

## When to collect resting-state data: The influence of odor on post-task resting-state connectivity



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### ABSTRACT

The human brain networks at rest represent spontaneous activity that is highly correlated between different brain regions. Previous studies have shown that these resting-state networks are flexible and dynamic, and they can be affected by performance of different types of tasks. Moreover, it has been suggested that the re-activation of a task-related brain network during rest promotes learning and improves the expertise on that task. However, it is still unclear whether the presence of different sensory information in the on-task state affects functional connectivity in subsequent resting-state fMRI even though the perception of the sensory information did not induce significant behavioral effects. To clarify this issue, we compared pre- and post-task resting-state fMRI of two groups of participants performing the same task either with an odor context (ODOR group) or without an odor context (AIR group). Seed-based functional connectivity analyses were performed with orbitofrontal cortex, piriform cortex and working-memory core network as seeds. The results showed that an odor context presented during an encoding task induced significant changes in the functional connectivity only within the olfactory network of the post-task resting-state compared to the same post-task situation without previous odor context. No significant difference in functional connectivity were found for the working-memory core network. This evidence emphasizes how the sensory context, in which a task is performed, is relevant for understanding the observed changes of functional connectivity during rest.

### 1. Introduction

It has been shown that the brain is not inactive “at rest” but presents considerable spontaneous activity that is highly correlated between different brain regions (van den Heuvel and Hulshoff Pol, 2010). Functional connectivity (FC) has been widely used to investigate the level of co-activation of multiple brain regions during rest and task conditions (van den Heuvel and Hulshoff Pol, 2010).

A common and convenient practice for collecting resting-state fMRI (rs-fMRI) is to perform the rs-fMRI run before or after task related-fMRI runs. However, recent studies have reported that the characteristics of resting-state networks are flexible and are affected by task performance (e.g. Hasson et al., 2009; Lewis et al., 2009; Grigg and Grady, 2010; Tambini et al., 2010; Wang et al., 2012; Zhang et al., 2014; Tailby et al., 2015; Muraskin et al., 2016). For example, previous studies have shown that the performance in a task can induce changes in spatial patterns

within the default mode network (DMN; Grigg and Grady, 2010; Tambini et al., 2010; Wang et al., 2012), a network of brain regions, consisting of the precuneus, the medial frontal, the inferior parietal cortical regions, and the medial temporal lobe, that shows deactivation during on-task states compared to resting-state (van den Heuvel and Hulshoff Pol, 2010). In particular, enhanced FC between the hippocampus and lateral occipital complex during rest following an encoding memory task (Tambini et al., 2010) has been reported. Moreover, a decrease in FC within regions associated with the DMN such as the posterior cingulate gyrus (PCgG) and the superior frontal gyrus (SFG) have been described after a language comprehension task (Hasson et al., 2009), and reduced FC between frontal-temporal areas and the DMN after a semantic-matching task (Wang et al., 2012). Changes of FC in post-task rs-fMRI are not limited to the DMN. For example, resting-state FC after motor imagery learning presented with decreased network strength in the DMN and increased strength in the fusiform gyrus and precuneus of

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the lateral visual network and sensory-motor network (Zhang et al., 2014).

Overall, these results support the notion that the engagement of task-related brain networks during a post-task resting-state might enhance the expertise on a task. Indeed, when subjects need to improve the performance on a task they covertly rehearse the task by activating task-dependent brain networks, which promotes learning and adaptation during rest (Zhang et al., 2014; Muraskin et al., 2016). Moreover, recent evidence points into the direction that not only the task per se is relevant for the effects on FC in rs-fMRI but also the context in which the task is performed. Indeed, if participants performed the task in a context that facilitates or enhances task performance, then one might hypothesize that the changes in FC during post-task resting-state are different from the case in which participants performed the task in a neutral context. This question was addressed by Hasson et al. (2009) by comparing the connectivity pattern during rest preceded by a comprehension listening task of unsurprising and less-informative sentences vs. surprising and more-informative sentences. The authors revealed that the FC during rest was sensitive to the antecedent task context: FC in the right PCgG and the medial aspect of the right SFG was stronger after listening to less-informative compared to more-informative contents. The results by Hasson et al. (2009) reflected differences in integration processes of linguistic content, as the two experimental conditions presented two similar sentences that had two different meanings.

A still open question is whether the mere presence of different sensory information in the on-task state could differently affect FC in subsequent rs-fMRI, even though the sensory information does not affect the task performance. Among sensory modalities that could be used as sensory context, the sense of smell is the one that fit best with the idea of “context”; indeed, even though most of the time, we are not consciously aware of different odors, almost every space or situation represents its own specific odor. At present, many studies have provided evidence that explicit or implicit odor perception can affect for example mood (Zucco et al., 2009), behavior (Chebat and Michon, 2003; Cecchetto et al., 2017), and memory (Larsson et al., 2017). This ability has been related to the unique anatomical organization of the olfactory system and its close anatomical connections to the limbic system which is involved in emotion and memory information processing (Gottfried and Zald, 2005; Lundström et al., 2011).

The goal of the present study was to elucidate whether the presence of an odor context during an fMRI task differently affects network FC in post-task rs-fMRI. To this end, we compared pre- and post-task rs-fMRI of two groups of participants performing the same incidental memory-encoding task during an odor context (ODOR group) or without an odor context (AIR group). The incidental-memory task was therefore only the medium to investigate the influence of this perceptual information, and, indeed, the only difference between the two groups of participants stood on the different odor information. The performance of the participants during the incidental memory-encoding task, as well as the task's neuronal correlate, were part of a bigger fMRI study (Reichert et al., 2017).

Since the only difference between groups lied on odor conditions, we hypothesized that the odor context would have changed the FC within the olfactory network. For this reason, seed-based functional connectivity analyses were performed with the bilateral orbitofrontal cortex (OFC) and the bilateral piriform cortex (PC) as seeds. Moreover, to control for differences between groups in the working memory network, due to a possible interaction between odor context and the incidental memory-encoding task, and to confirm that the odor information would affect only the olfactory network and not the network related to the actual task (memory task), seed-based functional connectivity analysis was performed with the working-memory core network (WMN, Rottschy et al., 2012) as seed. Finally, to make sure that there are not systematic changes between groups and pre-post-task rs-fMRI, an additional seed-based functional connectivity analysis was performed in a perceptual network not involved in olfactory perception, so with the bilateral primary

auditory cortex (Heschl's gyrus, Zatorre et al., 2002) as seed. Since Reichert et al. (2017) showed no behavioral significant differences in task performance between the two groups, we could hypothesize that the mere perception of the odor context, without any improvement of the task performance, would alter the subsequent functional connectivity of the olfactory network but not of the working memory network or of the auditory network.

## 2. Material and methods

### 2.1. Participants

Thirty-four right-handed volunteers with normal olfactory function took part in the study. Participants were part of a subgroup of volunteers recruited for an fMRI study (Reichert et al., 2017). Exclusion criteria were contraindication for MRI measurements, olfactory dysfunction, neurological or psychiatric diseases and cardiovascular, or chronic respiratory diseases. Participants were assigned to an odor group (ODOR; N = 17, females = 8; age, mean = 25.24, SD = 5.81) or to a control group (AIR; N = 17, females = 10; age, mean = 27.26, SD = 6.66). The study was approved by the local ethics committee of the University of Graz (Austria) in accordance with the Helsinki Declaration of 1975 and its later amendments. All participants provided written informed consent before participation in the study. Participants were compensated with course credits.

### 2.2. Assessment of olfactory functions

Before fMRI measurements, normal olfactory function of participants was confirmed using the “Sniffin’ Sticks” test (Hummel et al., 1997). Odors were presented to the participants in felt-tip pens, placed approximately 2 cm below both nostrils. Three different olfactory functions were assessed. First, the odor detection threshold was determined for n-butanol with 16 stepwise dilutions. The odor threshold was measured using the single staircase technique based on a three-alternative forced choice task (3AFC). Second, odor discrimination was assessed over 16 trials. For each discrimination, three pens was presented, two containing the same odor and the third containing the target odor (3AFC task). Third, odor identification was measured by presenting 16 common odors, each presented with four verbal descriptors in a multiple forced-choice format (three distractors and one target). A summated score TDI above 30.5 was considered to be within the normosmic range (Hummel et al., 2007). Only participants obtaining a TDI score in the normosmic range were included in the study (TDI ODOR group, mean = 36.37, SD = 2.37; TDI AIR group, mean = 35.07, SD = 2.68).

### 2.3. Olfactory stimulus

Before the initial fMRI study, a pilot study was performed for the selection of the stimulation odor. Twenty healthy normosmic participants (who did not participate in the fMRI study; mean (SD) age = 26.31 (5.52), TDI score = 36.86 (3.31), 10 female) were asked to rate intensity, pleasantness, familiarity, and nameability of a battery of 20 odors. On this basis, lavender odor (5% v/v in 1, 2 propylene glycol; Roth, CAS No. 90063-37-9; mean (SD) intensity = 7.55 (1.15), pleasantness = 6.80 (2.02), familiarity = 7.55 (1.85), nameability = 4.1 (3.34)) was used as the context odor (Reichert et al., 2017).

### 2.4. Procedure

The performance of the participants during the incidental memory-encoding task were part of a bigger fMRI study aimed to clarify whether a congruent contextual odor would enhance picture recognition performance compared to an incongruent contextual odor (Reichert et al., 2017). The first resting-state fMRI (PRE-rs-fMRI) was acquired for 5

min before participants performed the incidental memory-encoding task during fMRI scanning. In this encoding task, that lasted about 9 min, 60 abstract line drawings were displayed to participants, who were asked to decide whether the figure presented as predominantly round, had edges or was of mixed shape. Participants answered with their right hand through a response-button device. During this task, lavender odor was presented to the ODOR group while odorless air was presented to the AIR group. Participants of both ODOR and AIR groups were told that during the task they might perceive an odor. Both odor and odorless air were delivered through an MRI-compatible olfactometer, described in details by Lundström et al. (2010), at 0.5 L/min for 500 ms at random intervals ranging from 5 to 12 s. To minimize tactile cues resulting from channel opening, a continuous odorless airstream of 1 L/min was delivered as the principal flow (Reichert et al., 2017). Following the encoding task, the second rs-fMRI (POST-rs-fMRI) was acquired for 5 min. During both rs-fMRI acquisitions, a black fixation cross was displayed on a white background and participants were asked to lie still with their eyes opened (Kollndorfer et al., 2013). No odors were presented during PRE and POST-rs-fMRI acquisitions (see Fig. 1 for an overview of the study procedure).

To evaluate whether the odor context would present side effects, participants were asked to complete questionnaires regarding mood, assessed with a visual analogue scale (VAS; range 0–100, with 0 = not good at all, 100 = exceptionally good mood) and affective states, measured using the Positive and Negative Affect Schedule (PANAS; Janke and Glöckner-Rist, 2014; Watson et al., 1988) before and after entering the MRI scanner. Mixed-measures ANOVA analysis was used to analyze these data and results revealed that there were no significant differences between PRE and POST time points and between groups (Reichert et al., 2017).

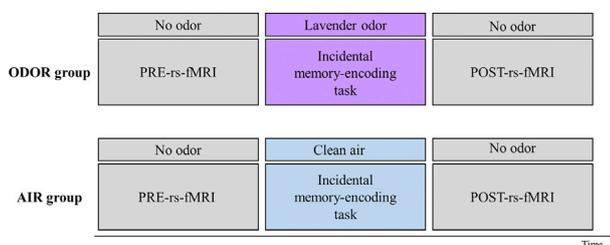
## 2.5. MRI data acquisition and preprocessing

Functional and anatomical images were acquired with a 3-T MRI (Skyra, Siemens, Erlangen, Germany) using a 32-channel head coil using a multiband EPI sequence (axial slices TR/TE/FoV/matrix size/voxel size = 32/1.99 s/27 ms/256 × 256 mm<sup>2</sup>/64 × 64/4.0 × 4.0 × 4.0 mm<sup>3</sup>). T1-weighted 3D gradient echo sequence scans (MP-RAGE, sagittal slices/TR/TE/slice thickness/FoV = 176/1.56 s/2.07 ms/1 mm/256 × 256 mm<sup>2</sup>) were acquired coplanar with the functional scans.

Neuroimaging data were analyzed using SPM 12 (<http://www.fil.ion.ucl.ac.uk/spm/>) implemented in MatlabR2014b, and the CONN functional connectivity toolbox version 17 (<http://www.nitrc.org/projects/conn/>; Whitfield-Gabrieli and Nieto-Castanon, 2012). Image preprocessing involved fieldmap distortion correction, motion correction, slice time correction to the middle slice and realignment to account for motion, spatial normalization using DARTEL algorithm (Ashburner, 2007) and spatial smoothing (8-mm Gaussian kernel) (Behzadi et al., 2007) (Behzadi et al., 2007).

## 2.6. Functional connectivity analysis

Seed-to-voxel analysis was performed using the CONN toolbox. This analysis correlates the mean resting-state time-series of the seed region



**Fig. 1.** Overview of the study procedure. PRE-rs-fMRI = first resting-state fMRI; POST-rs-fMRI = second resting-state fMRI.

(predefined ROI) with the time-series of all other regions, resulting in a functional connectivity map which defines the significant functional connections with the predefined brain region (van den Heuvel and Hulshoff Pol, 2010). The bilateral OFC, the bilateral piriform cortex (PC), the working-memory core network (WMN, Rottschy et al., 2012) and the bilateral primary auditory cortex (Heschl's gyrus; cortical ROIs from the FSL Harvard-Oxford Atlas) were inserted as seed points (see Fig. S1 of the Supplementary material). OFC and PC ROIs were used in a previous study and obtained from functional data of 40 individually published olfactory fMRI studies (Seubert et al., 2013). The WMN was the results of a meta-analyses performed on neuroimaging studies on working memory presenting different working tasks, designs and contrasts (Rottschy et al., 2012): the regions included are the bilateral posterior medial frontal cortex, the bilateral anterior insula, the bilateral intraparietal sulcus and the bilateral inferior frontal gyrus (Brodmann areas 44 and 45). The original images were first convert into binary images and then imported in the CONN toolbox as seed ROIs.

Previous studies have shown that seed based functional connectivity analysis requires further preprocessing steps to exclude temporal confounds like residual subject motion and physiological artifacts from the single voxel BOLD signal time-series (Power et al., 2012; Van Dijk et al., 2009). For this step the default CONN preprocessing was applied, including a combination of aCompCor method (Behzadi et al., 2007), scrubbing, motion regression and filtering (bandpass filter between 0.008 and 0.09).

Temporal correlations between these seeds and all other voxels of the brain were derived and finally Fischer z-transformed. These procedures were applied to both ODOR and AIR groups and for PRE- and POST-rs-fMRI sessions, respectively. For the second-level analyses, 2 × 2 ANOVAS with the factors odor contexts (odor/no-odor) and sessions (pre/post) were conducted separately for OFC, PC and WMN seeds. To investigate the directionality of functional connectivity differences assessed by the interaction term linear contrasts were employed. Seed-to-voxel results are reported when significant at a voxel wise threshold of  $p < 0.001$  uncorrected and a cluster-level threshold of  $p < 0.05$  FDR corrected. Moreover, in order to further analyze FC changes from PRE to POST-rs-fMRI sessions between ODOR and AIR groups,  $\beta$  effect size means of the significant clusters were extracted for each participants and for each sessions through the REX toolbox implemented in CONN, and t-tests on the POST minus PRE session difference scores were performed using R (version 2.10.1; <http://www.r-project.org/>).

## 2.7. Framewise displacement calculation

Subject motion addresses a general problem in the analysis of fMRI data, in particular in functional connectivity MRI (Power et al., 2014), which has to be taken care of by compensatory spatial registration or regressing out motion estimates. To exclude systematic differences in motion between the two groups and the pre and post rs-fMRI, we computed the framewise displacement metric on the surface of a sphere of radius 50 mm as described in Power et al. (2012, 2014). From this metric, we then compared the mean per subject between the two groups and pre and post sessions using repeated-measure ANOVA.

## 2.8. TSNR analysis

The Temporal Signal-to-Noise Ratio (tSNR; Parrish et al., 2000) was calculated to estimate the temporal stability of the measured time course BOLD weighted echo planar data across the three ROIs used as seeds (OFC, PC and the working-memory core network), groups and pre-post-rs-fMRI. Pre-processed data (fieldmap distortion correction, motion correction, slice time correction to the middle slice and realignment to account for motion, spatial normalization using DARTEL algorithm and spatial smoothing) were extracted as they were entered in the connectivity model. Voxel-wise tSNR was calculated as mean across time of voxel's time series divided by standard deviation across time of voxel's

time series. Then, the mean of the single-voxel tSNR values was calculated within the given ROIs per subject. Finally, this way calculated ROI specific tSNR values were compared between the ROIs, the two groups and pre and post sessions using  $3 \times 2 \times 2$  repeated-measure ANOVA. No significant main effects or interactions were observed (minimal  $p$  value  $> 0.09$ ).

### 3. Results

The seed-to-voxel analysis within the olfactory network revealed two clusters for the OFC and other two clusters for the PC. For the OFC, the first cluster was located in the right angular gyrus (rAG; see Table 1): the  $t$ -test on the POST minus PRE session difference scores of the ODOR and AIR group were significantly different ( $t(32) = -3.11$ ,  $p = 0.004$ ) implying that the AIR group presented an increase of FC (POST-PRE session  $\beta$  estimate, mean = 0.18, SD = 0.23) compared to the ODOR group (POST-PRE session  $\beta$  estimate, mean = -0.12, SD = 0.33) which showed weaker FC in the POST-task session (see Fig. 2A). The second cluster was located in the right middle temporal gyrus (rMTG; see Table 1): the  $t$ -test on the POST minus PRE session difference scores of the ODOR and AIR group was significant ( $t(32) = -3.85$ ,  $p < 0.001$ ) suggesting that the AIR group presented an increase of FC (POST-PRE session  $\beta$  estimate, mean = 0.15, SD = 0.24) compared to the ODOR group (POST-PRE session  $\beta$  estimate, mean = -0.13, SD = 0.19) which instead seems to present with weaker FC in the POST-task session (see Fig. 2A).

For the PC, the first significant cluster was found in the left inferior temporal gyrus (IITG; see Table 1): the  $t$ -test on the POST minus PRE session difference scores revealed a significant difference between the ODOR and AIR group ( $t(32) = 4.58$ ,  $p < 0.001$ ), which indicated that the ODOR group presented higher increased FC (POST-PRE session  $\beta$  estimate, mean = 0.11, SD = 0.24) compared to the AIR group (POST-PRE session  $\beta$  estimate, mean = -0.21, SD = 0.17; see Fig. 2B). The second cluster was located in the ISFG (see Table 1): the POST minus PRE session difference scores of the ODOR and AIR group resulted significant ( $t(32) = -4.94$ ,  $p < 0.001$ ) thus the AIR group seemed to display a higher increase of FC (POST-PRE session  $\beta$  estimate, mean = 0.16, SD = 0.10) compared to the ODOR group (POST-PRE session  $\beta$  estimate, mean = -0.18, SD = 0.17; see Fig. 2B). See Supplementary Figures S2, S3 and S4. Contrary to previous literature, the FC analysis performed within the working-memory core network did not present significant results. Finally, no significant results were found for FC analysis with the bilateral primary auditory cortex as seed.

To exclude that the results were affected by differences in motion between the two groups and sessions, the framewise displacement metric was computed. No significant main effects or interaction (all  $p > 0.57$ ) were found for the mean framewise displacement for groups and sessions (ODOR group pre = .27 mm, SD = 0.073; ODOR group post mean = .27 mm, SD = 0.084; AIR group pre = .26 mm, SD = 0.075; AIR group post mean = .28 mm, SD = 0.076).

### 4. Discussion

The present study explored the effects of the presence of an odor

**Table 1**

Seed-to-voxel analysis results showing significantly different connectivity for the interaction groups and rs-fMRI session. Anatomical labels follow the nomenclature of the Automated Anatomical Labelling (AAL). Voxel wise threshold of level of  $p < 0.001$  uncorrected and a cluster-level threshold of  $p < 0.05$  FDR corrected. OFC = orbitofrontal cortex; PC = piriform cortex; MTG = middle temporal gyrus; AG = angular gyrus; SFG = superior frontal gyrus; ITG = inferior temporal gyrus.

Seed	Cluster	MNI	Beta	k	T	p
OFC	Right MTG	56 -40	2 -0.26	94	-5.13	0.01
	right AG	52 -50	46 -0.3	73	-4.38	0.02
PC	left SFG	-26 -16	60 -0.28	186	-5.27	<0.001
	left ITG	-46 -60	-14 0.33	116	4.92	0.003

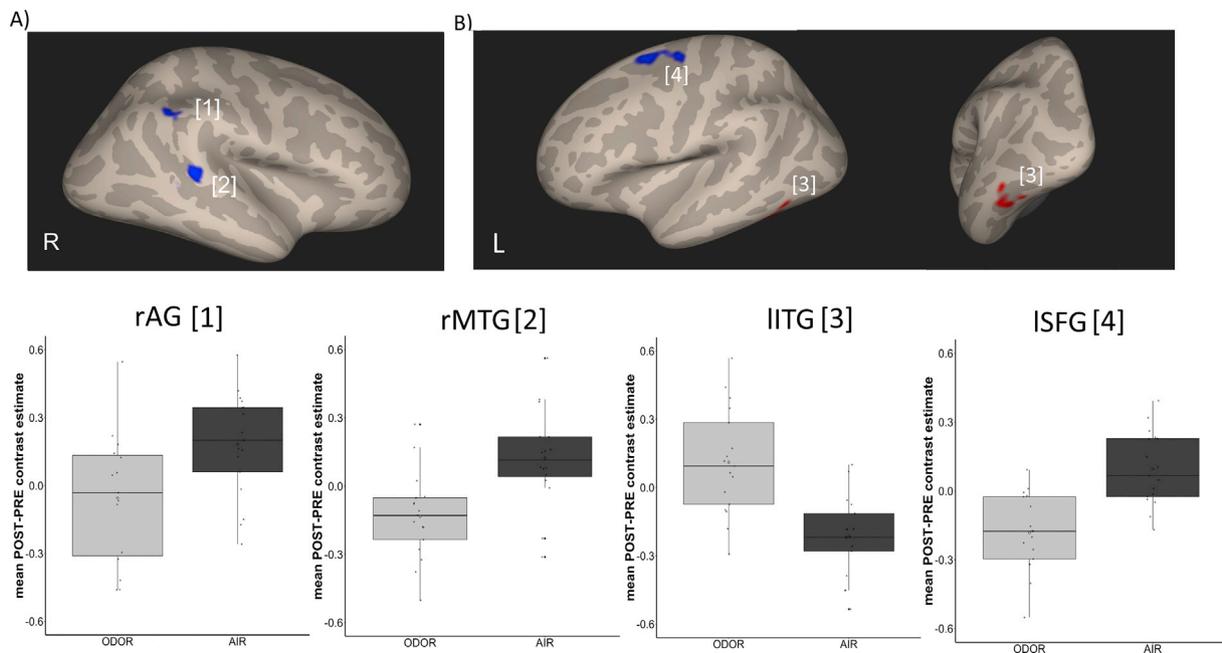
context on post-task resting-state FC. Previous studies have shown significant changes in FC networks from pre-task resting-state to resting-state acquired after performance of tasks such as encoding memory, language comprehension or visuomotor tasks (e.g. Hasson et al., 2009; Grigg and Grady, 2010; Tambini et al., 2010; Wang et al., 2012; Zhang et al., 2014; Tailby et al., 2015; Muraskin et al., 2016). However, it is still not clear whether a sensory (background) information during the task can affect FC in post-task resting-state, even though this sensory information does not affect the performance of the task. In order to clarify this aspect, we compared FC of PRE- and POST-resting-states from the OFC, the piriform cortex, and the working-memory core network in two groups performing the same incidental memory-encoding task with or without odor context. Since the groups of participants differed only because of the presence or absence of odor context, we performed the seed-to-voxel analysis with OFC and PC as seed regions, to investigate the emerging network (olfactory network). Moreover, as control, we also investigated FC differences between groups also in the working memory network (with the working-memory core network as seed).

Our results highlight that changes of FC from OFC and piriform cortex between PRE- and POST-rs-fMRI sessions were significantly different for the group performing the task during the odor context compared to the group that performed the same task without the odor context. No significant differences between groups were found for FC within the working-memory core network, suggesting that the FC differences between the groups were specific for the odor perception and not related to the task or to the interaction between the odor perception and the task. Moreover, no significant results were found within the auditory network, further strengthening our hypothesis that the presence of sensory information significantly affects FC of post-task resting-state measurements only in neural network specific to the sensory information (i.e. olfactory network).

Seed-to-voxel analysis revealed that the ODOR group in POST-rs-fMRI compared to the AIR group showed stronger FC in the IITG but weaker FC in ISFG, rAG and rMTG. The stronger FC displayed by the ODOR group between the PC and IITG, which has been previously associated with visual object representations (Kriegeskorte et al., 2008; McKee et al., 2014) and with episodic encoding success (Spaniol et al., 2009), might indicate an integration of the olfactory information with the visual information. This result is in line with the hypothesis that during rest the task-dependent brain networks are reactivated to enhance learning and memory (Zhang et al., 2014; Muraskin et al., 2016).

In addition, the AIR group presented stronger FC in the rMTG and the ISFG compared to the ODOR group. Previous studies investigating functional connectivity in olfactory networks (Kollndorfer et al., 2015) and the neural substrates of olfactory processing (Seubert et al., 2013) have reported rMTG and the ISFG as included in the olfactory network in healthy, normosmic participants. Even though the stronger FC in these areas for the AIR group was not expected, the observation is suggested to be triggered by the stimulus exception, as all participants, regardless of the group specification, received the same instructions (that they could perceive an odor during the task).

Moreover, our analysis revealed stronger FC between the PC and the rAG for the AIR group compared to ODOR group. The rAG which is included in the inferior parietal cortex, has been associated with the DMN across different types of tasks and paradigms (Laird et al., 2009; Seghier, 2013). The DMN remains more active during rest than during task performance (van den Heuvel and Hulshoff Pol, 2010) and its spatial patterns have showed to change during post-task resting-state (Hasson et al., 2009; Tambini et al., 2010). We can hypothesize that the weaker FC in the rAG for the ODOR group is related to the higher cognitive demand that this group were asked to face: indeed the integration of the olfactory input with the visual input in ODOR group might have affected DMN activity as previously shown with task demands like semantics (Wang et al., 2012), previous memory (Hasson et al., 2009), and even with subtle task differences like content (Hasson et al., 2009). Since no effect has been observed within the working memory network, we can



**Fig. 2.** Regions presenting significant changes in functional connectivity between groups and PRE/POST resting-state fMRI. Fig. 1 (A) displays regions with OFC as seed while Fig. 1(B) showed regions with PC as seed. Blue/red = significant negative/positive effects, R = right; L = left; rAG = right angular gyrus; rMTG = right middle temporal gyrus; IITG = left inferior temporal gyrus; ISFG = superior frontal gyrus.

propose that the higher cognitive demand faced by the ODOR group is only due to the odor perception which might have acted as a distractor (Parma et al., 2013; Cecchetto et al., 2017).

We are certainly aware that these findings might be due to odorant residuals that could have been still present for the ODOR group. Even though it is not possible to totally discard this hypothesis, it has been shown that odorous molecules are removed from the peri-receptor environment by clearance mechanisms such as nasal submucosal blood flow, nasal mucociliary clearance and expiratory desorption (Pellegrino et al., 2017; Dalton, 2000; Dahl and Ding, 2003). Philpott et al. (2008) revealed that the average total clearance time for a saturated solution of PEA after full habituation at prolonged exposure was 170 s, however, studies recording electro-olfactograms (EOG) from the olfactory epithelium (Poletti et al., 2017; Cavazzana et al., 2018) set the inter-stimulus trial between one odor presentation and another one at about 30 s suggesting that after this time odorant residuals are removed. To our knowledge, there are no studies investigating the clearance time of lavender, however, it should be noted that, in our study, the odor was presented at low flow and for a short time (0.5 L/min flow for 500 ms at random intervals of 5–12 s) to avoid habituation. Moreover, the continuous odorless airstream of 1 L/min was presented for 2 s after the end of the fMRI task to minimize odor residuals (Seubert et al., 2014), afterward the olfactometer was inactivated for the POST-resting-state session in order to prevent contamination from the tubes. Finally, at least 2 min were needed between the last odor presentation and the resting-state run to debrief the participant, to give the instruction and to start the new run. For these reasons, we are strongly convinced that at the beginning of the POST-resting-state session no odorant residuals were still present in the nasal epithelium of the participants.

Intriguingly, when extracting beta values of PRE-rs-fMRI sessions, different distributions between groups were observed. This could be attributed to the intrinsic differences of participants enrolled in the two groups or more likely to the different experimenters that executed and supported the testing procedure. We concede that such effects cannot be completely eliminated since experiments always require some kind of interaction between experimenter and subject. However, although the same standardized instruction was used for all subjects, minor variations

during instruction presentation could have affected these differences in the PRE-task session, as recently shown by Kawagoe et al. (2017). Since we do not have the possibility to test this hypothesis on our database, it is an open question for future investigations. Therefore, we control for these differences in the PRE-task condition by considering in our analysis the POST minus PRE session difference scores. Furthermore, it should be noted that the lavender odor used as context in the present study was not perceived as neutral and unfamiliar but rather it has been rated as pleasant and familiar. Even though, the analysis of the mood and affective states questionnaires confirmed that no significant differences were presented before and after entering in the MRI scanner and between ODOR and AIR groups, other cognitive effects could have affected the present results. Finally, as described above, the goal of the present study did not embrace the investigation of the odor context effects on the incidental memory-encoding task; we invited the readers of referring to Reichert et al. (2017) for results of the performance of the incidental-memory encoding task.

In conclusion, the present study points out that an olfactory stimulus presented as context during an incidental encoding memory task induces changes in the FC in olfactory networks of post-task resting-state that are significantly different from the changes induced by the same task without an odor context. Further investigations are needed to clarify whether different odors can have different effects on FC of post-task resting-state. Our study extends previous literature on FC of resting-state and it emphasizes how the sensory context in which a task is performed is relevant for understanding the observed changes of FC during rest. In light of our and other results, the importance of information regarding pre-gathered data and their context in resting-state MRI data bases becomes evident. Open source data collections have become one of the most powerful tools in recent neuroscientific research. Since the current resting-state data bases do not comprise information on pre-gathered task-based scans, we strongly recommend including this information in future data bases.

#### Conflicts of interest

The authors declare no conflicts of interest.

## Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.neuroimage.2019.02.050>.

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