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RESEARCH ARTICLE

Valence, Arousal, and Gender Effect on Olfactory Cortical Network Connectivity: A Study Using Dynamic Causal Modeling for EEG

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ABSTRACT The cortical network including the piriform (PC), orbitofrontal (OFC), and entorhinal (EC) cortices allows the complex processing of behavioral, cognitive, and context-related odor information and represents an access gate to the subcortical limbic regions. Among the several factors that influence odor processing, their hedonic content and gender differences play a relevant role. Here, we investigated how these factors influence EEG effective connectivity among the mentioned brain regions during emotional olfactory stimuli. To this aim, we acquired EEG data from twenty-one healthy volunteers, during a passive odor task of odorants with different valence. We used Dynamic Causal Modeling (DCM) for EEG and Parametric Empirical Bayes (PEB) to investigate the modulatory effects of odors' valence on the connectivity strengths of the PC-EC-OFC network. Moreover, we controlled for the influence of arousal and gender on such modulatory effects. Our results highlighted the relevant role of the forward and backward PC-EC connections in odor's brain processing. On the one hand, the EC-to-PC connection was inhibited by both pleasant and unpleasant odors, but not by the neutral one. On the other hand, the PC-to-EC forward connection was found to be modulated (posterior probability (Pp)>0.95) by the arousal level associated with an unpleasant odor. Finally, the whole network dynamics showed several significant gender-related differences (Pp>0.95) suggesting a better ability in odor discrimination for the female gender.

INDEX TERMS DCM, EEG, effective connectivity, gender, hedonic olfaction.

I. INTRODUCTION

The neural processing of olfactory information is a complex phenomenon involving the activation of several brain areas, not limited to the olfactory network, but also involved in memory and emotion processing [1]. The olfactory information is preprocessed, at the first stage, by the olfactory bulb that projects to a number of cortical structures traditionally designated as olfactory cortex. The two largest olfactory cortical areas are the anterior olfactory nucleus (AON), which regulates information flow between nearly every region where odor information processing occurs,

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and the piriform cortex (PC), which is often referred to as ''primary olfactory cortex''. However, unlike ''primary'' cortical structures in other sensory systems that are devoted to processing a single type of sensory information, the PC shows an extensive network of interconnections with both cortical areas such as the orbitofrontal cortex (OFC) and entorhinal cortex (EC), and subcortical regions such as the amygdala (AM) and hippocampus (HIP) [1], [2], [3], [4], [5], [6], [7]. More in detail, the connection with the OFC is known to assign affective value to olfactory stimuli [8], whereas the EC, one of the brain centers for associative memory, is considered the access gate to the HIP and participates in the local processing of the olfactory information through dense bidirectional projections with the PC [9], [10]. Finally, the AM, closely connected to the HIP, plays a key role in enhanced memory performance associated to emotional odors [11], [12]. In summary, the network at cortical level including PC, OFC and EC allows the complex processing of behavioral, cognitive and context-related odor information and represents an access gate to the subcortical-level network in the limbic regions (i.e., AM and HIP), which is directly related to the emotion processing. Accordingly, studying the PC-OFC-EC network dynamics may give relevant insight into the neural processing of the hedonic properties of odors.

The hedonic characteristics of odors are typically defined according with two principal dimensions: i.e., valence and arousal [13], [14]. The arousal of the odor perception is related to the intensity of the odorant [15]. On the other hand, the perception of valence is not only related to the chemical features of the odorant but also to the perceptual memories built upon prior exposure to the same odorant [16], [17], [18]. In this context, previous EEG studies have found a time varying activation of cortical brain areas following the onset of inspiration of pleasant and unpleasant olfactory stimuli, respectively [19], [20]. More specifically, after the onset of a hedonic odor, primary olfactory structures such as PC and EC are first activated. Afterwards, it is possible to observe the spread of olfactory information to other cortical regions and, in particular, to the OFC. This has been interpreted as a further evidence of the role played by PC and EC in the early stages of odor recognition. Instead, the role of OFC was associated with higher-order functions such as the discrimination of odors' hedonic properties [19], [20]. In another study with fMRI data, the authors have found an increase in the connectivity between PC and OFC during an unpleasant odor stimulation compared to a pleasant one [21]. This indicates that differences in the hedonic perception of odors could be reflected by changes in the connectivity between brain areas, in addition or even rather than their activation.

In the context of brain connectivity analysis, both functional and effective connectivity techniques have been proposed [22], [23]. Functional connectivity regards statistical dependencies between coupled brain sources. On the other hand, effective connectivity is related to the influence that one neural system exerts over another [22]. Among the latter, Granger-Causality based measures [24] have been successfully applied to EEG data to evaluate frequency-specific bidirectional interactions between brain sources [25], as well as between the OB and the PC by combining EEG and electrobulbographic data [26] during olfactory stimulation. However, also other methods are available in the literature for the estimation of effective connectivity [22]. In this context, Dynamic Causal Models (DCMs) are biophysically inspired spatiotemporal models designed to answer questions about the architecture of underlying neuronal dynamics and to make inferences about key neuronal parameters that has been extensively used to estimate effective connectivity among coupled brain regions from either fMRI or EEG data [27], [28]. Previous studies using DCM for fMRI have highlighted an increased connectivity strength among PC, OFC and AM during odor stimulation when an anxiety state has been experimentally induced [29]. A specific thalamic pathway linking PC to OFC has been also found by a further DCM for fMRI study when subjects have been asked to focus to upcoming emotional olfactory stimuli [7]. Nevertheless, to the best of our knowledge, none of these studies on hedonic olfaction processing have combined the key features of DCM with the unmatched temporal resolution of EEG, which allows to measure the cortical brain processes at the time scale at which they occur.

In this paper, we develop and apply a DCM to EEG data acquired during the administration of pleasant, unpleasant and neutral olfactory stimuli. Specifically, we test the hypothesis that the valence of odors exert a modulatory effect on EEG connectivity at the group-level. Additionally, we control for both the gender and the perceived level of arousal on such modulatory effect of valence. There are known differences in the processing of olfactory information between males and females, based on chemical, anatomical and functional aspects [30], [31], [32], [33], [34], [35], [36], [37], and which are reflected also at the behavioral level in many odor tasks. For example, females outperform males in odor-associated memory tasks [38] and score higher valence ratings of perceived odors [39], [40], [41]. Interestingly, authors in [42] found that differences in odor's valence rating were likely to be reflected also by differences in the chemosensory event-related potentials (CSERPs) between males and females. Accordingly, it has been proposed that perceptual gender differences may origin at a higher level of neural processing. In this view, it could be hypothesized that gender differences may arise also from the interactions among different brain regions, rather than their individual activation. In this context, DCM for EEG represent a powerful framework to study gender differences characterizing the neural processing of hedonic odors, although it has never been used.

The EEG data analyzed in this study was already found to carry relevant information about interacting cortical brain areas during the olfactory stimulation [25]. More in detail, in such a previous study, connectivity measures derived from multivariate autoregressive models (MVAR) have confirmed the central role of the OFC in the processing of emotional

olfactory stimuli [43], [44]. In addition, significant interactions between the OFC and the parahippocampal gyrus (PHG) has been found during positive odor stimulation. The PHG is a large region surrounding the HIP, which is involved in complex emotive processes and includes both the PC and the EC [45]. In agreement with these previous findings and the aforementioned evidence from the literature, here we aim at further exploring the cortical network including the OFC, and targeting the possible roles of PC and EC regions exploiting the potential of DCM. The Parametric Empirical Bayes (PEB) framework is used to infer average group connectivity and between-subject differences from single-subject DCM connectivity estimates [46], [47]. Three different odors, namely *n-butanol*, *vanillin* and *isovaleric acid*, are purposely selected to convey neutral, positive and negative valence respectively [48]. We estimate the modulatory effect of odor valence on the single-subject connectivity between PC, EC and OFC as well as the influence of gender and arousal at the group level. A preliminary analysis limited to the investigation of average-group effects of odors' valence can be found in [49].

This paper is structured as follows: in Section II we describe methodological aspects related to the experimental protocol, data acquisition and preprocessing, and data analysis using DCM; in Section III we report our results; in Section IV we discuss our main findings together with methodological aspects and limitations; finally, in Section V we provide the main conclusions of our work.

II. MATERIALS AND METHODS

A. SUBJECTS

The study was conducted according with the guidelines of the Declaration of Helsinki, and approved by the Bioethics Committee of the University of Pisa Review No. 14/2019, May 3rd, 2019.

Twenty one healthy volunteers (age 26 ± 2, 8 females) were enrolled to the study. Volunteers were not allowed to have any food nor drink in the 30 minutes preceding the experiment. We recruited volunteers in the same years of age and with similar cultural background, since these are potential confounding factors on studies of gender differences [50], [51], [52], [53]. Subject's olfactory threshold was determined by submitting subjects to a double-blind forced-choice olfactory test [54]. Briefly, we diluted a mother solution of n-butanol into 10 solutions whose concentration followed an increasing power law of 2 (from 8 to 4096), and which were stored into separate vials. Starting from the weakest concentration value, subjects were asked to distinguish between the n-butanol solution and a vial containing distilled water. For each incorrect answer, we increased the concentration on the next trial. Conversely, a correct choice led to the presentation of the same concentration of n-butanol solution. The test was considered concluded when the subjects correctly distinguished n-butanol compared to distilled water for 4 consecutive times. All the subjects showed a similar olfactory threshold and were included in the study, ensuring a homogeneous panel in terms of olfactory perception [55], [56]

B. STIMULI

Vanillin ($152.15 g/mol$), n-butanol ($74.12 g/mol$) and isovaleric acid ($102.13 g/mol$) were used to convey positive, neutral and negative valence, respectively [48]. Odorants' concentrations were purposely chosen to obtain isointense solutions, and they were stored into separate vials.

C. EXPERIMENTAL PROTOCOL

The experiment consisted of a single session in which participants performed 3 minutes of *initial rest* and three blocks of olfactory stimulation. Each block consisted of 1 minute of *pre-stimulus rest*, 5s of *stimulus administration*, 1 minute of *post-stimulus rest* and an average of 15s of self-assessment questionnaire, during which participants scored the stimulus in terms of valence (from -2 to $+2$ with a step size of 1) and arousal (from $+1$ to $+5$ with a step size of 1) according with the Self-Assessment Manikin (SAM) test [57], [25], [58], [59], [60], [61]. Stimuli were administered by approaching the vials containing the odorant at about 2cm from participant's nostrils. The order of presentation was randomized across participants. The experiment was conducted in an isolated room, and participants were instructed to sit on a chair keeping their eyes closed throughout the whole session to reduce artifact effects and avoid visual interference when approaching the vials.

D. EEG ACQUISITION AND PREPROCESSING

For the EEG acquisition, we employed a 128-channel Geodesic EEG System 300 from Electrical Geodesics, Inc. (EGI). Electrodes were referenced to the vertex of the cap (i.e., Cz channel) and their impedances were always maintained below $20k\Omega$ during all acquisitions. A sampling frequency of 500Hz was used.

EEG preprocessing was performed through the Matlab toolbox EEGLAB [62]. First, data was downsampled at 100Hz, after proper antialiasing filtering, to reduce the computational complexity of subsequent analysis. Then, we high-pass filtered the data above 1Hz to improve stationarity. Afterwards, we removed flat and poorly correlated channels by exploiting the method presented in [63]. Briefly, each channel is compared with its reconstructed version obtained from the spherical interpolation of its neighbors, and is removed if the correlation coefficient is less than a user defined threshold. Here, we used a correlation threshold of 0.8. Moreover, we repaired nonstationary high-amplitude artifacts with the Artifact Subspace Reconstruction (ASR) algorithm [63], using optimal parameters as recommended in [64]. Specifically, the ASR, first, searches for the cleanest part of the data to use it as calibration data. Then, a sliding window is applied to the data, and for each window the EEG signal is decomposed into its principal components (PCs) through Principal Component Analysis (PCA). The PCs whose variance exceeds a component-specific cutoff

threshold are detected as artifact and thus removed. Finally, the removed PCs are interpolated based on the remaining ones, and the cleaned data is finally backprojected to its native space [63]. The component-specific thresholds are based on the variance of the calibration data's PCs, multiplied by a user-specified factor which determines how many times the variance of the PCs of the windowed data should exceed the variance of the calibration data's PCs in order to be considered an artifact. Higher values of such factor imply a very conservative filtering, whereas lower values correspond to a very sensitive one, with the consequence of removing not only artifacts but also relevant information from the data [64]. In this work, we adopted a conservative factor of 30, which has been shown to remove the majority of the artifacts, while preserving the information contained in the data [64]. We then visually inspected the EEG signal, to remove bad data not successfully repaired by the ASR. More than the 92.74% of the original data was retained at the end of this process. Removed channels were recovered via spherical interpolation and the data was re-referenced to its average. Lastly, we decomposed the EEG signals with Independent Component Analysis (ICA) by means of the Adaptive Mixture ICA (AMICA) algorithm [65]. AMICA approximates the probability distribution function (PDF) of each independent component (IC) through a mixture of generalized Gaussian distributions [65]. Compared to other standard methods for ICA decomposition, which assume pre-defined PDFs for sub-Gaussian and super-Gaussian sources, AMICA has shown higher mutual information reduction, while unveiling a larger number of biophysically plausible dipolar sources [66], [67] Accordingly, we obtained components reflecting either brain activity or artefacts. Components which were likely to reflect artefactual activity were removed from the data (e.g., eye blinks, muscle activity, and other non-stereotyped artefacts).

E. SAM STATISTICAL ANALYSIS

We tested for significant differences in valence ratings among olfactory stimuli, while controlling for the effect of arousal ratings, through analysis of covariance (ANCOVA), with stimuli as group factor and arousal ratings as within-group covariate. Then, we performed a two-way ANOVA on the valence ratings, with stimuli and gender as grouping factors. Accordingly, we tested for significant differences in the perceived valence between genders, regardless of the olfactory stimulus, as well as for differences between genders depending on the olfactory stimulus.

F. DYNAMIC CAUSAL MODELING

We analyzed preprocessed EEG data with SPM12. Specifically, we modeled steady-state dynamics between coupled cortical sources using DCM for Cross-Spectral Densities (CSDs) [68]. This method allows to characterize neuronal dynamics from single-trial data, by inferring connectivity changes based on the modulation of both the amplitude and the phase properties of the observed EEG spectra. This framework attempts at reproducing the observed CSDs by modeling hidden brain sources dynamics with a bio-physically inspired class of models, called neural mass models, and using an observer equation to combine an project their activity onto the scalp:

$$\dot{x} = f(x, \theta, u) \tag{1}$$

$$y = h(\theta) = Lx + \epsilon \tag{2}$$

Each source is modeled by means of three types of neuronal populations: i.e., inhibitory interneurons, excitatory spiny stellate cells and excitatory pyramidal neurons, whose activity is parameterized in terms of membrane potentials and currents x. Endogenous inputs (i.e., neuronal innovations) u enter the spiny stellate cells layer and are represented by a mixture of white and pink Gaussian noise [69]. Brain sources are coupled together by means of *extrinsic connections*. Such connections are classified into forward, backward and lateral according with the hierarchical organization of the cortex [70].

The underlying neuronal activity is projected to the scalp by means of an electromagnetic forward model (2), characterized by a *lead-field matrix* L. Specifically, each column in L specifies how the electromagnetic field generated by brain sources spreads towards a given EEG channel, according with the volume conductor properties of the head. Here, we exploited the single equivalent current dipole (ECD) model to parameterize L. Nevertheless, other different spatial source models also exist [71]. Accordingly, the lead-field matrix was parameterized in terms of the three location and three moment parameters of the sources based on the ECD model.

Overall, the generated data y depends on both the neural mass model and the forward model parameters [69]. Under Gaussian assumptions, the likelihood associated with the observation model in (2) is:

$$p(y|\theta, \lambda) = N(h(\theta), Cov(\epsilon)) \tag{3}$$

Following the Bayes' rule, the likelihood is combined with a Gaussian prior density $p(\theta)$ over model parameters to give a posterior density:

$$p(\theta|y) = \frac{p(y|\theta, m)p(\theta)}{p(y|m)} \tag{4}$$

where m is the DCM model. Priors are introduced in the DCM framework to put physiological constraints on the parameters [28]. In particular, the variance is used to reflect the amount of prior knowledge about the parameter, with a small variance corresponding to more certainty about its expected value. Instead, the normalizing term $p(y|m)$ is called model evidence and has a central role in the DCM framework to compare different models. Particularly, the ratio between the model evidence of two different models allows to choose for the best model describing the data [72]. We used a Variational Bayes approach to estimate model parameters. Briefly, model parameters are iteratively updated to minimize the divergence between the conditional and the true posterior densities [72]. This can be viewed as an expectation-maximization (EM)

algorithm that performs a gradient descent on the free-energy objective function F:

$$\text{E step:} \quad q \leftarrow \min_{q} F(q, \lambda, m) \tag{5}$$

$$\text{M step:} \quad \lambda \leftarrow \min_{\lambda} F(q, \lambda, m) \tag{6}$$

$$F(q, \lambda, m) = D(q(\theta)||p(\theta|y, \lambda, m)) - \ln p(y|\lambda, m) \tag{7}$$

where, the conditional density $q(\theta)$ is approximated as Gaussian with mean η and covariance Σ, and D is the Kullback-Leibler divergence between the conditional and the true posterior densities. During the E-step (5), the gradient descent on F is performed with respect to the conditional moments η and Σ, whereas in subsequent M-step (6) F is optimized with respect to hyperparameters λ. Such procedure is performed iteratively until convergence is reached.

A feature of DCM is the possibility to evaluate the modulatory effect of an experimental condition (e.g., a task) onto a given set of parameters θ, with respect to another condition (e.g., a baseline). This effect is modeled by a subset of parameters θ_{mod}, which takes into account the additional effect of a deviant condition over a standard one. Here,we are interested in the parameters θ_{mod} encoding the modulatory effect of odor valence onto the weight of the extrinsic connections.

G. NETWORK SPECIFICATION

In DCM framework, the set of brain sources and their anatomical location can be specified a priori. In this work, we modeled a fully connected network including three brain sources: the PC, the EC and the OFC, due to their key role in the early stages of olfactory processing. Specifically, the PC represents the main cortical component of the primary olfactory region, and is implicated in olfactory pattern recognition and associative learning, due to dense bidirectional interactions with the AM at the subcortical level and top-down projections from both the OFC and the EC at the cortical level [2]. Particularly, the connections with the EC [11], [12] provide a bidirectional cortical access route to the emotional memory through the HIP [1]. Further, the OFC, i.e., the main target of primary olfactory areas, has a key role for the attribution of both reward and emotional valence meaning to olfactory stimuli [3], [8], [25].

Based on previous literature [1], [2], [10], [73], we defined the hierarchy of the network in terms of forward (bottom-up) and backward (top-down) connections among the sources. Accordingly, we specified PC→EC, PC→OFC and OFC→EC as forward connections, and EC→PC, OFC→PC and EC→OFC as backward connections (Fig.1). Finally, to reduce model complexity and in line with the notion of a left lateralization of human processing [74], [75], [76], [77], [78], we limited the analysis to nodes in the left hemisphere: PC x $= -24$, y $= -4$, z $= -12$, OFC x $= -5$, y $= 31$, z $= -13$, and ECx $= -8$, y $= -11$, z $= -20$ [79], [80], [81].

H. EFFECTIVE CONNECTIVITY ANALYSIS

We evaluated the modulatory effects of odors valence onto the group connectivity by exploiting the Parametric Empirical Bayes (PEB) framework [46]. Such framework builds upon a statistical hierarchical model of connectivity parameters according with the following set of equations:

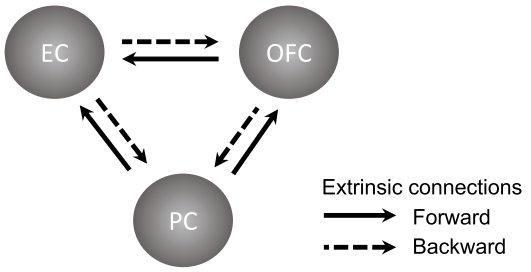

FIGURE 1. Modeled effective connectivity in a network comprising the PC, OFC and EC. Solid lines correspond to forward connections, whereas dashed lines correspond to backward connections.

$$Y_i = \Gamma(\theta_i^{(1)}) + \epsilon_i^{(1)} \tag{8}$$

$$\theta^{(1)} = (X_b \otimes X_w)\theta^{(2)} + \epsilon^{(2)} \tag{9}$$

where the first level (8) models the single-subjects observations (i.e., Y_i) as being generated by a DCM $\Gamma(.)$ with unknown parameters $\theta_i^{(1)}$, plus a zero-mean white gaussian noise residual $\epsilon^{(1)}$. The second level (9) models the first level parameters $\theta^{(1)}$ with a General Linear Model (GLM) having design matrix $X = (X_b \otimes X_w)$, where X_b models the between subject variability (i.e., the covariates), X_w models the within-subject variability (i.e., which model parameters are influenced by the between-subject effects), $\otimes$ denotes the Kronecker product, and $\theta^{(2)}$ represents second level parameters. Any unexplained between-subject difference (e.g., non-modeled sources of variations, random effects) is modeled by the zero-mean white gaussian residuals $\epsilon^{(2)}$. Finally, the prior distribution of $\theta^{(2)}$ is defined as a gaussian distribution, with fixed expected value η and covariance $\Sigma^{(3)}$. Furthermore, η is equal to the prior mean of the first-level parameters, whereas $\Sigma^{(3)}$ is equal to the first-level covariance adjusted for the scaling of the design matrix X (for more details see [46]).

I. FIRST LEVEL ANALYSIS

We modeled the modulatory effect of odors' valence on the single-subject connectivity by specifying the contrast between the 5sec stimulus-administration interval relative to each odor and the last 5sec of *initial rest* condition. Accordingly, we defined three different conditions: i.e., pleasant (*vanillin vs. resting-state*), neutral (*n-butanol vs. resting-state*) and unpleasant (*isovaleric acid vs. resting-state*) valence.

In DCM, the data is reduced to a few numbers of spatial components, or eigenmodes, through PCA. Particularly, the observed data can be modeled more into detail by increasing the number of modes. However, on the one hand, selecting too many modes may result in a computationally infeasible DCM, especially when using high-density EEG. On the other hand, increasing the number of modes has the drawback of capturing noise at the expense of meaningful neuronal dynamics [71], [82]. Here, we decomposed the data into

8 eigenmodes, which is the default value in SPM12 [82]. Such a choice allowed to retain the 99% of data variance while reducing computational load. Then, we estimated the CSDs between eigenmodes in the frequency range between 4-30Hz by using Bayesian multivariate autoregressive modeling with the default model order of 8 [83]. Such frequency range was chosen to take into account the EEG dynamics of the θ $(4-8)$Hz, α $(8-12)$Hz, and β $(12-30)$Hz bands. We adopted the ERP neural mass model to describe hidden brain sources' dynamics [84].

Concerning the forward model, we modeled the spatial activity of brain sources through equivalent current dipoles (the ECD option in SPM12) on the gray matter surface. The passive volume conduction effects of source's dipoles were described through a boundary element model (BEM) of the head, based on the standard head model template from Montreal Neurological Institute (MNI; Montreal, Canada). Here, we used a BEM model made of three layers, i.e., cortex, skull and brain, whose conductances were set to 0.33, 0.0042 and 0.33 S/m, respectively. Dipoles' projection from the cortex to the channels was determined by parameterizing the lead-field matrix L in terms of the three location and three moment parameters of the sources.

Since premature convergence issues may arise due to the presence of free-energy local maxima (see [85], [86]), we inverted each single-subject model (8) by following a two-step procedure. First, we increased the value of the hyperparameter responsible for the expected precision of the data (i.e., hE = 20), and we fitted the DCM models until convergence. On the one hand, such a procedure biases the model fitting towards the observed data, rather than towards the priors set. On the other hand, the fitting accuracy is increased at the expense of an increase in model complexity. Then, the obtained parameter and hyperparameter estimates were used as the starting point of a new model fitting procedure where the modified hyperparameter (i.e. hE) was restored to its original value.

J. SECOND LEVEL ANALYSIS

For each stimulus, we grouped together the parameters of the modulatory effects across subjects. Accordingly, we had three distinct sets of parameters $\theta^{(1)}_{mod_j} = [\theta^{(1)}_{mod_{j,1}}, \ldots, \theta^{(1)}_{mod_{j,i}} \ldots, \theta^{(1)}_{mod_{j,N}}]^T$, where $j = 1, 2, 3$ are the stimuli and $i = 1, \ldots, N$ are the subjects. For each stimulus j, we fitted a PEB model with design matrices X_b and X_w as depicted in Fig.2. Specifically, we constructed X_b as a three-column matrix, where the first column was a constant vector of ones modeling the commonalities across subjects, the second column was a categorical variable representing the gender and the third column was the perceived arousal of the j-th stimulus for the i-th subject. Both gender and arousal were mean-centered, endowing the first covariate (i.e., the commonalities) with the interpretation of the group mean effective connectivity [46]. Gender was coded with males as 1 and females as -1. We chose X_w as the identity matrix. Accordingly, each parameter could be influenced by the between-subject effects.

For each PEB model, we applied a greedy search to find the combination of second-level parameters that best described the commonalities, the effect of arousal and the effect of gender, respectively (*spm-dcm-peb-bmc*). In particular, we used Bayesian Model Reduction (BMR) to prune away parameters not contributing to the model evidence [46]. All the models were assumed to be equally probable a priori. Finally, we calculated a Bayesian Model Average (BMA) over the models resulted from the final iteration of the greedy search. BMA performs an average of the parameters posterior densities across models, weighted for their model posterior probability (Pp). Accordingly, a set of parameters estimates was obtainted. Such estimates were no longer conditional on the particular model assumed. We finally thresholded the BMA results of each stimulus. Specifically, we pruned away the parameters having probability of being influenced at the group level (i.e., the probability associated to the difference between the log evidences of the models with and without a given parameter, respectively) lower than 0.95. In particular, we based such thresholding on the free-energy of the models, to also consider the full covariance of parameters when assessing their contribution to the model evidence (see Appendix 3 of [46]).

K. CONNECTIVITY ANALYSIS SUMMARY

Here, we aim at resuming the implementation steps of the connectivity analysis.

As schematically represented in Fig.3, after EEG data preprocessing, for each subject we performed:

- extraction of 5sec-long EEG epochs for the three odor's administration conditions and for the last 5sec of resting-state (Fig.3a);
- data reduction to the first 8 principal modes, and estimation of the CSDs relative to each EEG epoch and for each mode, with a Bayesian MVAR with default order of 8, in the 4-30Hz frequency range (Fig.3b);
- specification of the contrasts between the odors' administration conditions and the resting-state CSDs to model the modulatory effect of odors' valence (Fig.3c);
- definition of the network nodes, in terms of their position in the MNI space and of their hierarchical connections: i.e., PC→EC, PC→OFC and OFC→EC as forward connections, and EC→PC, OFC→PC and EC→OFC as backward connections. All the connections are allowed to be modulated by odors' valence (Fig.3d);
- specification of the ERP NMM to model the evolution of sources' dynamics (Fig.3e);
- specification of the standard forward model provided by SPM12 with the ECD option (head model: standard MNI template; three-layer BEM for volume conduction effects) (Fig.3f).
- Model inversion with the hyperparameter hE=20. Parameter estimates are used to initialize the final fitting scheme, with the default value of hE=8 (Fig.3g).

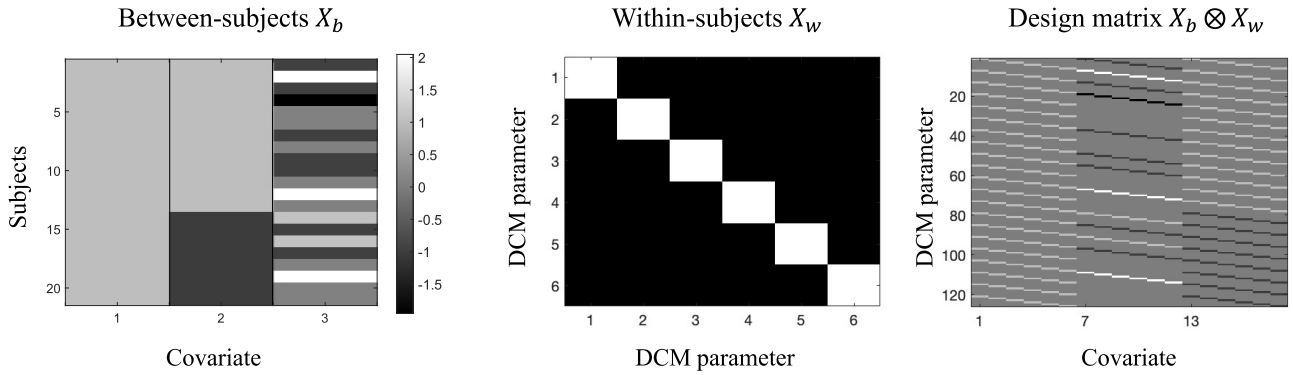

FIGURE 2. The group level design matrix. Left: between-subject design matrix X_b, with covariates modeling the group mean, gender and perceived arousal. Both gender and arousal covariates are mean-centered, endowing the first covariate (i.e., the commonalities) with the interpretation of the mean group connectivity. Accordingly, for the gender, females and males are decoded with -1 and 1 respectively, whereas the transformed arousal range is represented by the colorbar. Middle: the within-subjects design matrix X_w, whose diagonal specifies which DCM parameters are influenced by the between-subjects effects. Right: the model design matrix X, where each column is a covariate associated to a particular DCM parameter, and each row correspond to a DCM parameter of a given subject.

The parameter estimates indicating the modulatory effect of odors' valence on the connectivity were put together across the subjects for the second level analysis. Then, we constructed the within-subject and between-subject level matrices as follows:

- definition of X_b with gender and arousal as between-subject effects, mean-centered with respect to the first column of ones (i.e., mean group connectivity; added by default in SPM12);
- definition of $X_w = I$, to allow each parameter to be influenced by X_b;

Finally, for each different odor:

- fit a PEB model with X_b and X_w as above (Fig.3h);
- for each between-subject effect: greedy search with BMR on the corresponding PEB estimates and BMA across all the explored model space; pruning of those connections having Pp$<$ 0.95 of being present vs. absent based on the free-energy principle (Fig.3i).

III. RESULTS

A. SAM STATISTICAL ANALYSIS

The estimated scores (mean±standard error (SE)) for the valence and the arousal were 1.43±0.18 and 2.95±0.24 for the pleasant odor, -0.67±0.19 and 2.57±0.29 for the neutral odor, and -1.43±0.15 and 2.33±0.28 for the unpleasant odor respectively. The results of the ANCOVA test are summarized in Table 1. We report the main effect for both stimuli and arousal, along with their standard error and the t-statistic against the null hypothesis of no effect. The model was significant against the null hypothesis of equal effect sizes among the stimuli ($F_{4,59} = 52.2$, $p = 1.34 \times 10^{-16}$). Furthermore, from the t-statistic, we observed a significant effect for each of the three stimuli on the valence scored, while we found no significant correlation between the arousal and the valence ratings given for each stimulus. Post-hoc analysis showed significant differences among all three odorants. The results of the two-way ANOVA on valence ratings are reported in Table 2. As expected by the previous ANCOVA test, we observed a significant main effect for the stimuli ($F_{2,57} = 69.46$, $p = 5.22 \times 10^{-16}$). On the other hand, we found no significant main effect for both the gender and the interaction between stimuli and gender. The post-hoc analysis among the three stimuli highlighted significant differences in each pairwise comparison, as reported in Fig.4. Specifically, subjects rated vanillin as significantly most pleasant (mean valence $= +1.44$) while the isovaleric acid as significantly most unpleasant (mean valence $= -1.37$). The n-butanol showed a middle rating (mean valence $= -0.71$) significantly different from both the vanillin and the isovaleric acid.

TABLE 1. Summary of the ANCOVA on the subjective valence ratings, with stimuli as factors and arousal ratings modeling within-group variance.

	Estimate	SE	tStat	pValue
Vanillin	1.8202	0.28894	6.2996	4.0937e-08
n-butanol	-2.1458	0.24057	-8.9197	1.5552e-12
Isovaleric acid	-2.9393	0.24367	-12.062	0
arousal	-0.13266	0.079442	-1.6699	0.10023

TABLE 2. Summary of the two-way ANOVA on the subjective valence ratings, with factors stimuli and gender.

	Sum Sq.	d.f.	Mean Sq.	F	Prob>F
stimuli	85.635	2	42.8173	69.46	5.22e-16
gender	0.12	1	0.1197	0.19	0.6612
stimuli*gender	1.698	2	0.8491	1.38	0.2605
Error	35.135	57	0.6164	0.10023	
Total	128.889	62			

B. FIRST LEVEL ANALYSIS

The principal eigenmodes in our data showed a marked peak in the α band, and a secondary peak in the β band. Fig.5 shows the observed CSDs, together with the spectra predicted by the DCM model after inversion for an exemplary subject. As depicted, DCMs were able to accurately capture

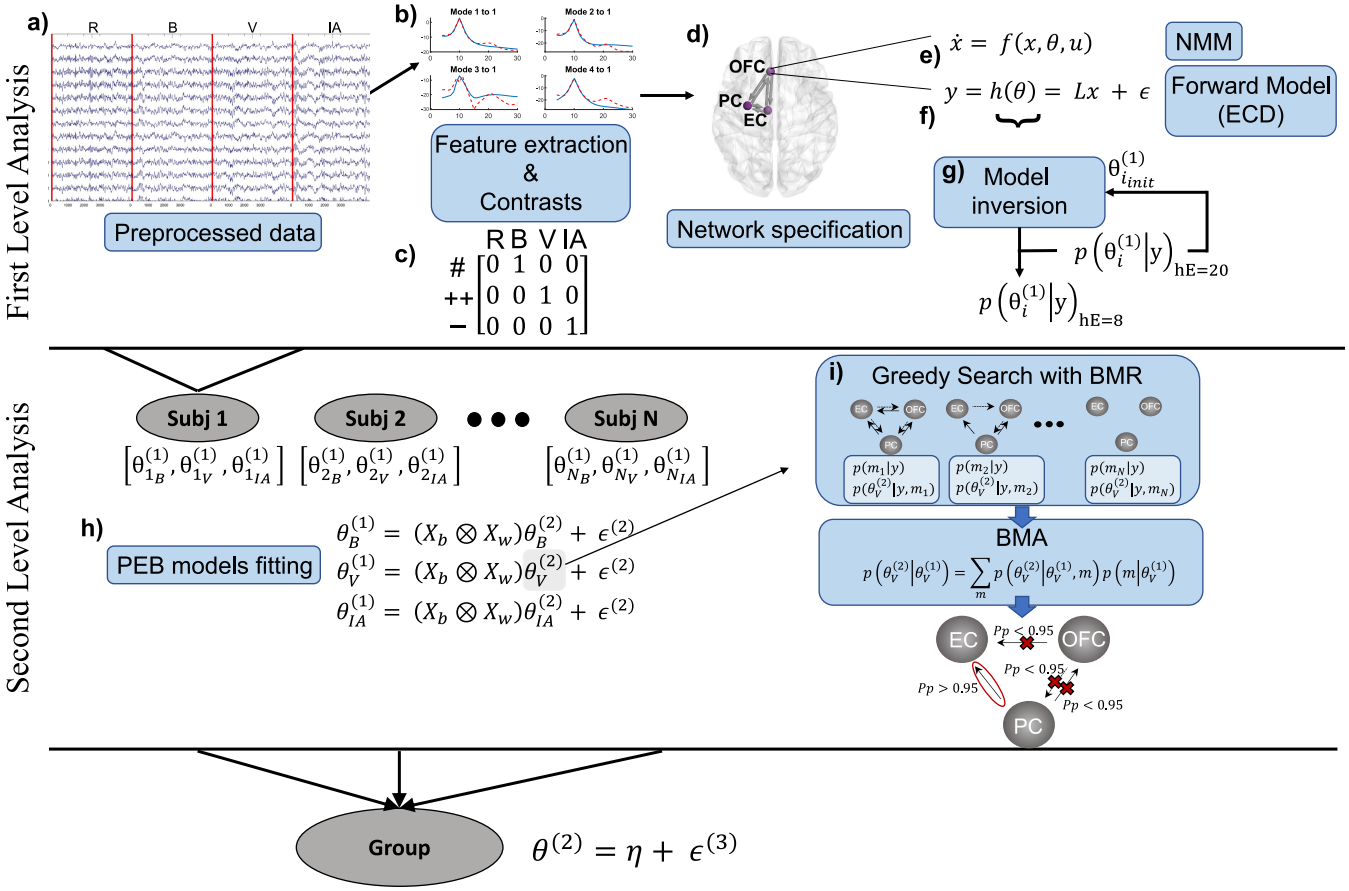

FIGURE 3. Schematic illustration of the connectivity analysis performed with DCM. In the first level analysis (top): (a) preprocessed EEG data is segmented into 5sec-long epochs consisting of the three odors' administration conditions (i.e., n-butanol (B), vanillin (V) and isovaleric acid (IA)), and the last 5sec of resting-state (R). (b) The data is then reduced to its first 8 principal modes, and for each condition and for each mode, the cross-spectral densities (CSDs) are estimated through a Bayesian multivariate autoregressive (MVAR) model of order 8 in the frequency range (4-30)Hz. (c) The modulatory effect of valence on the connectivity is specified through the between-trial effects matrix, which models the contrast between the observed CSDs relative to the odor conditions and the resting-state. Accordingly, three experimental manipulations are defined, namely *neutral* (#), *pleasant* (++) and *unpleasant* (−−) valence. (d) The network is defined by specifying the (x, y, z) position of the nodes in the MNI space and their reciprocal extrinsic connections. (e, f) The ERP neural mass model is used to emulate sources' dynamics, whose activity is then projected to the electrodes on the scalp with the standard ECD forward model provided by SPM12. (g) The initial parameter estimates for model inversion (i.e., $\theta^{(1)}_{i_{init}}$) are obtained by fitting the model with hE=20. Then, the model inversion procedure is repeated using the obtained $\theta^{(1)}_{i_{init}}$ and the default value of hE=8. (h) Parameter estimates of the valence modulatory effects $[\theta^{(1)}_{i_B}, \theta^{(1)}_{i_V}, \theta^{(1)}_{i_{IA}}]$ are taken to the second level, and are put together across the subjects into the $\theta^{(1)}_B$, $\theta^{(1)}_V$ and $\theta^{(1)}_{IA}$ group terms respectively. A PEB model is fitted on each of these subsets of parameters, with group-mean connectivity, gender and arousal modeling the between-subject effects. (i) A greedy search with Bayesian Model Reduction (BMR) is applied on the estimates $\theta^{(2)}_{B,V,IA}$ of each PEB model for each second-level effect in X_b, followed by Bayesian Model Averaging (BMA) to obtain a unique model of connectivity, given by those connections with the greatest evidence. Finally, connections having a posterior probability $Pp < 0.95$ of being present *vs.* absent based on the free-energy principle are pruned away. (bottom) The prior distribution of second-level parameters is a Gaussian distribution with expected value η and covariance $\Sigma^{(3)}$.

the frequency content in the θ band, together with the most prominent part of the spectra, i.e., the α peaks. Nonetheless, the fitting of secondary spectral features was found to be more challenging, as the observed β peaks were sometimes not considered by the models. For each subject, DCM models were successfully fitted without observing any problem of early convergence. The explained variance of the models was 80.92% on average, ranging from 65.15% to 98.02%, indicating an overall good representation of the data.

C. SECOND LEVEL ANALYSIS

Results of BMA are depicted in Fig.6 for the *n-butanol*, *vanillin* and *isovaleric acid*, respectively. Specifically, for each condition and for each second-level effect, i.e., the mean-group connectivity (commonalities), the gender and the arousal, we report the PEB parameters relative to the connections with the highest evidence of being modulated and having a Pp of being non-zero greater than 95%. Particularly, for each of the parameters that survived the threshold, we report its estimated posterior effect size and the corresponding 90% credibility interval, through a black bar and a pink error bar, respectively.

1) COMMONALITIES

The commonalities encode what is common to all the subjects, and they indicate the average modulatory effect of

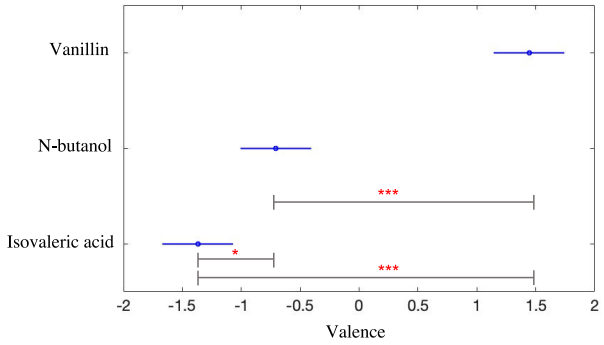

FIGURE 4. **Post-hoc analysis of the two-way ANOVA (Mean ± standard error; corrected with the Tukey-Kramer critical value). We observed the valence ratings to be different for each of the three stimuli, with vanillin rated as pleasant and isovaleric acid rated as unpleasant. The n-butanol was rated as slightly unpleasant. *p<0.05, **p<0.01, ***p<0.001.**

odors' valence on the group connectivity. Negative values in the effect size of commonalities indicate an inhibitory effect on the connectivity, whereas positive values indicate an excitatory effect. Indeed, such an effect size operates as log-scaling parameter on the prior mean of connectivity strengths. In our analysis, the administration of *n-butanol* did not show any significant effect ($Pp < 0.95$) at the group level, indicating that none of the connections in the network was either inhibited or strengthened. On the other hand, we observed a negative effect size on the backward connection from EC to PC for both *vanillin* (effect size = -0.56; $Pp = 0.99$) and *isovaleric acid* (effect size = -0.28; $Pp = 1.00$).

2) GENDER

Considering the results of the gender covariate, negative values of the effect size estimates indicate that the modulatory effect of the odors' valence on the connectivity was greater in females than in males based on the modeling setup. As for the commonalities, these effect sizes have the meaning of log scaling parameters on the connectivity strengths. The valence of the odors consistently showed a greater modulatory effect on the connectivity of females, compared to males. Particularly, during the stimulation with *n-butanol* we observed a negative effect size for the PC→EC forward connection (effect size = -0.45; $Pp = 0.99$), and for the backward connections EC→OFC (effect size: -0.24; $Pp = 0.97$) and OFC→PC (effect size: -0.29, $Pp = 0.98$). These results indicate a greater modulatory effect of *n-butanol* in females, with respect to males, on the strengths of PC→EC, EC→OFC and OFC→PC. During the stimulation with *vanillin*, we found higher connectivity strengths of the forward connections PC→OFC (effect size = -0.18; $Pp = 0.97$) and PC→EC (effect size = -0.45; $Pp = 1.00$) in females, with respect to males. Finally, during the stimulation with *isovaleric acid*, we found higher connectivity strengths of the PC→EC forward connection (effect size = -0.28; $Pp = 1.00$) and the OFC→EC backward connection (effect size = -0.16; $Pp = 0.97$). Interestingly, we always found a negative effect size of gender on the PC→EC forward connection. This indicates that such a connection was always stronger in females than in males, regardless of the stimulus.

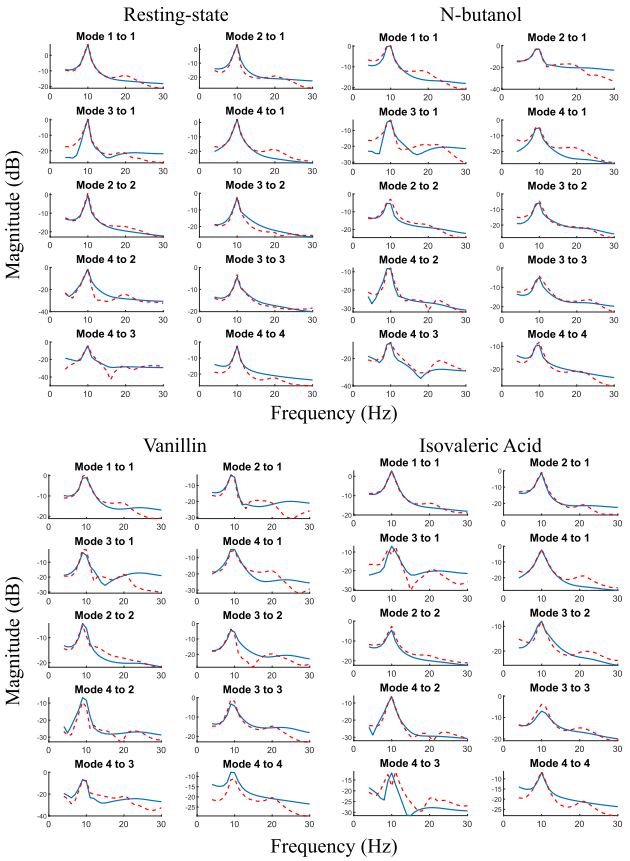

FIGURE 5. **Cross-spectral densities (CSDs) for the first 4 principal eigenmodes of EEG channel mixtures for an exemplary subject during the last 5sec of initial resting-state (top-left), and during the 5sec of odor administration for the *n-butanol* (top-right), *vanillin* (bottom-left) and *isovaleric acid* (bottom-right) respectively. Observed CSDs are depicted in red, whereas model-predicted CSDs are depicted in blue.**

3) AROUSAL

Concerning the analysis of the arousal level as covariate, a positive effect size indicates that the higher the perceived arousal, the stronger the excitatory effect of odors' valence on the connectivity. On the other hand, a negative effect size indicates that the higher the perceived arousal, the higher the inhibitory effect of valence. We did not observe any significant effect in response to the administration of both *n-butanol* and *vanillin*, on any of the network connections ($Pp < 0.95$). This indicates that there were no interactions between the modulatory effect of the valence of these odors and the perceived level of emotional arousal. On the contrary, we observed a positive effect for the arousal on the PC→EC forward connection during the negative stimulation with *isovaleric acid* (effect size = 0.22; $Pp = 0.97$). This means that the strength of such connection was greater in subjects who perceived the stimulus as more arousing.

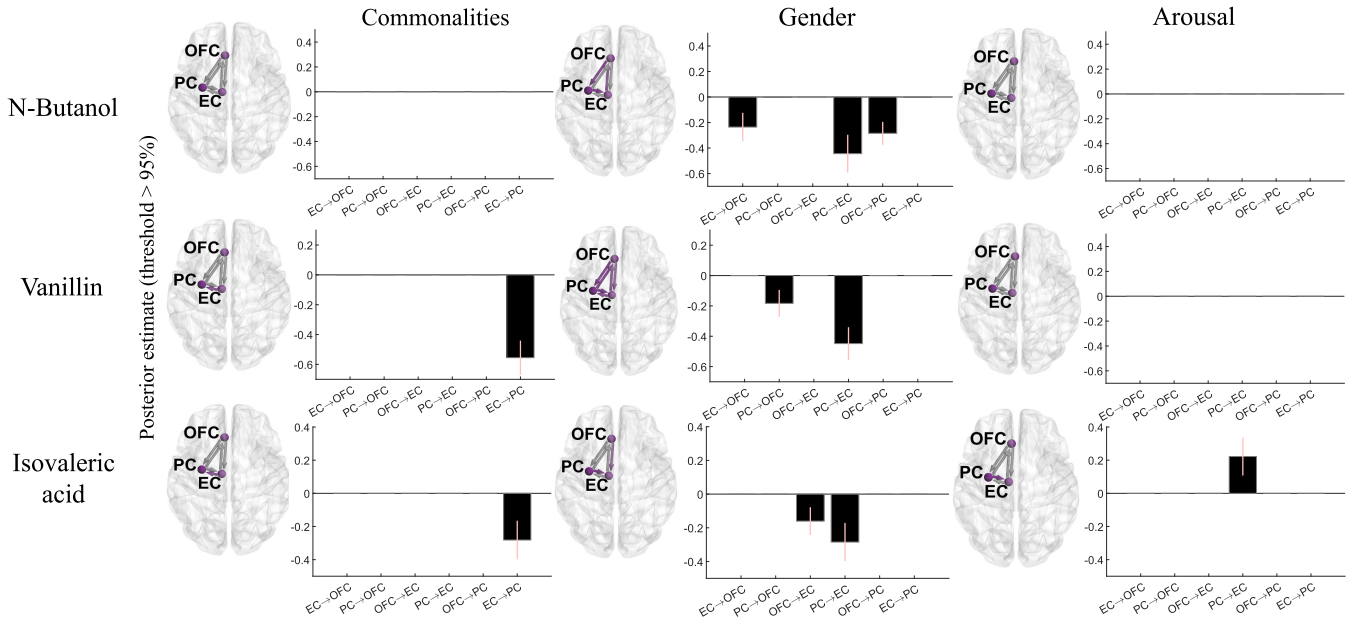

FIGURE 6. Results of BMA. For each stimulus (rows), the height of the black bars indicates the 95%-over threshold parameters showing the modulatory effect of odor's valence among subjects (first column; ***Commonalities***), the effect of gender (second column; ***Gender***) and the effect of arousal (third column; ***Arousal***) onto each connection. Pink error bars indicate the 90% credibility interval around each posterior estimate. The brain figures depict the rendering of our network on the axial plane. For each condition, the connections reporting a significant modulation are shown in purple.

IV. DISCUSSION

In this work, we used olfactory stimuli with different emotional valence to investigate the effects of the hedonic properties of odors on group-level effective brain connectivity. In addition, we considered between-subject differences determined by both gender and the perceived level of arousal on such connectivity changes induced by odors' valence. To this aim, we analyzed a fully connected cortical network directly involved in olfaction, emotion, and memory processing: i.e., the PC-EC-OFC network, focusing on the left hemisphere. Indeed, the left lateralization in human olfactory processing is widely reported in the literature [74], [75], [76], [77], [78]. Structural connectivity and electrophysiological studies demonstrated stronger intra-hemispheric connectivity between the primary and the secondary olfactory regions in the left hemisphere, and robust asymmetrical activation of the left-PC during odor discrimination learning. [77], [78]. We used DCM for CSD to estimate changes in the cortico-cortical interactions of such network induced by odor stimuli with different valence at the single-subject level. Then, for each stimulus, we used the PEB framework to estimate the average modulatory effects (commonalities) of odors' valence, and the between-subject effects of both gender and arousal on the effective connectivity at the group level. Therefore, we limited the influence of single-subject uncertainty on the parameter estimates at the group level. Our results suggest that well-known gender differences in olfactory perception [30], [31], [32], [33], [34], [35], [36], [37] are also reflected by changes in the effective connectivity of the olfactory cortical network under study.

We found a negative modulatory effect induced by both the pleasant odor and the unpleasant odor on the EC→PC backward connection. Accordingly, we may suggest that the effect of valence was reflected by the inhibition of a specific connection, which happens independently by the sign of the valence. Consistently, we found no modulatory effect of the neutral odor on any connection. Our results confirmed previous evidence describing EC as the gateway to the odor's emotional processing [9], [10]. Furthermore, EC→PC backward connection can be associated with top-down modulation of fine odor discrimination [10]. In this view, perceiving a neutral odor could reflect a more active tuning than a pleasant/unpleasant odor perception, due to greater difficulty in evaluating its potential meaning (e.g., threat or reward). It is important to remark that such observations are referred to the average effect on the group connectivity.

Further relevant findings were shown by the analysis of the effect of gender on the connectivity. We observed differences between genders at least in one connection of the network, for all three stimuli. This result is in line with previous studies showing a gender effect on olfactory sensitivity, olfactory emotional responses, and functional differences in response to olfactory cues [37], [39], [40], [41], [42], [87], [88]. Specifically, the effect size of females was always greater compared to males. Interestingly, we found the forward connection from PC to EC to be strongly modulated in females, compared to males, irrespective of the odorant. In this view, we may speculate that females have better performances in odor-associated learning, irrespective of odors' valence. In addition, during the exposure to *n-butanol*,we observed a greater

modulatory effect on females, compared to males, on the EC→OFC and OFC→PC backward connections. Since the PC has a role in the integration of odors' representation with other information coming from higher-order structures [89], we may consider these effects as the activation of a top-down modulation path starting from the EC and terminating down to the PC (i.e., EC→OFC→PC). Given the role of OFC in the discrimination of odors' valence [3], we may suggest that a stronger activation of such top-down pathway in females confers them a better performance in the pattern recognition of neutral odors, which may be more difficult to discriminate compared to emotional odors [2]. However, we found such a top-down path to be no longer activated in females when an odor with emotional content was administered. Indeed, when the pleasant stimulus (i.e., *vanillin*) was presented, part of the same pathway in females was activated but in the opposite direction (i.e., bottom-up direction). Specifically, we observed a stronger activation of the forward connection from PC to OFC. Conversely, when the unpleasant odor (i.e., *isovaleric acid*) was administered, the forward connection from OFC to EC was more activated in females, compared to males. Previous results have shown a role of the OFC in the evaluation of pleasant/unpleasant odors [3], [8]. In this view, we may relate the stronger connection from PC to OFC for *vanillin* to a greater reward component [3]. On the other hand, we suggest that the stronger connection from OFC to EC could be related to a greater cognitive control/attention women have shown for negative odors [90], [91].

Concerning the arousal role in affective odor processing, we found an effect of arousal on the connectivity during the administration of *isovaleric acid*. On the other hand, no effect of the arousal was present during the exposure to either *n-butanol* or *vanillin*. This is in line with previous literature, suggesting that negative stimuli are typically more arousing than positive stimuli [12], [92]. In particular, we observed that higher perceived arousal was associated with a greater increase of the connection strength from PC to EC. The PC has a role in the association between odors and behavioral, cognitive, and contextual information, provided by the reciprocal connections with higher-order structures (e.g., EC, perirhinal cortex, prefrontal cortex) [2], [89]. Specifically, it has been hypothesized that the bidirectional interactions between PC and EC have a role in odor-associative learning and memory retrieval [89]. Here we speculate that the associative learning due to PC→EC is enhanced by the arousal level of unpleasant odors.

SAM analysis showed that subjects perceived all three stimuli as having a different valence content. However, we did not observe any correlation of the valence with the arousal, within any stimulus. Furthermore, we found neither an effect of gender on the valence nor an interaction between stimuli and gender, meaning that there was no difference in the valence ratings between males and females. The discrepancy between SAM results and the results from the connectivity analysis is not totally unexpected. Indeed, differently from odor perception, the performance of affective ratings is a slower process in which odor information is elaborated and integrated with top-down influences such as odor knowledge and prior experience [93], [94], [95]. Accordingly, it could be possible that the affective ratings of olfactory stimuli may be the result of partially different processes not taken into account in our analysis.

Our considerations are based on the assumption that the observed average modulatory effect on the group-level connectivity (i.e., the commonalities) would reflect the processing of the valence of odors. However, we should consider that other effects, such as those related to the processing of different odors, may influence the observed dynamics. Such ambiguity has been mitigated by the experimental design and data modeling strategies: first, we designed a cortical network selecting brain regions that are known to be involved in the processing of hedonic olfaction; secondly, we used three isotonic and isointense solutions that have been previously proven to convey pleasant, neutral and negative emotional valence [48]. This choice was also supported by the statistical analysis of the reported SAM, which confirmed a strongly significant difference in the valence of the odors (and not in the arousal). Finally, our findings on the connectivity highlighted a significant modulation due to the administration of both the pleasant and the unpleasant odor, while no connectivity changes were observed due to the administration of the neutral odor. Accordingly, we believe that our model was able to reflect the processing of the valence of odors, while mitigating potential effects related to other dynamics of no interest.

A potential limitation of our study is related to the deepness of the cortical regions considered in our network. More specifically, the EEG inversion may fail in localizing activity in such deep regions [25]. Here, we used the positions of the PC, EC and OFC in a standard space (i.e., the MNI template), and exploited the key feature of DCM for EEG of estimating interactions among sources for a set of pre-specified regions. Future analyses could consider the identification of cortical sources contributing to the EEG signals by solving the EEG inverse problem without any *a priori* hypothesis.

Moreover, the choice of limiting our study on the PC-EC-OFC cortical network could exclude other brain regions involved in the neural processing of hedonic olfaction, such as AM, HIP and insula (INS) [1], [96], [97]. However, investigating the activity of such subcortical regions using EEG remains challenging, due to both their distance from the scalp and complex cellular architectures compared to cortical areas [98]. Hence, the integration of EEG with other techniques such as fMRI may be necessary. Nevertheless, we can still assume to indirectly capture part of their contribution, since bidirectional projections among AM, HIP, INS and the nodes of our network exist [1], [96]. Other cortical regions, such as superior temporal gyrus (STG), precuneus (PCC/PCu) and cingulate gyrus (CgG) have been also found [25] in our previous study using MVAR on the same olfactory data. Although, these regions are known to participate in the processing of emotions and memory [99],

[100], [101], they may have less specific roles in the processing of hedonic olfaction, as compared to PC, OFC and EC [1], [19]. Indeed, STG, PCC/PCu, and CgG are involved in a variety of processes different from olfactory perception, such as high-order auditory processing of speech, visuo-spatial imagery, and processing of painful stimuli [102], [103], [104]. Accordingly, we limited our analysis to a smaller network that could be more specific of the early olfactory processing stages.

Future works could evaluate the role of inter-hemispheric connections on the neural processing of hedonic odors by extending our modeled PC-EC-OFC network to the right hemisphere. In addition, we could expand the PC-EC-OFC network to other salient cortical nodes as those resulted from our previous findings: i.e., STG, PCC/PCu, and CgG [25]. In particular, such future works must consider data collected from a greater number of subjects, to improve result reliability on larger networks.

V. CONCLUSION

In this work, we applied DCM to EEG data to investigate the impact of the hedonic content of odors (i.e., valence and arousal) and gender on the group effective connectivity of the PC-EC-OFC cortical network. The central role of the EC-PC backward and forward connections is clear in the results. Indeed, whereas the backward connection was modulated by the odor valence suggesting the necessity of finer discrimination for neutral and probably more ambiguous odors, the forward connection is modulated by the gender difference, regardless of the kind of odor under consideration, and by the arousal during the negative olfactory stimulus. EC has then confirmed as the gateway to the odor's emotional processing. We believe that this study will pave the path for further investigations on the neural processing of odors at the effective connectivity level.

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