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Multisensory mental imagery of *fatigue*: Evidence from an fMRI study

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Abstract

Functional imaging experimental designs measuring *fatigue*, defined as a subjective lack of physical and/or mental energy characterizing a wide range of neurologic conditions, are still under development. Nineteen right-handed healthy subjects (9 M and 10 F, mean age 43.15 ± 8.34 years) were evaluated by means of functional magnetic resonance imaging (fMRI), asking them to perform explicit, first-person, mental imagery of *fatigue*-related multisensory sensations. Short sentences designed to assess the principal manifestations of *fatigue* from the Multidimensional Fatigue Symptom Inventory were presented. Participants were asked to imagine the corresponding sensations (Sensory Imagery, SI). As a control, they had to imagine the visual scenes (Visual Imagery, VI) described in short phrases. The SI task (vs. VI task) differentially activated three areas: (i) the precuneus, which is involved in first-person perspective taking; (ii) the left superior temporal sulcus, which is a multisensory integration area; and (iii) the left inferior frontal gyrus, known to be involved in mental imagery network. The SI fMRI task can be used to measure processing involved in mental imagery of *fatigue*-related multisensory sensations.

KEYWORDS
fatigue, fMRI, mental imagery, precuneus, superior temporal sulcus, vividness

1　|　INTRODUCTION

In addition to being a physiological condition, *fatigue* represents one of the most common symptoms of a wide range of neurologic disorders. It is one of the so-called invisible symptoms. *Fatigue* is characterized by physical and/or mental tiredness. Patients report that this sensation is persistent and heavy. Clinically, fatigue can be defined as "a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities" (Multiple Sclerosis Council for Clinical Practice Guidelines, 1998, p. 2). As such, *fatigue* exerts an impact on the persons' quality of life.

Fatigue indeed has been much studied in the clinical model of MS, as it affects approximately 70%–90% of patients with MS (Kobelt et al., 2017; Schapiro, 2015), and it results that more than 50% of persons with MS reporting *fatigue* as their most disabling symptom (Schapiro, 2015).

Several behavioral measures have been designed to quantify *fatigue*, such as questionnaires or cognitive or motor tasks increasing in their difficulty levels. Differently, functional imaging experimental

designs measuring *fatigue* are less developed (for a review Bertoli & Tecchio, 2020). One reason for this is that it is very difficult to measure the construct objectively. Second, *fatigue* has multiple dimensional factors (DeLuca, 2005), namely central, peripheral, behavioral, and psychological ones. Resting state is the less demanding approach and it allows detecting differences in brain activation or deactivation in the default mode network between patients experiencing *fatigue* and those who do not. Bisecco, Nardo, Docimo, et al. (2018) applied the resting-state paradigm in a group of 59 patients with multiple sclerosis (MS). They found that the resting-state connectivity in patients with MS experiencing *fatigue* (vs. healthy controls) was stronger in the posterior cingulate cortex, and reduced in the anterior cingulate cortex. Similarly, the resting-state connectivity in patients with MS experiencing *fatigue* (vs. those who did not) was increased in the posterior cingulate cortex, in the primary motor cortex, and in the supplementary motor area, and reduced in the anterior cingulate cortex. The resting-state approach in this study allowed to conclude that *fatigue* mainly impacts on nonmotor resting-state networks. Another example of resting-state approach in patients with MS shows the presence of alterations of the functional connectivity in temporoparietal areas, correlating with increased *fatigue* levels (Buyukturkoglu et al., 2017; see also Engstrom, Flensner, Landtblom, Ek, & Karlsson, 2013 for another example). A different approach to measurement of the neural correlates of *fatigue* consists in presenting patients with demanding motor tasks and in measuring whether in patients reporting *fatigue* (vs. those who do not) there are significant differences in activations of the sensorimotor areas. This approach is focused on the study of the physical factor of *fatigue*. For example, Specogna et al. (2012) asked 24 patients with MS to perform a sequential finger tapping with the right hand. They found that patients reporting *fatigue* (vs. those who did not) demonstrated greater activation of the right premotor area, of the putamen, and the dorsolateral prefrontal cortex, which are involved in motor planning and conscious motor adaptation. In another study (Filippi et al., 2002) authors found that patients reporting fatigue (vs. those who did not) had less activation in areas involved in motor planning and execution, such as the ipsilateral (to the moved hand) precuneus, ipsilateral cerebellar hemispheres, contralateral middle frontal gyrus, and contralateral thalamus. A last approach has been used to study the mental/cognitive factor of *fatigue* presenting patients with highly demanding cognitive tasks and measuring whether patients who report *fatigue* show increased activation in areas related to attention/cognitive efforts related areas. For example, DeLuca, Genova, Hillary, and Wylie (2008) presented patients with four functional magnetic resonance imaging (fMRI) sessions of a symbol digit modality test assessing psychomotor speed. They found that patients (vs. healthy controls) were significantly slower (indicating *fatigue*) and showed an increased activation in the basal ganglia, frontal areas (including superior, medial, middle, and inferior regions), parietal regions (precuneus and cuneus), thalamus and the occipital lobes. A combination of motor and cognitive task can be obtained by presenting patients with a motor task, and in Stage 2, a highly demanding attention task (the paced auditory serial addition test), followed by a motor task again in Stage 3. With this method, Tartaglia, Narayanan, and Arnold (2008) showed that in patients with MS reporting fatigue (vs. healthy controls) the motor task performed after the cognitive task (as compared to the motor task performed before it, in Stage 1) increased activation in the cingulate gyrus and post-central gyrus bilaterally and in the right prefrontal cortex.

Sensory mental imagery is the ability to see with the mind's eye (Kosslyn, 1980) in the absence of a real percept. The same holds for other sensory or motor systems. Neuroimaging studies have shown that there is an imagination–perception parallelism and that the same areas activated during real sensory perception are triggered when a person imagines the corresponding sensory scene (Djordjevic, Zatorre, Petrides, Boyle, & Jones-Gotman, 2005; Ehrsson, Geyer, & Naito, 2003; Kobayashi et al., 2004; Stippich, Ochmann, & Sartor, 2002; Tomasino, Ceschia, Fabbro, & Skrap, 2012; Tomasino, Maieron, Guatto, Fabbro, & Rumiati, 2013; Tomasino, Vorano, Skrap, Gigli, & Rumiati, 2004; Tomasino, Weiss, & Fink, 2010; Tomasino, Weiss, & Fink, 2012; Tomasino, Werner, Weiss, & Fink, 2007).

Based on this framework, we developed an additional paradigm taken from experimental psychology that can be additionally used to measure *fatigue*-related fMRI changes. We used explicit, first-person, multisensory mental imagery to induce activity in cerebral structures involved in processing *fatigue*-related sensations. We presented participants with randomly derived stimuli from the "Multidimensional Fatigue Symptom Inventory (MFSI)", which is an 83-item self-report measure designed to assess the principal manifestations of *fatigue* (Stein, Martin, Hann, & Jacobsen, 1998). We asked participants to explicitly imagine, in a first-person perspective, a series of sensations (Sensory Imagery, SI). The task of interest was contrasted with a control task (Visual Imagery, VI) in which participants were explicitly asked to imagine in a first-person perspective a series of visual scenes. Predictions were made based on the above-mentioned functional parallelism between perception and multisensory imagery. The VI task is expected to activate areas related to VI in basal occipitotemporal cortex (e.g., Ganis, Thompson, & Kosslyn, 2004) and to control for activations related to reading the short phrases, language processing, and general mental imagery activations, that will be subtracted out when contrasted with SI. The latter is expected to activate areas recruited by mental imagery for SI (e.g., McNorgan, 2012; Mesulam, 1998; Olivetti Belardinelli et al., 2004; Olivetti Belardinelli et al., 2009).

2 | METHODS AND MATERIALS

2.1 | Participants

Nineteen right-handed (Oldfield, 1971) healthy subjects (9 M and 10 F, mean age 43.15 ± 8.34 years) participated in the study. They were all monolingual native speakers of Italian. The study was approved by the local Ethics Committee (*Prot. no. 19944/CEUR*) and written informed consent was obtained from each adult participant.

2.2 | Experimental design

2.2.1 | Stimuli

We used 84 short phrases, describing a visual picture (50%) or a body sensation (50%). For the body sensation items, a sub-set selection of items was randomly derived from the "Multidimensional Fatigue Symptom Inventory (MFSI)", which is an 83-item self-report measure designed to assess the principal manifestations of fatigue (Stein et al., 1998). A forward translation from English to Italian of the instructions, items, and response choices was done by a consultant—English native speaker. A backward translation was also performed to verify the reflection of the same content of the original MFSI questionnaire. For the visual picture items, we created a list of items describing a visual scene of comparable length as the body sensation items ($t[41] = -1.92$, $p > .05$).

2.2.2 | Task and experimental paradigm

The fMRI protocol consisted of a blocked design with two TASKS. Participants were asked to imagine the sensations (SI) or to imagine the visual scenes (VI) described in the short phrases.

Participants were instructed to silently read the series of short phrases and make a vividness rating on a four-level scale [1–4, from poor vividness (1) to vivid as real (4)] by pressing the corresponding button. They were also explicitly asked to imagine in a first-person perspective.

Instruction lasted 5 s. Fourteen blocks of task (15 s) and 15 blocks of rest (12.5 s) were alternated. The order of SI and VI blocks was pseudo-randomized. Each block included four short phrases. Each short phrase ($n = 84$, 28 SI, 28 VI) had a duration of 3,750 ms.

Visual stimulation was generated by using Presentation (Neurobehavioral Systems Inc., Albany, CA) and presented by using the VisuaStimDigital (Resonance Technology Inc., Los Angeles, CA) Goggle system. Responses were given by pressing four keys of an MRI Compatible Keypad (Resonance Technology Inc.) with the fingers of the right hand. Subjects practiced the task outside the scanner, prior to the magnetic resonance experiment, and utilized the dominant hand to respond.

2.2.3 | MRI acquisition

Images were acquired using a 3T Achieva MR whole-body scanner (Philips, The Netherlands) with a standard eight-channel head coil. High-resolution anatomical images were acquired using a 3D T1-weighted Turbo-Gradient Echo sequence (TR: 8.388 ms, TE: 3.85 ms, voxel size: 1 mm × 1 mm, thickness: 1 mm, number of slices: 190, field of view: 240 mm × 190 mm × 240 mm, acquisition matrix: 240 × 240, flip angle: 8°). Functional images were obtained using a T2*-weighted Gradient-Echo Echo-Planar Imaging EPI sequence (TR: 2500 ms, TE: 35 ms, voxel size: 1.797 mm × 1.797 mm, thickness: 3 mm, number of slices:

29, field of view: 230 mm × 88.33 mm × 230 mm, acquisition matrix: 128 × 128, flip angle: 90°, number of volumes: 308). Slices were acquired in the axial plane, parallel to the anterior commissure/posterior commissure (ACPC) line. The total scanning time was 15 min (7 min the fMRI task plus the anatomical T1 acquisition).

2.2.4 | Multidimensional fatigue symptom inventory

Participants compiled the MFSI, which is an 83-item self-report measure designed to assess the principal manifestations of fatigue. Items are rated on a 5-point scale indicating how true each statement was for the respondent during the previous week (0 = not at all; 4 = extremely). The MFSI takes about 10 min to complete. Higher scores indicate more fatigue. Following the scoring for the empirically derived scales, we derived scores for a general scale in addition to a physical scale, an emotional scale, a mental scale, and a vigor scale.

2.3 | Data analysis

2.3.1 | Behavioral data

Behavioral performance was analyzed using SPSS 21.0 (SPSS, Inc., Chicago, IL) on subjects' reaction times and vividness by performing an ANOVA with, as factor, the task (SI and VI). Scores for the scales derived from the MFSI were compared by performing an ANOVA with, as factor, the scale (general scale, physical scale, an emotional scale, a mental scale, and a vigor scale).

2.3.2 | fMRI data processing

fMRI preprocessing and statistical analysis were performed using MATLAB18r (The Mathworks, Inc., Natick, MA) and SPM12 (Statistical Parametric Mapping software, SPM; Wellcome Department of Imaging Neuroscience, London, UK www.fil.ion.ucl.ac.uk/spm). The first four volumes of each functional dataset were discarded from analysis in order to allow for T1 equilibration effects.

We spatially realigned the images to the reference volume (i.e., the now first/previously seventh acquired volume) and then co-registered to the mean EPI image. The mean EPI image was normalized to the standard single subject template in MNI space. A Gaussian kernel of 6 mm full-width half-maximum was used for smoothing to meet the statistical requirements of the theory of Gaussian fields according to the General Linear Model employed in SPM and to compensate for interindividual variability in macro- and micro-anatomical structures across subjects (Friston, Frith, et al., 1995; Friston, Holmes, et al., 1995).

For this experiment, three event types were defined and then used as conditions for the model specification: (a) sensory imagery, "SI," (b) visual imagery, "VI," and (c) resting, "Rest." A General Linear

Model (GLM) was thus applied to each voxel of the functional dataset. We used an event-related analysis and the BOLD response for each event type was modeled with the canonical Hemodynamic Response Function (HRF) and its temporal derivative. A temporal high-pass filter of 1/128 Hz and linear trend removal were employed. The three translation and the three rotation movement parameters obtained from the initial spatially realignment were included as further regressors.

Specific effects were assessed by applying appropriate linear contrasts of the parameter estimates of the four experimental conditions and the baselines resulting in t-statistics for each voxel. The set-statistics were then Z-transformed to statistical parametric maps (SPM{Z}) of differences between the experimental conditions and between the experimental conditions and the baseline. SPM{Z} statistics were interpreted in light of the probabilistic behavior theory of Gaussian random fields (Friston, Frith, et al., 1995; Friston, Holmes, et al., 1995). For each subject, we calculated the following contrast images: the simple contrasts tasks (SI and VI), and the main effect of the task [SI–VI] and [VI-SI]. Second level Random Effects Analyses was performed by using a t-test to create an SPM{T} on contrast images obtained from individual participants, in order to obtain significant activations specific for each contrast on a group level. We used a threshold of $p < .05$, corrected for multiple comparisons at the cluster level, with a height threshold at the voxel level of $p < .001$, uncorrected. Anatomical localization of the activations was done by using the SPM Anatomy Toolbox 3.0 (Eickhoff et al., 2005).

3 | RESULTS

3.1 | Behavioral data

3.1.1 | Vividness

The ratings significantly differed between tasks ($F[1,18] = 18.44$, $p < .001$). Participants rated (range 1–4) stronger vividness for VI (3.081 ± 0.452) as compared to SI task (2.326 ± 0.676, see Figure 1a, left side of the panel).

3.1.2 | Reaction times

RTs did not differ significantly ($F[1,18] = 0.47$, $p > .05$, n.s.) between the SI task (1.918 ± 0.455) and the VI task (1.866 ± 0.474, see Figure 1a, middle of the panel).

3.1.3 | Multidimensional fatigue-symptom inventory

Participants' mean score on the general scale was 3.98 ± 4.2 (according to the MFSI, higher scores indicate more fatigue experienced within the previous week). There was a significant effect of

scale ($F[4,72]) = 4.022$, $p < .05$) with significantly lower scores for physical scale versus general scale ($t[18] = -2.25$, $p < .05$), versus emotional scale ($t[18] = -2.77$, $p < .05$) and versus vigor scale ($t[18] = -2.6$, $p < .05$) and for mental versus emotional ($t[18] = -2.72$, $p < .05$; see Figure 1a, right side of the panel).

3.2 | fMRI data

3.2.1 | The SI task-related network

Figure 1b shows that the task-related network involved areas localized in the: (i) calcarine cortex, bilaterally, (ii) brain stem, (iii) right postcentral gyrus (extending to the inferior parietal cortex), (iv) brain stem, (v) right superior temporal gyrus (extending to the middle temporal gyrus), (vi) left middle temporal gyrus, and (vii) left inferior frontal gyrus (extending to the supplementary motor area and to the supramarginal gyrus and superior parietal lobe).

3.2.2 | The VI task-related network

Figure 1c shows that the task-related network involved areas localized in the (i) calcarine cortex bilaterally, (ii) left postcentral gyrus (extending to the left precentral gyrus), (iii) right supramarginal gyrus, (iv) left middle temporal gyrus, (v) right inferior frontal gyrus, and (vi) right middle frontal gyrus.

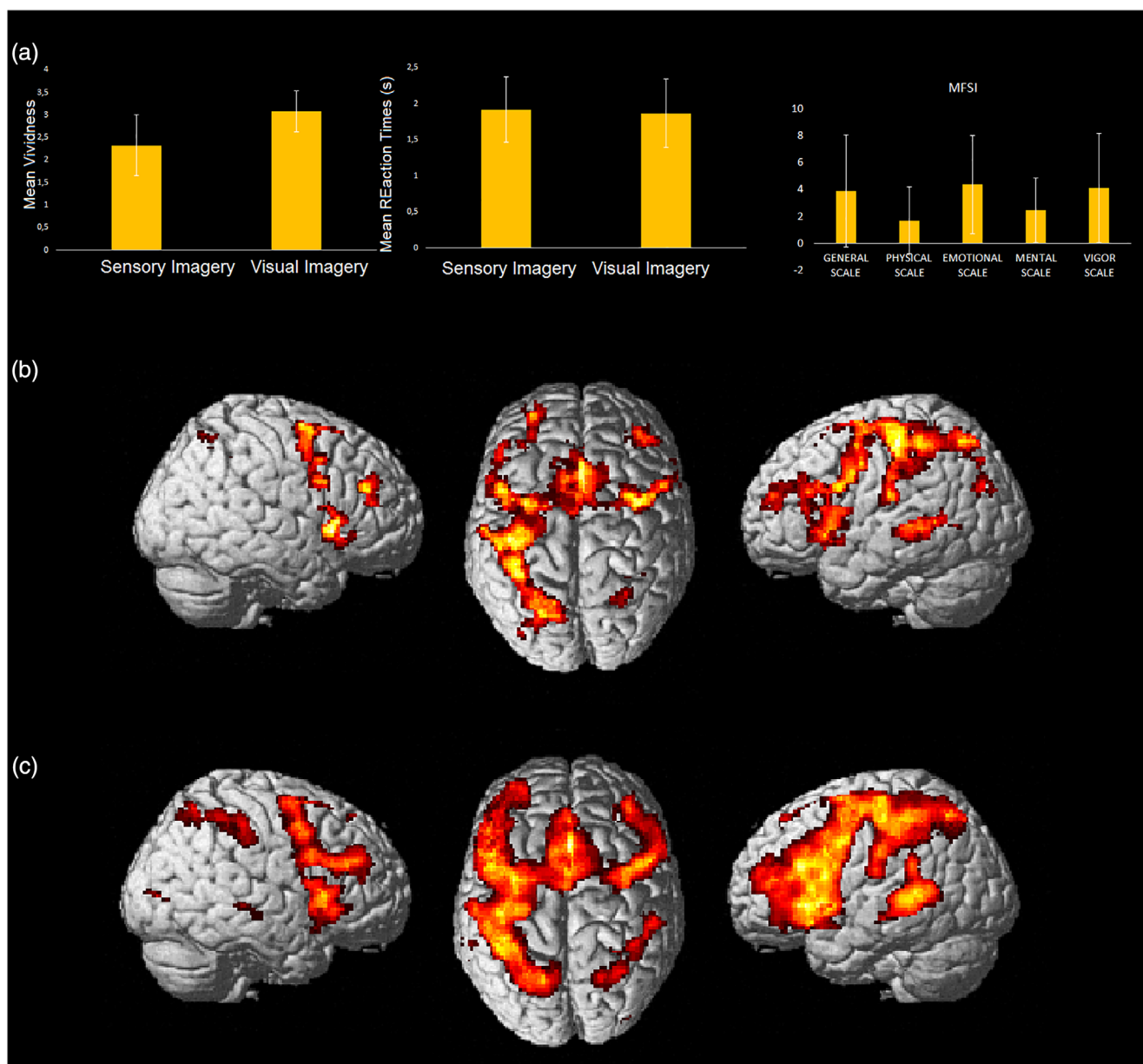### 3.2.3 | Main effect of task: SI task–VI task (and vice versa)

The SI task (vs. VI task) differentially activated the (i) cuneus/precuneus bilaterally, (ii) left superior temporal sulcus, and (iii) left inferior frontal gyrus (Figure 2a).

The reverse contrast (VI task vs. SI task) showed activations in the (i) calcarine cortex, bilaterally, (ii) left middle occipital gyrus, and (iii) right inferior frontal gyrus (Figure 2b).

4 | DISCUSSION

Using fMRI with healthy participants, we investigated the neural correlates of mental imagery of *fatigue*-related multisensory sensations. To do so, subjects imagined the corresponding content of items from the MFSI designed to assess the principal manifestations of *fatigue* (Stein et al., 1998).

Our experimental design was suitable for disentangling the neural correlates of the two types of mental imagery processing. The VI (vs. SI) activated areas related to visual perception such as the calcarine cortex, bilaterally, and left middle occipital gyrus. Being these well-known activation sites (e.g., Ganis et al., 2004) and being the VI used as a control task, results related to VI will be not further discussed. In
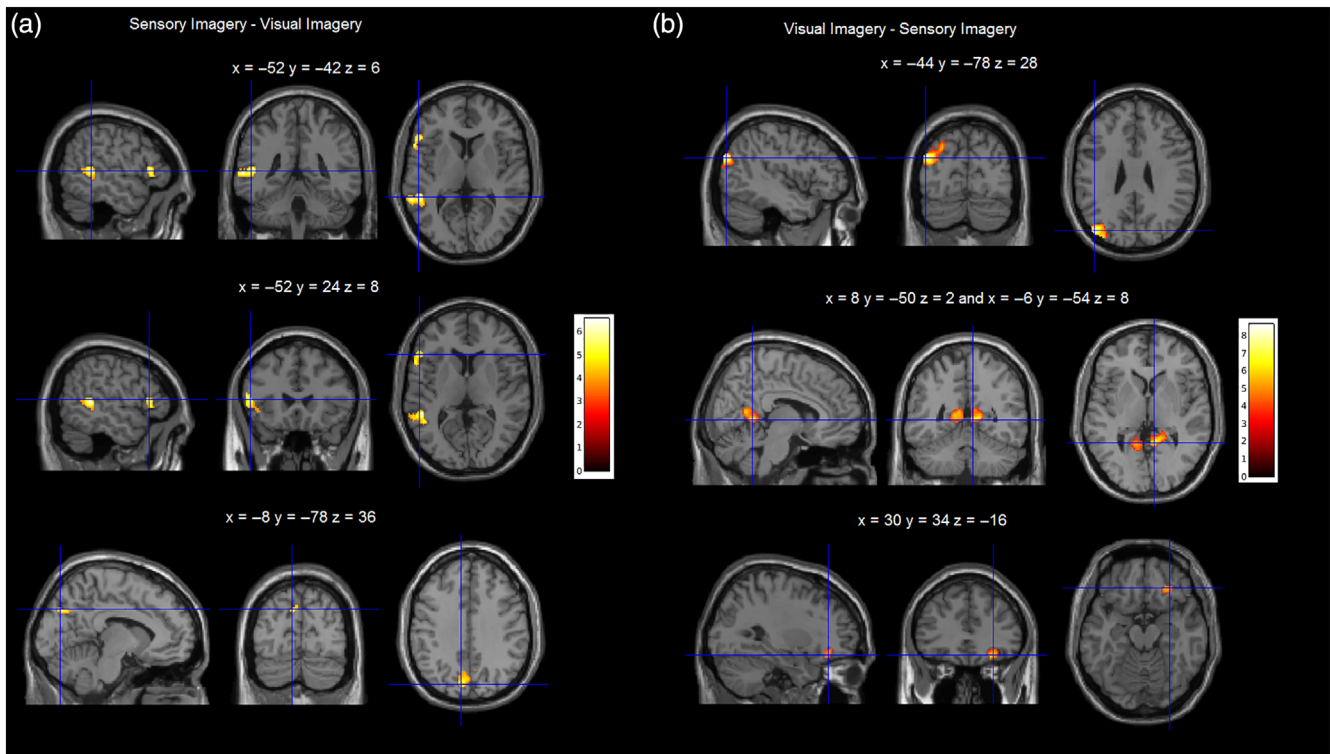
FIGURE 1 Behavioral results (a): mean Vividness and mean Reaction Times (s) of participants performing the Sensory and Visual Imagery fMRI tasks (left side of the panel), together with their Multidimensional Fatigue Symptom Inventory (MFSI) performed offline (right side of the panel). Relative increases in neural activity associated with the Sensory Imagery (b) and the Visual Imagery (c) ($p < .05$, corrected at the cluster level; Table 1) are displayed on a rendered template brain provided by SPM12

contrast, our main result is that the Sensory (vs. Visual) Imagery task activated the precuneus, the left superior temporal sulcus (STS), and the left inferior frontal gyrus (IFG).

First, it is known that the precuneus is involved in first-person perspective taking (Cavanna & Trimble, 2006). Interestingly, the SI task requires to mentally simulate a sensation of (mainly physical) fatigue involving body parts. The task likely triggers specific memory contents. This is consistent with studies showing that the precuneus is activated in episodic memory retrieval, for example, (Gilboa, Winocur, Grady, Hevenor, & Moscovitch, 2004; Lundstrom, Ingvar, & Petersson, 2005), and as such, it triggers self-related processing

because it has autobiographical reference (Cavanna & Trimble, 2006). Activations in the precuneus have been found in a study presenting participants with individually tailored faces and words referring to personality traits (Kircher, Senior, Phillips, et al., 2000) or in a study asking subjects to think intensively about how they would describe their own personality traits and physical appearance versus a neutral reference person (Kircher et al., 2002). With specific relation to mental imagery processing, the precuneus has been found activated during the generation of episodic autobiographical mental images (Gardini, Cornoldi, De, & Venneri, 2006) given its role in episodic memory retrieval during imagery (Fletcher et al., 1995). Our results thus are in

FIGURE 2   The activation clusters in the left Superior Temporal Sulcus, left Inferior Frontal Gyrus and precuneus differentially recruited by the Sensory Imagery (relative to Visual Imagery) contrast (a), and the activation clusters in the left middle occipital gyrus, calcarine cortex, and right Inferior Frontal Gyrus differentially recruited by the Visual Imagery (relative to Sensory Imagery) contrast (b)

agreement with the view that mental image generation requiring reactivation of a stored percept (Gardini et al., 2006) activates the precuneus. Instructions of the SI task explicitly required participants to perform the task in a first-person perspective. There are studies (Vogeley et al., 2001) presenting short stories written in the first-person (vs. third-person perspective), showing that the precuneus was activated when the persons were involved as an agent in the particular story (first-person perspective taking). We already found activation of the precuneus during imagery in first-person perspective (e.g., Tomasino et al., 2007; Tomasino et al., 2013; Tomasino et al., 2018; Tomasino, Fabbro, & Brambilla, 2014). We added here further evidence of a role of the precuneus in mental imagery of self-related re-enacted precepts.

Second, we found that SI activated the left STS. This area is considered a multisensory integration area, and it has been called STSms (Beauchamp, 2005; Beauchamp, Argall, Bodurka, Duyn, & Martin, 2004). In macaque studies, this area was labeled as superior temporal polysensory area, since its neurons are responsive to visual, auditory, and somatosensory stimulation (Bruce, Desimone, & Gross, 1981). Evidence from functional imaging showed that the posterior STSms is activated by auditory and visual stimulation (Beauchamp, Lee, Argall, & Martin, 2004; Calvert, 2001; Noesselt et al., 2007; Van Atteveldt, Formisano, Goebel, & Blomert, 2004; Wright, Pelphrey, Allison, McKeown, & McCarthy, 2003), in addition to somatosensory processing (Burton, McLaren, & Sinclair, 2006; Disbrow, Roberts, Poeppel, & Krubitzer, 2001; Golaszewski et al., 2002).

In particular, Beauchamp, Yasar, Frye, and Ro (2008) found that STSms is activated by all three modalities, namely vibrotactile somatosensory, auditory, and visual stimuli. Authors showed that activation in this area was triggered by active and passive unisensory vibrotactile stimuli and, similarly, by simultaneous auditory-tactile stimulation. We added further information by showing that this area was activated during SI. Interestingly, it is known that STS provides visual input to the mirror neuron system (Iacoboni, 2005; Iacoboni et al., 2001; Iacoboni & Dapretto, 2006). The role of STS is contributing to the matching between sensory predictions of imitative motor plans and a visual description of observed actions, suggesting an involvement in sensory predictions. Mental imagery corresponds to anticipate and simulate internal states in the corresponding sensory modality, and as such, our task could have activated the STS. According to its rich spatial organization (Deen, Koldewyn, Kanwisher, & Saxe, 2015), the STS could be involved in integrating information from different sources (e.g., Liebenthal, Desai, Humphries, Sabri, & Desai, 2014), also internal ones, such as it happens in SI.

Finally, as far as the activation in the left inferior frontal gyrus is concerned, in addition to its well-known role within the action observation network (e.g., Binkofski et al., 2000), this area is known to be part of the motor imagery network (e.g., for a quantitative meta-analysis of fMRI results see Hétu et al., 2013). Interestingly, there are several studies showing that the IFG is activated by other imagery modalities, such as tactile imagery (Schmidt & Blankenburg, 2019). In our study, the left IFG was activated during SI, while the right IFG was

TABLE 1 Brain regions showing significant relative increases of BOLD response associated with each comparison of interest

Side	Region	MNI coordinates			T	Size (k_E)
		x	y	z		
Visual imagery—rest						
LH	Calcarine cortex	−4	−56	2	8.32	1,257
RH	Calcarine cortex	18	−50	5	5.26	
LH	Postcentral gyrus	−36	−26	48	8.46	8,380
LH	Precentral gyrus	−42	−2	40	8.16	
RH	Supramarginal gyrus	38	−42	42	4.85	135
LH	Middle temporal gyrus	−62	−30	2	6.46	430
RH	Inferior frontal gyrus	46	14	2	6.46	531
RH	Middle frontal gyrus	38	36	24	6.12	294
Sensory imagery—rest						
RH	Calcarine cortex	2	−54	−8	6.68	612
LH	Calcarine cortex	−12	−70	6	6.07	
M	Brain stem	−4	−32	−4	7.28	265
RH	Postcentral gyrus	44	−30	38	6.39	1,112
RH	Inferior parietal lobe	30	−52	46	6.19	
RH	Pallidum	12	4	−4	6.18	329
RH	Superior temporal gyrus	48	−28	−2	4.91	124
RH	Middle temporal gyrus	50	−24	10	4.45	
LH	Middle temporal gyrus	−58	−34	4	9.44	1,519
LH	Inferior frontal gyrus	−50	12	16	14.88	20,455
LH	Supplementary motor area	−8	14	54	11.84	
LH	Supramarginal gyrus	−34	−42	38	11.19	
LH	Superior parietal lobe	−24	−60	52	10.43	
Main effect TASK [SI > VI]						
M	Cuneus/precuneus	−8	−78	36	5.68	174
LH	Superior temporal sulcus	−52	−42	6	6.56	310
LH	Inferior frontal gyrus	−52	24	8	6.03	215
Main effect TASK [VI > SI]						
LH	Calcarine cortex	−12	−54	6	6.69	885
RH	Calcarine cortex	8	−56	12	5.61	
LH	Middle occipital gyrus	−44	−78	28	8.62	499
RH	Inferior frontal gyrus	30	−34	−16	5.64	100

Note: For each region of activation, the coordinates in MNI space are given referring to the maximally activated focus within an area of activation as indicated by the highest *T*-value. All the activations are significant at *p* < .05 (corrected for multiple comparisons at the cluster level, height threshold *p* < .001, uncorrected).

Abbreviations: LH/RH, left/right hemisphere; M, medial; size, number of voxels in a cluster.

activated by VI. The IFG has been shown to be an area involved in inhibition mechanisms (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Aron & Poldrack, 2006; Chambers et al., 2006; Xue, Aron, & Poldrack, 2008), which is particularly relevant as the tasks used involve mental imagery and not real perception.

Taken together, these results show areas that are selectively activated when one imagines *fatigue*-related sensations. Does this mean that participants experience *fatigue*? Based on the imaging literature on the parallelism between imagery and perception (Djordjevic

et al., 2005; Ehrsson et al., 2003; Kobayashi et al., 2004; Stippich et al., 2002; Tomasino et al., 2004; Tomasino et al., 2005; Tomasino et al., 2007; Tomasino et al., 2010; Tomasino et al., 2013; Tomasino, Ceschia, et al., 2012; Tomasino, Weiss, & Fink, 2012) it is assumed that they experience the *fatigue*-related sensations because they imagine them and estimate the corresponding vividness. Vividness for SI is significantly lower than that for VI, indicating that it is likely that imagining the somatosensory sensations is more difficult than imagining a visual scene; nonetheless, reaction times are not significantly

different to perform sensory or VI. In addition, the MFSI revealed that within the week preceding the fMRI measurements, our subjects did not experience *fatigue*-related sensations, as they obtained significantly lower scores exactly for physical and mental fatigue scales. This result indicates that the MFSI is reliable and it would be interesting the comparison of these data with a group of patients actually experiencing *fatigue* to see how the different scales will change. We could speculate that if we would administer this fMRI task to neurological patients who in their everyday life really do experience fatigue, the areas activated in our sample of healthy controls would be hyper or hypo-activated, but this issue will be the subject of future investigations. This prevision is supported by already available evidence of fMRI activations in the superior temporal gyrus, cingulate regions, and inferior frontal regions, increased as a function of time on task in patients who experience *fatigue* (Cook, O'Connor, Lange, & Steffener, 2007).

CONFLICT OF INTEREST

The authors have declared no conflicts of interest for this article.

AUTHOR CONTRIBUTIONS

Conceptualization: Barbara Tomasino, Maria Rosaria Valente, and Gian Luigi Gigli. Data curation: Barbara Tomasino, Riccardo Garbo, and Ilaria Del Negro. Formal analysis: Barbara Tomasino. Acquisition: Barbara Tomasino, Riccardo Garbo, Ilaria Del Negro, and Serena D'Agostini. Supervision: Barbara Tomasino, Maria Rosaria Valente, and Gian Luigi Gigli. Writing – original draft: Barbara Tomasino, Maria Rosaria Valente, and Gian Luigi Gigli. Writing – review & editing: All authors.

DATA AVAILABILITY STATEMENT

The datasets analyzed for this study will be made available from the authors upon request.

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