Clinical Neurology and Neurosurgery 189 (2020) 105626

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

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

The influence of mental fatigue on the face and word encoding activations

Seyed Amir Hossein Batouli[a,b], Razieh Alemi[c,d,e], Haleh Khoshkhouy Delshad[f], Mohammad Ali Oghabian[b,g,*]

[a] Department of Neuroscience and Addiction Studies, School of Advanced Technologies in Medicine, Tehranf University of Medical Sciences, Tehran, Iran
[b] Neuroimaging and Analysis Group, Research Center for Molecular and Cellular Imaging, Tehran University of Medical Sciences, Tehran, Iran
[c] Department of Otolaryngology, Faculty of Medicine, McGill University, Montreal, QC, Canada
[d] Centre for Research on Brain, Language, and Music (CRBLM), Montreal, QC, Canada
[e] International Laboratory for Brain, Music, and Sound Research (BRAMS), Montreal, QC, Canada
[f] Department of Cognitive Science, Faculty of Human Sciences, Macquarie University, Australia
[g] Department of Medical Physics and Biomedical Engineering, Tehran University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Keywords:
Functional MRI
Mental fatigue
Episodic memory

ABSTRACT

Objectives: Memory is an important brain function, and is impaired with brain lesions. Resection of the lesion is one solution for that, but presurgical planning (PSP) is needed to guide the surgery for maximum removal of the lesion, as well as maximum preservation of the function. Functional Magnetic Resonance Imaging (fMRI) is one of the best approaches for such a purpose, but performing an fMRI study needs careful consideration of the factors which influence its results. Studies have shown that mental fatigue does have the potential to alter brain functions, and therefore this study aims to identify if mental fatigue should also be considered as a confounding factor when performing an fMRI study, particularly for clinical purposes.

Patients and methods: Using 57 healthy young volunteers, face and word encoding tasks were performed, with half of the participants performing the memory tasks after a set of language tasks and half of them before that.

Results: The results showed that mental fatigue led to increased activity in the bilateral thalamus and caudate in the face encoding task, and in the right thalamus, posterior cingulate and medial temporal lobe in word encoding. In addition, activation was declined with mental fatigue in the left lingual, precuneus, and posterior cingulate gyri in face encoding.

Conclusion: This study has shown the importance of the number and sequence of cognitive/mental tasks when performing an fMRI study, which could help to obtain more reliable fMRI maps in clinical applications. This finding is also important for performing research/cognitive studies using fMRI.

1. Introduction

Memory is a substantial part of our cognitive abilities, as it gives us the capability to learn, to adapt to new conditions by taking advantage of previous experiences, and to build new skills [1]. Brain lesions cause deficits in human memory by affecting the relevant brain regions, mostly observable in explicit (episodic) memories [2]. One solution to brain lesions is resection. Presurgical Planning (PSP) is a process performed to assess the feasibility of the surgical removal of brain tumors and tries to balance the maximum resection of the tumor while preserving the maximum function of the patient [3]. This is performed by identifying brain neural networks relevant to a specific function and then estimating the distance between the lesion and the eloquent brain areas for that function [4]. Functional Magnetic Resonance Imaging (fMRI) is currently one of the best non-invasive approaches for PSP purposes, as it can predict the potential risks of surgery on functional deficits [5], determine the dominant hemisphere of the brain for a function [4], and efficiently guide the neurosurgical procedure [6]; however, performing fMRI for PSP purposes needs a precise methodology [4], which should be considered.

Using fMRI needs careful attention to the confounding effects of external conditions. In a previous study of our group on 120 patients who had undergone presurgical planning by fMRI, the stimulus task, lesion location, and age showed significant influences on the fMRI results [4]; the influence of other factors such as task stimulus [7], task performance [8], fMRI data analysis method [9], and task types [10],

* Corresponding author at: Neuroimaging and Analysis Group (NIAG), Research Center for Molecular and Cellular Imaging (RCMCI), Tehran University of Medical Sciences (TUMS), Tehran, Iran.
E-mail address: oghabian@sina.tums.ac.ir (M.A. Oghabian).

https://doi.org/10.1016/j.clineuro.2019.105626
Received 30 August 2019; Received in revised form 23 November 2019; Accepted 27 November 2019
Available online 28 November 2019

are also reported. These show the importance of an optimal scanning situation to obtain reliable fMRI results, particularly for PSP purposes.

Mental fatigue could also be important in fMRI. Engaging in a continuous cognitive task increases the demand for more sources of fresh blood in the brain [11]; this raised demand following cognitive effort leads to a temporary effort-related fatigue, called fatigability [12,13]. Several definitions elucidate the state of fatigability, including a neurobiological perspective which explains this sense to be related to increasing of cytokines or chemokines in different brain areas following a period of keeping attention on doing an exercise [14,15].

Studies have tried to take advantage of non-invasive techniques to reach a uniform definition for this complicated feeling. For instance, Electro- and Magneto-encephalography studies have demonstrated the possibility of monitoring brain activation during fatigue condition by measuring the variation of power spectral densities of brain waveforms [16,17]. These studies showed that fatigue sensation could happen after listening to repeated sounds such as a metronome, in which insular cortex might be the key neural substrate for this feeling. Others showed that mental fatigue influences brain oscillatory activities, i.e., the beta wave, in precentral, right middle, or superior frontal gyri [17], and the prefrontal cortex [16]. fMRI offers more detailed information about the spatial localization of brain areas engaged in fatigability, and such studies have shown that fatigue has a widespread and non-specific effect on brain regions associated with working memory and executive functions, specifically in the parietal, cingulate, inferior frontal, superior temporal, and cerebellar areas [18,19].

The above reports show the association of mental fatigue with brain activation alteration. In PSP, some patients are needed to perform more than one fMRI task, either due to the lesion invading several brain regions associated with different functions, or because different aspects of a function may need to be tested; for example we showed that the word production, auditory responsive naming, and visual semantic decision tasks are needed when examining brain language areas [20]. Performing several cognitive tasks in a single fMRI session could cause mental fatigue, resulting in a different brain activation pattern compared to the situations with a limited number of tasks. This could mislead the surgical decision.

Due to the importance of a precise PSP, we were interested in determining the fatigability effects on the task-related brain activation maps. To do so, using 57 healthy young volunteers, we performed face- and word-encoding tasks randomly before or after performing a series of language tasks. Episodic memory plays an essential role in recalling events, objects, or people that we previously encountered, and it has been one of the primary functions usually tested in PSP. The principal aim of the study is to identify if brain activation patterns would alter when the number and sequence of fMRI tasks change, and this finding could be a help for fMRI applications in PSP.

2. Patients and methods

2.1. Participants

This study was performed under the Ethics Statement of Tehran University of Medical Sciences. All participants declared their assent during the telephone interview and after being informed about the general aims of the study, and they signed their consent forms on the test day. A gift card was presented to the participants for appreciation of their participation.

Recruitment of the participants was through public advertisement. An inclusion/exclusion questionnaire was prepared by a physician of the group and based on the criteria of the Iranian Brain Imaging Database [21]. It comprised the following sections: a) telephone screening, b) demographic and medical questionnaire, c) exclusion criteria, d) clinical assessments and e) Mini-Mental State Examination [22]. In summary, the inclusion criteria were: age range between 20 and 30 years old; being Right-handed (based on the Edinburgh Inventory [23]); minimum 14 years of education; and Persian race. The applicants were excluded due to any current or past chronic or acute Neurologic or Internal disorder, medicine consumption, surgery, or trauma; being overweight (over one-hundred Kilograms); having a severe family history of any disease; being smoker or drug/alcohol abuser; being claustrophobic; or having implants or any other metal objects in the body.

Based on the above criteria, we recruited 60 participants, of which 3 data were excluded due to excessive motion. This resulted in a sample size of 57 (28 M), with the mean age of 25.36 (± 3.1) years, and mean education of 16.72 (± 1.91) years. There were no significant male-female differences regarding age or education.

2.2. fMRI task stimuli

2.2.1. Memory tasks

As explained above, we targeted face- and word-encoding tasks for this study. For the face encoding task, we developed a database of pictures of unknown faces, with the following criteria: the included faces were not wearing glasses, had ordinary clothing and hairstyle, were of different races, were either neutral or smiling albeit with no emotional load, and the pictures were coloured. Based on that, 108 images were selected, which were implemented in a block-design paradigm. The task included 8 rest and 8 act blocks, starting with an additional 18 s rest for scanner transitions. The rest blocks were a black cross on a white background for 18 s. The act block, lasting for 36 s, included 9 faces, each for 4 s, being randomly selected and presented to the participant. Therefore, of the 108 faces, 72 faces were presented to the participant during the encoding phase in the MR scanner. The design of this paradigm was based on a number of previous works [24–26].

The paradigm of the word encoding task had a similar timing and design as the face encoding task. As a result, 108 words were selected, based on the Snodgrass & Wandervart database, normalized for the Iranian population and the Persian language [27], and the whole task lasted for 7:30 min.

Before imaging, the participants were instructed that they were required to memorize (encode) each item (face and word) and that they would be tested after the imaging session for the successful retrieval of the items. After the imaging, the participants were sitting in a quiet room, completing two tests with the 108 words and faces, with the exact timing of the main paradigm. They were asked to mark each face/word presented to them as “seen”, “not seen”, or “maybe seen”. Later, only the stimuli of the “seen” category were used for data analysis.

2.2.2. Mental fatigue

To study the association of mental fatigue with brain functionality during the encoding phase, the memory tasks were presented in two different modes. In the fatigue mode (FM), the subjects performed the memory tasks after they performed a set of language tests in the MRI scanner. In the non-fatigue mode (NFM), subjects performed the memory tasks before the language tests. Selecting either of the modes for a participant was random, and nearly 50 % of the participants were selected for the FM.

2.2.3. Language tasks

Word Production (WP), Auditory Responsive Naming (ARN), and Visual Semantic Decision (VSD) tasks were selected for the language tests. Details of these tasks have been published previously [4,20]. As a summary, the WP paradigm, mostly associated with speech production, included 4 control and 4 act blocks, each lasting 24 s, resulting in a total stimulus time of 3:12 min. Japanese alphabets were presented in control blocks, and Persian alphabets, which the participant had to add them together to produce a word and read silently, were presented in the act blocks. The ARN task, associated with the perception of meaningful short sentences, included presentation of multiple sounds lasting

for 3 s following by 3 s of silence. The sentences of the act block were between 6–9 syllables, and included implications such as "*This is the capital of Iran*" or "*This is the first season of the year*". This task also lasted for 3:12 min. The VSD task was to activate brain areas related to both language expression and perception, again with similar timing to the above. During the act block, 8 images, each lasting for 3 s, were presented to the participant. Each image included two words, which the participant had to read them and respond whether they could be regarded to be of the same category or not; examples for the same and different categories were "*food – pasta*", and "*food – shoe*", respectively.

2.3. Imaging

There had been a checklist to be followed by the examiner before each MRI scan. This list was designed to confirm performance of the telephone screening, not consumption of any doping food or medicine such as coffee or alcohol on the exam day, not consumption of any antineuropathic pain drug, performance of clinical checks by the physician, setting lenses for a better visualization of the goggle (if required) as well as goggle cleanness, training the participant with his/her fMRI tasks, asking the participant to respond silently to the questions with no mouth motion, setting the headset volume on a preset level, and accurate performance of the response box.

Magnetic Resonance Imaging of the brain was carried out using a SIEMENS 3 T MRI scanner (MAGNETOM Trio; Siemens Healthcare GmbH, Federal Republic of Germany) with an 8-channel head coil at the Medical Imaging Center, Imam Khomeini Hospital, Tehran, Iran. A 32-channel head coil was also available; however, the smaller size of this coil limited the use of goggles and headphones for the participant. Functional T2*-weighted images were collected using blood oxygen level dependent (BOLD) contrast (TR = 3000 ms, TE = 30 ms, flip angle = 90degree, FOV = 192mm^2, matrix size = 64 × 64, voxel size = 3 × 3 × 3 mm, slice thickness = 3 mm, and slice gap = 0 mm). Prior to the functional scan, a T1-weighted anatomical volume was acquired, using a gradient echo pulse sequence (TR = 1800 ms, TE = 3.44 ms, flip angle = 7degree, voxel size = 1 × 1 × 1 mm, FOV = 256mm^2, matrix size = 256 × 256, slice thickness = 1 mm and slice gap = 0 mm). After the scan, the participant was questioned about clear presentation of the visual and auditory stimulus during the exam.

To present the images and sounds to the participants during the scan, a goggle (800*600 pixel resolution in a 0.25 square area and refresh rate of up to 85 Hz) and earphone (30 dB noise-attenuating headset with 40 Hz to 40 kHz frequency response), which were suitable for up to 4.7 T magnetic fields were used (VisuaStim, The Pennsylvania State University, USA). Presentation of fMRI tasks to the participant was synchronized with the scanning, using the trigger pulse of the MRI scanner.

2.4. Data analysis

2.4.1. Pre-processing

All MRI data preprocessing was conducted in FSL (the FMRIB Software Library) v5.0.8[1] [28]. First, fieldmap-based unwarping of EPI data was applied using PRELUDE + FUGUE [29]. Next, motion correction was performed using MCFLIRT [30]. To prepare statistical group analyses all images were normalized to the 152-brain T1-weighted Montreal Neurological Institute (MNI) template using FLIRT [30,31] in two steps: first, an example fMRI image was registered to the same individual's high-resolution T1-weighted image using BBR algorithm; second, the high-resolution image was registered to the standard MNI template using a 12 DOF linear transformation. These two steps were then combined into one registration matrix which was used to register the EPI images into the MNI space. Coordinates (x, y, z) of activity are therefore reported here in the MNI space. All registration results were manually inspected to guarantee valid registration. Finally, the images were spatially smoothed using a Gaussian kernel with a Full Width at Half Maximum (FWHM) value of 5 mm. Structural images were skull-stripped using BET [32] and segmented into white matter (WM), gray matter (GM), and cerebrospinal fluid (CSF) using FAST [33]. The individuals' binarized GM, WM, and CSF masks were projected to the MNI space using inverse registration matrices that were created earlier and then were averaged to generate study-specific templates of different tissue types.

2.4.2. General linear model

The statistical analysis of time-series was carried out using FILM (FMRIB Improved Linear Model) pre-whitening to make the statistical approaches valid and maximally efficient, and a "z-score" was devoted to the corresponding BOLD signal. Although the paradigms were of block-design, the analysis was performed as an event-related paradigm, so that only those stimuli (faces/words) which were successfully encoded were included in the analysis. Next, cluster thresholding was carried out to reveal clusters that were significantly activated. Clusters with a z-stat greater than 2.6 and with a p-value less than 0.001 were considered to be significantly activated. Six contrasts were tested: I) face encoding network; II) word encoding network; III) FM > NFM in face encoding; IV) NFM > FM in face encoding; V) FM > NFM in word encoding; VI) NFM > FM in word encoding. Higher level analyses were later performed using FLAME (FMRIB's Local Analysis of Mixed Effects) for all the six contrasts, and with a p-value < 0.001.

3. Results

3.1. Face and word encoding networks

The maps relevant to brain activations during the face encoding stimulus are provided in Fig. 1. Multiple brain regions were observed active, with the characteristics of the activations provided in Table 1. Accordingly, brain areas involved in face encoding and in the NFM were bilateral fusiform gyrus (G.), precentral G., middle frontal G. (MFG), inferior frontal G. (IFG), postcentral G., intracalcarine G., cuneus, precuneus, lingual G., hippocampus, parahippocampus, amygdala, posterior cingulate cortex (PCC), pallidum, thalamus, and left paracingulate and superior frontal G. (SFG). Similarly, a number of brain areas were active during the same stimulus and in the FM including bilateral lingual G., IFG, MFG, Precentral G., thalamus, amygdala, hippocampus, parahippocampus, fusiform G., PCC, right frontal pole and right orbitofrontal G., as well as the left occipital (Occ.) pole and the putamen.

The maps of brain activations relevant to the word encoding stimulus are also provided in Fig. 2. As it illustrates, and in more detail in Table 1, the brain areas active during this stimulus and in the NFM were bilateral inf. Occ. and fusiform, right anterior (ant.) cingulate, and left hippocampus, parahippocampus, thalamus, insula, precentral G., paracingulate, MFG, postcentral G., lingual G, and caudate. In addition, active brain areas in the FM included bilateral fusiform, and left hippocampus, thalamus, inferior Occ., IFG, MFG, precentral G., superior Occ., paracingulate, superior frontal G. (SFG), and supplementary motor area (SMA).

3.2. Fatigue vs. non-fatigue mode

Our analysis included a contrast between the FM and NFM in both the face and word encoding tasks, to investigate the fatigue effects. As a result, and in the face encoding condition, bilateral thalamus and caudate, as well as the right putamen, SFG, and pallidum showed higher activations in the FM, compared to NFM (Fig. 1.d). On the other hand, left lingual G., precuneus, and PCC showed a higher level of activation in the NFM (Fig. 1.e).

[1] http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/

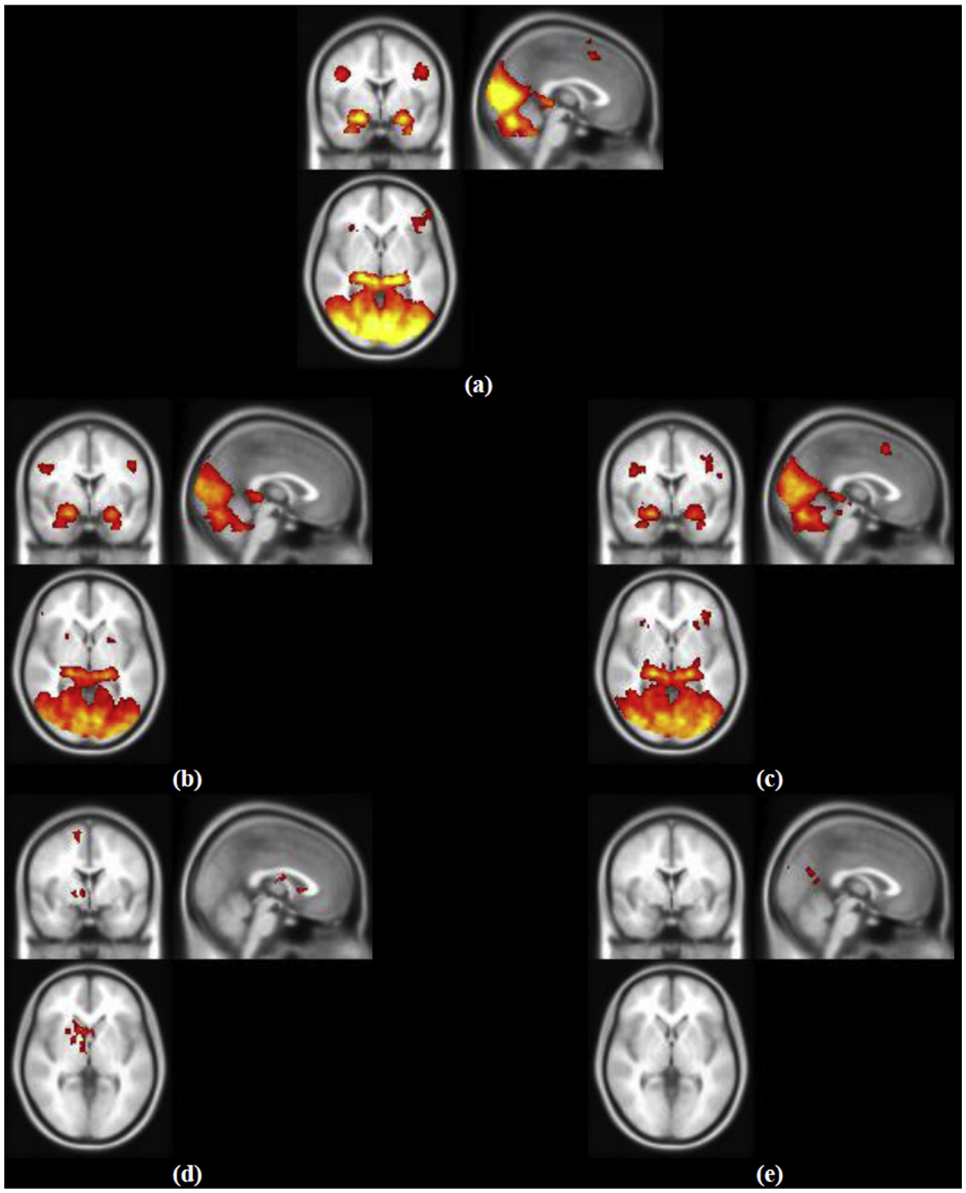

Fig. 1. Brain activation maps relevant to the 5 conditions of the face encoding stimulus; brain activations of a) the FM and NFM together; b) only the FM; c) only the NFM; d) the contrast of FM > NFM; e) the contrast of NFM > FM; FM: fatigue mode; NFM: non fatigue mode.

For the word encoding stimulus, we observed no areas with a higher activation in the NFM (Fig. 1.e), whereas right PCC, thalamus, middle temporal G. (MTG), SFG, and supramarginal G. showed higher activation in the FM (Fig. 1.d). All these results and differences were statistically significant, and the details are provided in Table 1.

4. Discussion

4.1. Summary of the results

The aim of this study was to examine if mental fatigue would alter the brain activations reported by fMRI. For this aim, we used face and word encoding tasks before and after a set of language stimuli, and the results showed that mental fatigue leads to increased activity in the bilateral thalamus and caudate in the face encoding task, and the right thalamus, PCC, and MTG in the word encoding task. In addition, activation was declined with mental fatigue in the left lingual G., precuneus, and PCC in face encoding, whereas no such effect was found in word encoding.

4.2. The importance of episodic memory

In this study, we examined the influence of mental fatigue on face and word encoding activations, which are subcategories of the episodic memory. The brain receives and registers information during encoding, and therefore encoding is the initial step in episodic memory. Performing episodic memory tasks for PSP, particularly when temporal structures are affected, is suggested in the previous reports [34,35]. Examples include the studies which have suggested examining face encoding brain areas during PSP for patients with right mesial temporal pathology, and similarly the word encoding tasks for patients with left mesial temporal pathology [36]. Another advantage of these tasks would be their ability to differentiate between the familiarity and recollection processes, both dependent to the temporal lobe structures; examples include perirhinal cortex which contributes to familiarity-based recognition [37], and lateral entorhinal which encodes information of distinct items (e.g., people, objects, events) and is involved in the recovery of specific item-item associations. These are all in addition to the importance of these functions in our daily life.

Table 1
The results of brain activations in the face and word encoding tasks, and in the 4 contrasts of FM, NFM, FM > NFM, and NFM > FM.

Task	Cluster	# voxels	Z-max	X,Y,Z	Cluster	# voxels	Z-max	X,Y,Z
Face Encoding	**FM- Average**				**NFM- Average**			
	1	32786	7.6	−24,-96,4	1	37079	8.3	−40,-80,-6
	2	1748	5.1	48,14,30	2	1516	5.3	42,8,30
	3	696	4.2	42,18,24	3	1328	5.4	44,10,28
	4	286	3.9	26,36,-22	4	441	4.5	6,16,50
	Brain areas: B lingual G.; B IFG; B MFG; B Precentral G.; B thalamus; B amygdala; B hippocampus; B parahippocampus; B fusiform G.; B PCC; R frontal pole; R orbitofrontal G.; L Occ pole; L putamen				**Brain areas:** B fusiform G.; B precentral G.; B MFG; B IFG; B postcentral G.; B intracalcarine G.; B cuneus; B precuneus; B lingual G.; B hippocampus; B parahippocampus; B amygdala; B PCC; B pallidum; B thalamus; L paracingulate; L SFG			
	FM > NFM				**NFM > FM**			
	1	469	4.4	18,16,8	1	547	4.7	16,-52,8
	2	295	6.4	16,18,58				
	Brain areas: B thalamus; B caudate; R putamen; R SFG; R pallidum				**Brain areas:** L lingual G.; L. precuneus; L PCC			
Word Encoding	**FM- Average**				**NFM- Average**			
	1	4724	6.9	−22,-98,0	1	7263	7.6	−36,-84,-6
	2	3483	6.1	40,-80,-10	2	5101	6.3	32,-90,2
	3	2903	5.1	−34,18,30	3	4558	5.2	−28,28,2
	4	607	3.9	−30,-58,46	4	1492	4.8	−26,-68,50
	5	435	3.5	−4,24,46	5	510	4.4	8,4,28
	Brain areas: B fusiform; L hippocampus; L thalamus; L inf Occ; L IFG; L MFG; L precentral G.; L sup Occ; L paracingulate; L SFG; L SMA				6	327	3.9	−16,-54,-14
					7	314	3.8	26,-66,10
					Brain areas: B Inf. Occ.; B fusiform; R ant cingulate; L hippocamp; L parahippocamp; L thalamus; L insula; L precentral G.; L paracingulate; L MFG; L postcentral G.; lingual G; L caudate			
	FM > NFM				**NFM > FM**			
	1	416	5.7	12,-24,38	No Effect.			
	2	305	5.9	62,-34,22				
	3	303	5.4	12,36,48				
	Brain areas: R PCC; R thalamus; R MTG; R SFG; R supramarginal G.							

Each activation pattern is reported by the number of clusters, number of voxels in each cluster, maximum z-value of the cluster, and the coordinates (x,y,z) of the voxel with the highest z-value in the cluster.
FM: fatigue mode; NFM: non-fatigue mode; B: bilateral; R: right; L: left; G: gyrus.

4.3. The involved brain regions

Neuroimaging reports have indicated a complex neural basis for encoding episodic memory, albeit with some disputes related to the hemispheric laterality of them, or the manner of interaction between the cortical and subcortical brain structures [38]; however, the brain regions which were among the most agreed responsible regions for encoding episodic memory included prefrontal cortex, medial temporal lobe, posterior parietal, and posterior cingulate cortices [39–42].

In our word encoding task, we found more unilateral activations in the left hemisphere in the hippocampus, parahippocampus, thalamus, caudate, precentral, MFG, and SMG. This hemispheric specialization and left-lateralized dominance for word encoding are documented in numerous previous studies [43,44]; an example is the essential roles of left SMG in word and phonological processing [45]. In an fMRI study with a large sample size, Szaflarski et al. [46] showed that language lateralization occurs during development and finalizes in early adulthood. Similarly, in a recent neurophysiological study, Dundas et al. [47] claimed that the left-lateralized activation following word stimuli is an adulthood pattern in which the brain is trained to devote the areas proximal to the language-related regions of the left hemisphere to literacy processing. The same study has also shown that the homologous areas of these regions in the right hemisphere are involved in face processing. This pattern of selectivity has been observed in our results as well, where the word encoding task activated left SMG, and the face encoding task activated bilateral precuneus and cuneus areas; we found more bilateral brain activations in our face encoding tasks which included a network of precentral and postcentral gyri, middle and inferior frontal gyri, cuneus and precuneus, along with activations in the hippocampus, parahippocampus, thalamus, pallidum, and amygdala, similar to older reports [48,49]. The involvement of precuneus/cuneus areas in the face and visual perception are also documented previously [43].

In addition, both our word and face encoding tasks activated bilateral fusiform areas; this is in opposite to the previous reports on the different functional roles of the right and left fusiform areas, known as the fusiform face area (FFA) and the visual word form area (VWFA), respectively [50]. Similar to our results, other studies have also indicated that the FFA and VWFA refer to the overlapping bilateral areas, proposing that they might share neural processes [51,52]. However, due to different methodologies and materials, which impact the symmetry of brain activations [53,54], these regions might show priority to process word or face stimuli, and subsequently, this primacy could cause a different laterality or robustness in the brain activation pattern [55,56]. We believe that bilateral activations of fusiform gyrus in both face and word encoding tasks might be related to different, yet overlapping, neural processing procedures. It is recently suggested that assigning labels, face vs. word, to the input stimulus is a researcher-related matter, while brain computes stimuli in a complex and vast neural network, using shared sources [57,58].

4.4. Fatigue influences functionality

There is evidence that fatigue plays a pivotal role in the cognitive control system, e.g., where it signals the anterior cingulate cortex on how to manage the effort and its reward [59]. Analysis of functional networks of the brain has indicated that connections between the frontal and temporal brain regions, and within the frontoparietal network, have a role in the cognitive decline and fatigue sense [60], suggesting that fatigue might impose broad effects on different brain areas, and can change the performance in the cognitive activities.

Mental fatigue led to increased excitability of particular brain areas in our results. In comparison to NFM in face encoding task, we found higher activations in the right superior frontal gyrus and subcortical structures including right putamen, pallidum, and bilateral thalamus and caudate in FM. Similarly, right PCC, thalamus, MTG, SFG, and

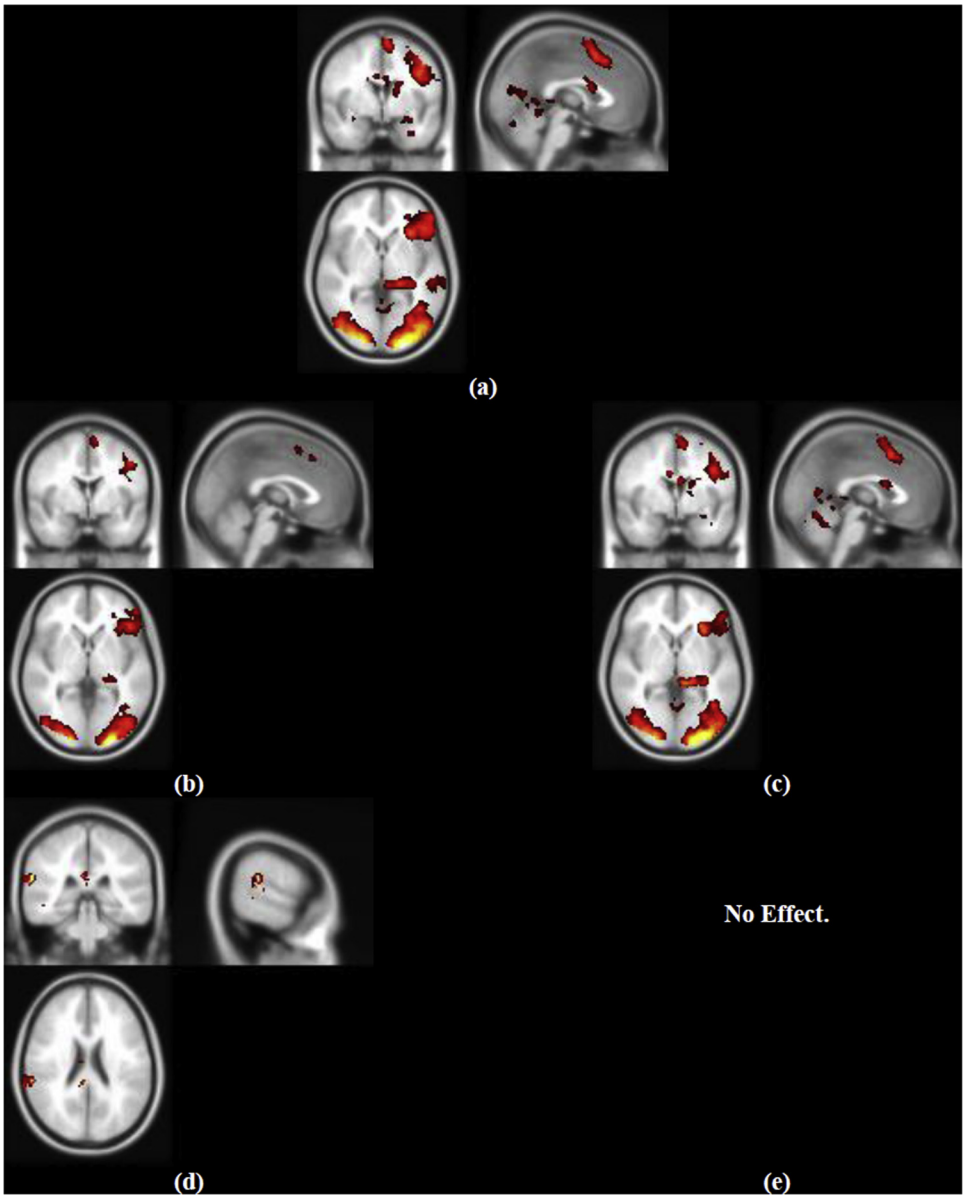

Fig. 2. Brain activation maps relevant to the 5 conditions of the word encoding stimulus; brain activations of a) the FM and NFM together; b) only the FM; c) only the NFM; d) the contrast of FM > NFM; e) the contrast of NFM > FM; FM: fatigue mode; NFM: non fatigue mode.

supramarginal G. showed higher activations in the FM of word encoding task. Increased activation in the right SFG, in FM of both tasks, could be related to the critical role of this area in sustained attention [61,62]; our participants intended to keep their attention on the task and encode the materials. However, due to the finite capacity of the brain for processing the presented materials at a limited time [63], the brain tries to recruit more areas as a help to continue the encoding [64]. This further engagement of brain areas and the internally imposed effort demand extra sources of blood, which is one possible reason for fatigability.

Besides, we found increased activation in subcortical brain areas during the FM. Recent studies have indicated that basal ganglia has connections with the hippocampus and hence this area might have prominent roles in memory consolidation and most specifically in encoding favored events [65,66]. Besides, it has been shown that motivation for memorizing preferred materials is related to the network of hippocampus-basal ganglia [67]; functional and structural connections between the frontal lobe, thalamus, and basal ganglia are also reported [68]. All these support the involvement of subcortical brain structures during encoding of visually presented items, and there is evidence for the alteration of the activation of subcortical brain regions with fatigability [69,70].

4.5. Strength and limitations

The current experiment provided evidence that fatigue plays a pivotal role in the cognitive control system of the brain, and causes changes in the level and network of its functionality, the finding which could be very helpful in both clinical and research applications of fMRI. The study used strict criteria for inclusion of healthy participants and included a considerable number of subjects, used a 3 T MRI machine as well as robust data analysis methods, and its language tasks had been validated in previous studies [4,20]. Despite these efforts to obtain reliable findings, there have been a number of limitations with the study. Although we aimed to study the neural mechanisms of mental fatigue, testing this hypothesis on the exact target group, i.e., patients who will undergo PSP, would obtain more accurate results. Also, although both groups were of the same demographics, the influence of

between-subject variations on the final results could not be neglected. Providing a behavioural measure for mental fatigue could strengthen our claim on the induction of mental fatigue. Human memory includes a large number of steps and functions, and replicating this study with other forms of memory such as semantic memory or other steps of it such as retrieval would be beneficial. And finally, the interpretation of our findings should be made with caution, as the specific strategy of each individual for encoding materials could alter and modulate the number of engaged brain areas in that function [71].

Author contribution

Seyed Amir Hossein Batouli: Performed the imaging and data analysis, prepared the manuscript

Razieh Alemi: Prepared the manuscript, prepared the language tasks

Haleh Khoshkhouy Delshad: Collected the data, analyzed the data, prepared the memory tasks

Mohammad Ali Oghabian: Supervised the project

Funding

Iranian Council for Cognitive Sciences and Technologies provided financial support for this study (grant number: 875). They had no role in the design or conduct of this research.

Ethics approval

All procedures performed in this study were in accordance with the ethical standards of Tehran University of Medical Sciences, based on the Helsinki declaration.

Informed consent

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

The authors of this manuscript have no conflicts of interest. All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Declaration of Competing Interest

The authors of this manuscript have no conflicts of interest. All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

References

[1] SeyedAmir Hossein Batouli, Minoo Sisakhti, Investigating a hypothesis on the mechanism of long-term memory storage, NeuroQuantology 17 (3) (2019) Retrieved https://www.neuroquantology.com/index.php/journal/article/view/1813/1346.

[2] E. Tramoni-Negre, I. Lambert, F. Bartolomei, O. Felician, Long-term memory deficits in temporal lobe epilepsy, Rev. Neurol. 173 (7) (2017) 490–497 Retrieved http://www.sciencedirect.com/science/article/pii/S0035378717305192.

[3] Michael Deppe, E. Bernd Ringelstein, Stefan Knecht, The investigation of functional brain lateralization by transcranial doppler sonography, NeuroImage 21 (3) (2004) 1124–1146 Retrieved June 20, 2015 http://www.ncbi.nlm.nih.gov/pubmed/15006680).

[4] SeyedAmir Hossein Batouli, Nafiseh Hasani, Sara Gheisari, Ebrahim Behzad, Mohammad Ali Oghabian, Evaluation of the factors influencing brain language laterality in presurgical planning, Phys. Med. 32 (10) (2016) 1201–1209 Retrieved http://www.sciencedirect.com/science/article/pii/S112017971630120X.

[5] Monica Baciu, Alexandra Juphard, Emilie Cousin, Jean François Le Bas, Evaluating FMRI methods for assessing hemispheric language dominance in healthy subjects, Eur. J. Radiol. 55 (2) (2005) 209–218 Retrieved June 24, 2014 http://www.ncbi.nlm.nih.gov/pubmed/16036149.

[6] Jeffrey R. Petrella, et al., Preoperative functional MR imaging localization of language and motor areas: effect on therapeutic decision making in patients with potentially resectable brain tumors, Radiology 240 (3) (2006) 793–802.

[7] Domenico Zacà, JoshuaP. Nickerson, Gerard Deib, Jay J. Pillai, Effectiveness of four different clinical FMRI paradigms for preoperative regional determination of language lateralization in patients with brain tumors, Neuroradiology 54 (9) (2012) 1015–1025, https://doi.org/10.1007/s00234-012-1056-2 Retrieved.

[8] Bernd Weber, et al., Presurgical language FMRI in patients with drug-resistant epilepsy: effects of task performance, Epilepsia 47 (5) (2006) 880–886 Retrieved http://www.ncbi.nlm.nih.gov/pubmed/16686653.

[9] M. Caulo, et al., Comparison of hypothesis- and a novel hybrid data/hypothesis-driven method of functional MR imaging analysis in patients with brain gliomas, AJNR Am. J. Neuroradiol. 32 (6) (2011) 1056–1064 Retrieved June 24, 2014 http://www.ncbi.nlm.nih.gov/pubmed/21393411.

[10] C. Rosazza, et al., Preoperative language lateralization in temporal lobe epilepsy (TLE) predicts peri-ictal, pre- and post-operative language performance: an FMRI study, Neuroimage Clin. 3 (2013) 73–83 Retrieved March 21, 2015 http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3807502&tool=pmcentrez&rendertype=abstract.

[11] Matthew T. Gailliot, Roy F. Baumeister, The physiology of willpower: linking blood glucose to self-control, Personal. Soc. Psychol. Rev. 11 (4) (2007) 303–327, https://doi.org/10.1177/1088868307303030 Retrieved.

[12] Maarten A.S. Boksem, Mattie Tops, Mental fatigue: costs and benefits, Brain Res. Rev. 59 (1) (2008) 125–139 Retrieved http://www.sciencedirect.com/science/article/pii/S0165017308000714.

[13] BenziM. Kluger, Lauren B. Krupp, Roger M. Enoka, Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy, Neurology 80 (4) (2013) 409–416 Retrieved https://www.ncbi.nlm.nih.gov/pubmed/23339207).

[14] Robert Dantzer, Cobi Johanna Heijnen, Annemieke Kavelaars, Sophie Laye, Lucile Capuron, The neuroimmune basis of fatigue, Trends Neurosci. 37 (1) (2014) 39–46 Retrieved https://www.ncbi.nlm.nih.gov/pubmed/24239063.

[15] Mary E. Harrington, Exercise strengthens circadian clocks, J. Physiol. 590 (23) (2012) 5929, https://doi.org/10.1113/jphysiol.2012.245308 Retrieved.

[16] Akira Ishii, Tanaka Masaaki, Watanabe Yasuyoshi, Neural mechanisms of mental fatigue, Rev. Neurosci. 25 (2014) 469 Retrieved https://www.degruyter.com/view/j/revneuro.2014.25.issue-4/revneuro-2014-0028/revneuro-2014-0028.xml.

[17] Yoshihito Shigihara, et al., Two types of mental fatigue affect spontaneous oscillatory brain activities in different ways, Behav. Brain Funct. 9 (1) (2013) 2, https://doi.org/10.1186/1744-9081-9-2 Retrieved.

[18] MonicqueM. Lorist, et al., The influence of mental fatigue and motivation on neural network dynamics; an EEG coherence study, Brain Res. 1270 (2009) 95–106 Retrieved http://www.sciencedirect.com/science/article/pii/S0006899309005162.

[19] Yu Sun, Julian Lim, Kenneth Kwok, Anastasios Bezerianos, Functional Cortical Connectivity Analysis of Mental Fatigue Unmasks Hemispheric Asymmetry and Changes in Small-World Networks, (2014).

[20] Razieh Alemi, SeyedAmir Hossein Batouli, Ebrahim Behzad, Mitra Ebrahimpoor, Mohammad Ali Oghabian, Not single brain areas but a network is involved in language: applications in presurgical planning, Clin. Neurol. Neurosurg. 165 (2018) 116–128.

[21] SeyedAmir Hossein Batouli, et al., Iranian brain imaging database (IBID): a neuropsychiatric database of healthy brain, Basic Clin. Neurosci. (2019) In Press.

[22] M.F. Folstein, S.E. Folstein, P.R. McHugh, 'Mini-Mental state'. A practical method for grading the cognitive state of patients for the clinician, J. Psychiatr. Res. 12 (3) (1975) 189–198.

[23] R.C. Oldfield, The assessment and analysis of handedness: the Edinburgh inventory, Neuropsychologia 9 (1) (1971) 97–113 Retrieved http://linkinghub.elsevier.com/retrieve/pii/0028393271900674%5Cnpapers3://publication/doi/10.1016/0028-3932(71)90067-4.

[24] AnanthaP.P. Anilkumar, et al., An FMRI study of face encoding and recognition in first-episode schizophrenia, Acta Neuropsychiatr. 20 (3) (2008) 129–138 Retrieved https://www.cambridge.org/core/article/an-fmri-study-of-face-encoding-and-recognition-in-firstepisode-schizophrenia/A3E27E5D33DA0222CDA48AFD7AD9E83F.

[25] Maria A. Rocca, et al., Mapping face encoding using functional MRI in multiple sclerosis across disease phenotypes, Brain Imaging Behav. 11 (5) (2017) 1238–1247, https://doi.org/10.1007/s11682-016-9591-9 Retrieved.

[26] R.A. Sperling, et al., FMRI studies of associative encoding in young and elderly controls and mild Alzheimer's disease, J. Neurol. Neurosurg. Psychiatr. 74 (1) (2003) 44 LP-50. Retrieved http://jnnp.bmj.com/content/74/1/44.abstract.

[27] Mehdi Bakhtiar, Reza Nilipour, Brendan S. Weekes, Predictors of timed picture naming in Persian, Behav. Res. Methods 45 (3) (2013) 834–841, https://doi.org/10.3758/s13428-012-0298-6 Retrieved.

[28] Mark Jenkinson, Christian F. Beckmann, Timothy E.J. Behrens, Mark W. Woolrich, Stephen M. Smith, FSL, NeuroImage 62 (2) (2012) 782–790.

[29] Mark. Jenkinson, Fast, automated, N-Dimensional phase-unwrapping algorithm,

Magn. Reson. Med. 49 (1) (2003) 193–197.
[30] Mark Jenkinson, Peter Bannister, Michael Brady, Stephen Smith, Improved optimization for the robust and accurate linear registration and motion correction of brain images, NeuroImage 17 (2) (2002) 825–841.
[31] M. Jenkinson, S. Smith, A global optimisation method for robust affine registration of brain images, Med. Image Anal. 5 (2) (2001) 143–156.
[32] M. Jenkinson, M. Pechaud, S. Smith, BET2: MR-Based Estimation of Brain, Skull and Scalp Surfaces, (2005).
[33] Y. Zhang, M. Brady, S. Smith, Segmentation of brain MR images through a hidden markov random field model and the expectation-maximization algorithm, IEEE Trans. Med. Imaging 20 (1) (2001) 45–57.
[34] Jeffrey R. Binder, Preoperative prediction of verbal episodic memory outcome using FMRI, Neurosurg. Clin. N. Am. 22 (2) (2011) 219–ix. Retrieved https://www.ncbi.nlm.nih.gov/pubmed/21435573.
[35] Woorim Jeong, ChunKee Chung, June Sic Kim, Episodic memory in aspects of large-scale brain networks, Front. Hum. Neurosci. 9 (2015) 454 Retrieved https://www.frontiersin.org/article/10.3389/fnhum.2015.00454.
[36] Silvia B. Bonelli, et al., Imaging memory in temporal lobe epilepsy: predicting the effects of temporal lobe resection, Brain 133 (4) (2010) 1186–1199 Retrieved http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2850579/.
[37] Wei-Chun Wang, Charan Ranganath, Andrew P. Yonelinas, Activity reductions in perirhinal cortex predict conceptual priming and familiarity-based recognition, Neuropsychologia 52 (2014) 19–26 Retrieved https://www.ncbi.nlm.nih.gov/pubmed/24157537.
[38] Melina R. Uncapher, LeunJ. Otten, Michael D. Rugg, Episodic encoding is more than the sum of its parts: an FMRI investigation of multifeatural contextual encoding, Neuron 52 (3) (2006) 547–556 Retrieved https://www.ncbi.nlm.nih.gov/pubmed/17088219.
[39] Robert S. Blumenfeld, Charan Ranganath, Prefrontal cortex and long-term memory encoding: an integrative review of findings from neuropsychology and neuroimaging, Neuroscientist 13 (3) (2007) 280–291, https://doi.org/10.1177/1073858407299290 Retrieved.
[40] H. Eichenbaum, A.P. Yonelinas, C. Ranganath, The medial temporal lobe and recognition memory, Annu. Rev. Neurosci. 30 (2007) 123–152 Retrieved https://www.ncbi.nlm.nih.gov/pubmed/17417939.
[41] R.J. Maddock, A.S. Garrett, M.H. Buonocore, Remembering familiar people: the posterior cingulate cortex and autobiographical memory retrieval, Neuroscience 104 (3) (2001) 667–676 Retrieved http://www.sciencedirect.com/science/article/pii/S0306452201001087.
[42] Melina R. Uncapher, Anthony D. Wagner, Posterior parietal cortex and episodic encoding: insights from FMRI subsequent memory effects and dual-attention theory, Neurobiol. Learn. Mem. 91 (2) (2009) 139–154 Retrieved https://www.ncbi.nlm.nih.gov/pubmed/19028591.
[43] A.J. Golby, et al., Material-specific lateralization in the medial temporal lobe and prefrontal cortex during memory encoding, Brain 124 (2001) 1841–1854.
[44] Urs Maurer, Bruno Rossion, Bruce D. McCandliss, Category specificity in early perception: face and word N170 responses differ in both lateralization and habituation properties, Front. Hum. Neurosci. 2 (2008) 18 Retrieved https://www.ncbi.nlm.nih.gov/pubmed/19129939.
[45] M. Oberhuber, et al., Four functionally distinct regions in the left supramarginal gyrus support word processing, Cereb. Cortex 26 (11) (2016) 4212–4226, https://doi.org/10.1093/cercor/bhw251 Retrieved.
[46] Jerzy P. Szaflarski, Scott K. Holland, Vincent J. Schmithorst, Anna W. Byars, FMRI study of language lateralization in children and adults, Hum. Brain Mapp. 27 (3) (2006) 202–212 Retrieved https://www.ncbi.nlm.nih.gov/pubmed/16035047.
[47] Eva M. Dundas, David C. Plaut, Marlene Behrmann, An ERP investigation of the co-development of hemispheric lateralization of face and word recognition, Neuropsychologia 61 (2014) 315–323 Retrieved https://www.ncbi.nlm.nih.gov/pubmed/24933662.
[48] Andrea E. Cavanna, Michael R. Trimble, The precuneus: a review of its functional anatomy and behavioural correlates, Brain 129 (3) (2006) 564–583, https://doi.org/10.1093/brain/awl004 Retrieved.
[49] TiloT.J. Kircher, et al., Towards a functional neuroanatomy of self processing: effects of faces and words, Cogn. Brain Res. 10 (1) (2000) 133–144 Retrieved http://www.sciencedirect.com/science/article/pii/S0926641000000367.
[50] Chris I. Baker, et al., Visual word processing and experiential origins of functional selectivity in human extrastriate cortex, Proc. Natl. Acad. Sci. U. S. A. 104 (21) (2007) 9087–9092 Retrieved https://www.ncbi.nlm.nih.gov/pubmed/17502592.
[51] Florence Bouhali, et al., Anatomical connections of the visual word form area, J. Neurosci. 34 (46) (2014) 15402 LP-15414. Retrieved http://www.jneurosci.org/content/34/46/15402.abstract.
[52] Richard J. Harris, Grace E. Rice, Andrew W. Young, Timothy J. Andrews, Distinct but overlapping patterns of response to words and faces in the fusiform gyrus, Cereb. Cortex 26 (7) (2016) 3161–3168 Retrieved https://www.ncbi.nlm.nih.gov/pubmed/26157025.
[53] Donald J. Bolger, Charles A. Perfetti, Walter Schneider, Cross-cultural effect on the brain revisited: universal structures plus writing system variation, Hum. Brain Mapp. 25 (1) (2005) 92–104, https://doi.org/10.1002/hbm.20124 Retrieved.
[54] Meike Ramon, Laurence Dricot, Bruno Rossion, Personally familiar faces are perceived categorically in face-selective regions other than the fusiform face area, Eur. J. Neurosci. 32 (9) (2010) 1587–1598, https://doi.org/10.1111/j.1460-9568.2010.07405.x Retrieved.
[55] Doris Y. Tsao, Sebastian Moeller, Winrich A. Freiwald, Comparing face patch systems in macaques and humans, Proc. Natl. Acad. Sci. 105 (49) (2008) 19514 LP-19519. Retrieved http://www.pnas.org/content/105/49/19514.abstract.
[56] Brian A. Wandell, Andreas M. Rauschecker, Jason D. Yeatman, Learning to see words, Annu. Rev. Psychol. 63 (2012) 31–53 Retrieved https://www.ncbi.nlm.nih.gov/pubmed/21801018.
[57] Kendrick N. Kay, Jason D. Yeatman, Bottom-up and top-down computations in word- and face-selective cortex edited by J. I. Gold, eLife 6 (2017) e22341, , https://doi.org/10.7554/eLife.22341 Retrieved.
[58] Adrian Nestor, Marlene Behrmann, David C. Plaut, The neural basis of visual word form processing: a multivariate investigation, Cereb. Cortex 23 (7) (2013) 1673–1684, https://doi.org/10.1093/cercor/bhs158 Retrieved.
[59] Glenn R. Wylie, Laura A. Flashman, Understanding the interplay between mild traumatic brain injury and cognitive fatigue: models and treatments, Concussion (London, England) 2 (4) (2017) CNC50-CNC50. Retrieved https://www.ncbi.nlm.nih.gov/pubmed/30202591.
[60] Fumihiko Taya, et al., Fronto-Parietal Subnetworks Flexibility Compensates For Cognitive Decline Due To Mental Fatigue, (2018).
[61] Elise Demeter, Luis Hernandez-Garcia, Martin Sarter, Cindy Lustig, Challenges to attention: a continuous arterial spin labeling (ASL) study of the effects of distraction on sustained attention, NeuroImage 54 (2) (2011) 1518–1529 Retrieved https://www.ncbi.nlm.nih.gov/pubmed/20851189.
[62] Natalia S Lawrence, Thomas J. Ross, Ray Hoffmann, Hugh Garavan, Elliot Stein, Multiple Neuronal Networks Mediate Sustained Attention, (2003).
[63] Neil W Mulligan, Pietro Spataro, Divided Attention Can Enhance Early-Phase Memory Encoding: The Attentional Boost Effect and Study Trial Duration, (2014).
[64] Harold Pashler, Dual-task interference in simple tasks: data and theory, Psychol. Bull. 116 (1994) 220–244.
[65] Yuhua Guo, Taylor W. Schmitz, Marieke Mur, Catarina S. Ferreira, Michael C. Anderson, A supramodal role of the basal ganglia in memory and motor inhibition: meta-analytic evidence, Neuropsychologia 108 (2018) 117–134 Retrieved https://www.ncbi.nlm.nih.gov/pubmed/29199109.
[66] Raphael Koster, Marc Guitart-Masip, Raymond J. Dolan, Emrah Düzel, Basal ganglia activity mirrors a benefit of action and reward on long-lasting event memory, Cereb. Cortex 25 (12) (2015) 4908–4917 Retrieved https://www.ncbi.nlm.nih.gov/pubmed/26420783.
[67] Niels Hansen, Denise Manahan-Vaughan, Dopamine D1/D5 receptors mediate informational saliency that promotes persistent hippocampal long-term plasticity, Cereb. Cortex 24 (4) (2014) 845–858 Retrieved https://www.ncbi.nlm.nih.gov/pubmed/23183712.
[68] Garrett E. Alexander, Michael D. Crutcher, Functional architecture of basal ganglia circuits: neural substrates of parallel processing, Trends Neurosci. 13 (7) (1990) 266–271 Retrieved http://www.sciencedirect.com/science/article/pii/016622369090107L.
[69] Abhijit Chaudhuri, Peter Behan, Fatigue and Basal Ganglia, (2000).
[70] Maria Engström, Gullvi Flensner, Anne-Marie Landtblom, Anna-Christina Ek, Thomas Karlsson, Thalamo-striato-cortical determinants to fatigue in multiple sclerosis, Brain Behav. 3 (6) (2013) 715–728 Retrieved https://www.ncbi.nlm.nih.gov/pubmed/24363974.
[71] Jodie Davies-Thompson, Samantha Johnston, Yashar Tashakkor, Raika Pancaroglu, Jason J.S. Barton, The relationship between visual word and face processing lateralization in the fusiform gyri: a cross-sectional study, Brain Res. 1644 (2016) 88–97 Retrieved http://www.sciencedirect.com/science/article/pii/S0006899316303602.