodges, J.R., Knopman, D., Mendez, M.F., Kramer, J.H., Neuhaus. J., … Miller, B.L. (2011). Sensitivity of revised diagnostic criteria for the behavioral variant of frontotemporal dementia. *Brain, 134*(Pt 9), 2456–2477. https://doi.org/10.1093/brain/awr179.

Robinson, G. A., Cipolotti, L., Walker, D. G., Biggs, V., Bozzali, M., & Shallice, T. (2015). Verbal suppression and strategy use: a role for the right lateral prefrontal cortex? *Brain, 138*, 1084–1096.

Robinson, G. A., Walker, D. G., Biggs, V., & Shallice, T. (2016). When does a strategy intervention overcome a failure of inhibition? Evidence from two left frontal brain tumour cases. *Cortex, 79*, 123–129.

Schroeter, M. L., Vogt, B., Frisch, S., Becker, G., Barthel, H., Mueller, K., Villringer, A., & Sabri, O. (2012). Executive deficits are related to the inferior frontal junction in early dementia. *Brain, 135*(Pt 1), 201–215. https://doi.org/10.1093/brain/awr311.

Shim, S. H., Kang, H. S., Kim, J. H., & Kim, D. K. (2016). Factors associated with careigiver burden in dementia: 1-year follow-up study. *Psychiatry Investigation, 13*(1), 43–49. https://doi.org/10.4306/pi.2016.13.1.43.

Thierry, A. M., Glowinski, J., Goldman-Rakic, & Christen, Y. (1994). *Motor and cognitive functions of the prefrontal cortex*. Berlin: Springer.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., … Joliot, M. (2002). Automated anatomical labeling of activation in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage, 15*(1), 272–289.

Varrone, A., Asenbaum, S., Vander Borght, T., Booij, J., Nobili, F. Någren, K., … Van Laere, K; European Association of Nuclear Medicine Neuroimaging Committee. (2009). EANM procedure guidelines for PET brain using [^{18}F]FDG, version 2. *European Journal of Nuclear Medicine and Molecular Imaging, 36*(12), 2103–2110. https://doi.org/10.1007/s00259-009-1264-0.

Volle, E., de Lacy Costello, A., Coates, L. M., McGuire, C., Towgood, K., Gilbert, S., Kinkingnehun, S., McNeil, J. E., Greenwood, R., Papps, B., van den Broeck, M., & Burgess, P. W. (2012). Dissociation between verbal response initiation and suppression after prefrontal lesions. *Cerebral Cortex, 22*, 2428–2440.

Yun, J. Y., Lee, D. Y., Seo, E. H., Choo, I. H., Park, S. Y., Kim, S. G., & Woo, J. I. (2011). Neural correlates of Stroop performance in Alzheimer's disease: a FDG-PET study. *Dementia Geriatric Cognitive Disorders Extra, 1*(1), 190–201. https://doi.org/10.1159/000329517.