Odor valence modulates cortico-cortical interactions: a preliminary study using DCM for EEG

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***Abstract*— Olfaction and emotions share common networks in the brain. However, little is known on how the emotional content of odors modulate dynamically the cortico-cortical interactions within these networks. In this preliminary study, we investigated the effect of odor valence on effective connectivity through the use of Dynamic Causal Modeling (DCM). We recorded electroencephalographic (EEG) data from healthy subjects performing a passive odor task of odorants with different valence. Once defined a fully-connected *a priori* network comprising the pyriform cortex (PC), orbitofrontal cortex (OFC), and entorhinal cortex (EC), we tested the modulatory effect of odor valence on their causal interactions at the group level using the parametric empirical bayes (PEB) framework. Results show that both pleasant and the unpleasant odors have an inhibitory effect on the connection from EC to PC, whereas we did not observe any effect for the neutral odor. Moreover, the odor with positive valence has a stronger influence on connectivity dynamics compared to the negative odor. Although preliminary, our results suggest that odor valence can modulate brain connectivity.**

I. INTRODUCTION

The intimate relationship between the sense of smell and emotions arises in the brain substrates shared between these two cognitive processes [1]. Indeed, once the olfactory information reaches the piriform cortex (PC) (i.e., the primary olfactory cortex), it is then projected to a variety of cortical and subcortical regions involved in memory and emotion. Particularly, the PC has bidirectional interactions with the orbitofrontal cortex (OFC) and lateral entorhinal cortex (EC) in response to olfactory stimuli with emotional content [2]–[5]. Moverover, it has been reported the role of the OFC in evaluating the valence of olfactory stimuli, by interacting with the PC and other regions [6], and a potential role of the EC in providing a highly odor-specific and memory-dependent feedback to the primary olfactory cortex [7]. The investigation of how the neural response to odor stimuli with different valence modulates the cortico-cortical interactions among these three regions may provide useful insights on the relationship between olfaction, emotions and memory processing.

Dynamic Causal Modeling (DCM, [8]) offers a powerful framework to estimate, and make inferences about, the dynamical coupling among brain areas. This method is particularly suitable when confirming/rejecting a specific hypothesis about effective connectivity (i.e., the influence that one neural system exerts over another, [9]). In this context, both DCM for fMRI and for EEG have been developed [8], [10] and applied to several applications. In the field of olfactory neural processing, DCM for fMRI has highlighted an increase of the connectivity strength between PC, OFC and amigdala (AM) in response to experimentally induced anxiety stimulation [11]. In another study, the modulatory effect of attention to odor perception showed the activation of a thalamic specific pathway from PC to OFC [12]. On the other hand, to the best of our knowledge, DCM for EEG has not been applied yet to analyze the neural correlates of olfaction. Accordingly, EEG offers several advantages such as the possibility of measuring the electrical activity of the cerebral cortical sources at the time scale of olfactory processes [13]. Indeed, using EEG data, previous studies have applied source reconstruction techniques to find temporal cascades of cortical activations related to the processing of pleasant and unpleasant olfactory stimuli [14], [15]. In this sight, the application of DCM to EEG could represent an ideal way to evaluate modulatory effects of emotional valence on brain effective connectivity, explicitly modeling the activity of neuronal populations through firings rates and voltages, and thus resulting in a biophysically detailed method [10].

In this preliminary study, we evaluated how olfactory stimuli with different valence modulate the interaction between cortical brain sources involved in the olfactory processing. To this aim, we acquired EEG data from healthy volunteers performing a passive odor task. Odorants were chosen to convey pleasant, unpleasant and neutral valence [16]. We used DCM for EEG to infer effective connectivity among PC, OFC and EC. Specifically, we hypothesized that the stimuli could modulate all the connections of the network. Finally, we used Parametric Empirical Bayes (PEB) [17] to investigate how emotional valence modulated effective connectivity at the group level.

II. MATERIALS AND METHODS

A. Subjects

Twenty one healthy volunteers (age 26 ±2, 13 males) participated in the study. Subjects were asked not to drink or eat in the 30 minutes preceding the experiment. Participants were selected based on their olfactory threshold to N-butanol, with respect to distilled water, in order to ensure a homogeneous panel in terms of olfactory perception.

B. Experimental protocol

The experimental protocol was approved by the Ethical Committee of the University of Pisa. All participants signed

This research has received partial funding from European Union Horizon 2020 Programme under grant agreement n 824153 of the project "POTION Promoting Social Interaction through Emotional Body Odours"and the Italian Ministry of Education and Research (MIUR) in the framework of the CrossLab project (Departments of Excellence).

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an informed consent prior to the experiment. The experiment consisted of a 10 minute session, in which we administered 3 different stimuli: i.e., vanillin ($152.15 g/mol$), n-butanol ($74.12 g/mol$) and isovaleric acid ($102.13 g/mol$). Odors were selected in order to convey positive (vanillin), neutral (n-butanol) and negative (isovaleric acid) valence, based on previous studies [16]. Furthermore, concentrations were chosen to guarantee isointense solutions, and odor stimuli were administered by approaching vials at $2cm$ from participants' nostrils. Participants were asked to sit on a chair in an isolated room, and to keep their eyes closed for the entire duration of the experiment. Participants first performed 3 minutes of *initial rest*. Then, for each stimulus, there were three phases comprising: 1 minute of *rest pre-stimulus*, 5 seconds of *odor administration* and 1 minute of *rest post-stimulus*. The order of the olfactory stimuli was randomized across subjects.

C. EEG data acquisition and preprocessing

EEG data were acquired using a 128-channel Geodesic EEG System 300 from Electrical Geodesics, Inc. (EGI), with a sampling frequency of 500Hz. Electrodes were referenced to Cz, and impedances were maintained below $20k\Omega$. EEG preprocessing steps were performed using EEGLAB. First, we applied an anti-aliasing filter and we downsampled the data to a sampling frequency of 100Hz. Then, we high-pass filtered the data at the cut-off frequency of 1Hz with a non-causal filter to improve stationarity. We removed flat channels, poorly correlated channels and short-time high-amplitude artifacts (e.g., head movements, electromyographic activity, and other non-stereotyped artifacts) by applying the artifact subspace reconstruction (ASR) method [18]. After the visual inspection of the data, we applied spherical interpolation to recover removed channels and we referenced the data to the average of the channels. Finally, we applied Independent Component Analysis (ICA) to EEG signals to remove non-brain activity such as eye artifacts, muscular activity and other non-stereotyped sources of noise.

D. Dynamic causal modeling

Preprocessed EEG data were analyzed with DCM using SPM12. Specifically, we used DCM for cross-spectral densities (CSD) to describe the steady-state dynamics of a network of coupled cortical sources [19]. DCM for CSD is a generative model of observed electrical scalp activity in which each brain source is modeled with a neural mass model of unknown parameters [20], and the signal registered on the scalp corresponds to the projection of such hidden activity through a spatial electromagnetic forward model [10]. Starting from the recorded EEG signal, it is possible to estimate the posterior probability densities of the unknown parameters of neural mass models and the forward model by Bayesian model inversion. Specifically, parameters are estimated by maximizing the model's *negative free-energy*, an approximation of the model evidence that accounts for the balance between accuracy and complexity (i.e., the deviation of posterior estimates from the priors) [21]. Here, we adopted the ERP neural mass model [20] and the default forward model implemented in SPM12.

In DCM, the anatomical locations of the brain sources (i.e., network nodes) need to be specified a priori. Here, we focused on a network consisting of three cortical nodes involved in olfactory processing: i.e., PC (MNI coordinates -24 -6 -12), EC (MNI coordinates -8 -11 -20) and OFC (MNI coordinates 0 31 -13) [3]–[5]. Then, we modelled effective connectivity between such nodes by means of forward and backward connections [22]. In particular, these two type of connections differ in terms of their origin and target subpopulation, describing bottom-up (i.e., forward) and top-down (i.e., backward) modulations. Here, we hypothesized a fully connected network with PC→EC, PC→OFC, and OFC→EC as forward connections, and EC→PC, OFC→PC, and EC→OFC as backward connections (Fig.1) [1], [7], [23]. Then, we inferred the effective connectivity between each pair of nodes by a model inversion to analyze how different odor stimuli modulate connectivity. Indeed, the DCM framework allows to model changes in the strength of connections among nodes by comparing two or more different conditions [10]. Here, we evaluated how positive, negative and neutral odor stimuli modulated connectivity with respect to a resting baseline. (Fig. 1). To this aim, we performed a two-level analysis with the Parametric Empirical Bayes framework (PEB) to infer such modulatory effect at the group level starting from single subject estimates [17]. Such framework specifies a hierarchical statistical model of connectivity parameters according to the following set of equations:

$$\theta^{(1)} = X\theta^{(2)} + \varepsilon^{(2)} \tag{1}$$

$$Y_i = \Gamma(\theta_i^{(1)}) + X_0\beta_i + \varepsilon^{(1)} \tag{2}$$

where the first level analysis (2) allows to infer single subject connectivity parameters $\theta_i^{(1)}$ of the DCM $\Gamma(.)$ from the EEG measurements Y_i. Here, any uninteresting known effect (e.g., the signal mean) is modeled by a general linear model (GLM) with design matrix X_0 and parameters β_i, whereas the observation noise is modeled as residuals $\varepsilon^{(1)}$. The second level analysis (1) gives an estimate of the group level parameters $\theta^{(2)}$ by modeling the first-level parameters $\theta^{(1)}$ with a GLM having design matrix X. The design matrix X encodes the hypotheses regarding differences across subjects, and it is constructed by specifying the between-subject X_b and the within-subject X_w effects. X_b models the variability across subjects (i.e., the covariates), where each column is a covariate and each row is a subject. X_w defines which model parameters (e.g., connections) are influenced by the between-subject effects. The group level design matrix is then obtained according to $X = X_b \otimes X_w$, where $\otimes$ is the Kronecker tensor product. Differences across subjects not captured by X are then defined as zero-mean additive noise $\varepsilon^{(2)}$. Finally, priors on the second level parameters $\theta^{(2)}$ are

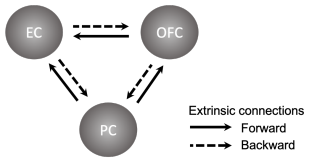

Fig. 1. Extrinsic connectivity between PC, EC and OFC. Solid and dashed arrows indicate forward and backward connections, respectively.

identical to the first level priors, except the prior variance is adjusted based on the scaling of the design matrix X (see [17] for a more detailed explanation).

E. First level analysis

Each experimental condition was modeled as a deviant condition with respect to a resting baseline. Specifically, we considered the last 5s of *initial rest* as the baseline, and the 5s long window of *odor administration* as deviants. Then, CSDs were computed using Bayesian multivariate autoregressive modeling [24] with the model order of 8 (SPM12 default), in the 4-30 Hz frequency range. Note that, CSDs were estimated on the first 8 principal eigenmodes of EEG channels mixture, in order to reduce data dimensionality while retaining the maximum amount of information [10]. Afterwards, we modeled each brain source as an equivalent current dipole on the cortical sheet and we chose the ERP neural mass model to model their activity [20]. Furthermore, we used a boundary element model of the head based on the template from Montreal Neurological Institute (MNI; Montreal, Canada) to model the passive volume conduction effects. The model described in (2) was inverted by maximizing the *negative free-energy*. Since model inversion may suffer from early convergence issues due to free-energy local minima (an exhaustive description of the problem is available in [25]), we adopted a two-stage procedure. First, we overfitted each model by setting the prior for the expected precision of the data to a higher value. This increases the reliability on achieving accurate fittings at the expense of model complexity [26]. Finally, we restored the prior to its original value and we repeated the fitting by initializing the priors with the posterior estimates of the previous step.

F. Second level analysis

We estimated the second level parameters (i.e., the modulatory effects of each stimulus at the group level) using three separate GLMs (1). To model the average connectivity across subjects, we defined $X_b = 1^T$, and we setted X_w as the identity matrix to include all the parameters in the analysis. Finally, we derived the second level design matrix as $X = X_b \otimes X_w$. After having estimated the parameters of the group level GLM, we performed an exhaustive search to test whether there was an effect of valence on the estimated connectivity using the PEB. Specifically, we hypothesized that valence could influence any connection in the network. Accordingly, we compared the evidence for reduced GLMs where certain combinations of parameters were 'switched off' (i.e., fixed at their prior expectation of zero). Specifically, we estimated the GLM parameters and posterior probabilities of all possible reduced GLMs, and derived group weighted-average connectivity through Bayesian model averaging (BMA, [17]):

$$p(\theta^{(2)}|\theta^{(1)}) = \sum_m p(\theta^{(2)}|\theta^{(1)},m)p(m|\theta^{(1)}) \qquad (3)$$

where the group level parameter distribution $p(\theta^{(2)}|\theta^{(1)})$ is obtained from the average over models m of the second-level GLMs parameters distribution $p(\theta^{(2)}|\theta^{(1)},m)$, weighted by their model posterior probability $p(m|\theta^{(1)})$. Such weighted-average gives the parameters which best explain the effect of odor valence on connectivity changes. Finally, we thresholded the results to retain only those parameters whose probability of being present *vs.* absent (i.e., the probability associated to the difference in evidence between the GLMs with/without a particular parameter) was greater than 0.95, which constitutes strong evidence [27].

III. Results

DCMs at the first level were successfully fitted for each subject, reporting no indications of early convergence. Specifically, the average explained variance was 80.92% (in the range 65.15-98.02%), indicating a good description of the data.

Second level analysis results are outlined in Fig.2. Specifically, we report the BMA of each stimulus under study (i.e., positive, negative and neutral) for each connection. The height of grey bars represent the effect size of the stimulus, whereas pink error bars indicate the 90% credibility interval. For the neutral odor (Fig.2a), we did not observe any strong evidence for a modulation of the connectivity between any node of the network. On the other hand, the connectivity strength of EC→PC decreased in response to both pleasant and unpleasant odors (Fig.2c,d), indicating the presence of an inhibitory effect (Fig.2b). Moreover, we observed that *Vanillin* had a stronger effect on such a connection with respect to *Isovaleric Acid*.

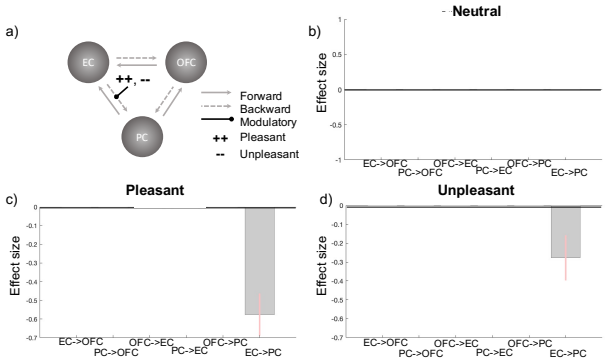

Fig. 2. BMA results. a) Effective connectivity and modulatory effects of odor valence between PC, OFC, and EC. b-d) Modulatory effects of neutral, pleasant and unpleasant odors on the group-connectivity. The grey bars represent the effect size of the stimulus, whereas pink error bars indicate the 90% credibility interval.

IV. Discussion and Conclusions

In this preliminary work, we investigated the modulatory effects of odor valence on effective brain connectivity through DCM for EEG. Specifically, we focused on a brain network made of reciprocally connected regions involved in olfactory, emotional and memory processing: i.e., PC, OFC and EC. Based on this network, we exploited the PEB framework to investigate the effects at the group-level of positive, negative and neutral odor stimuli on effective connectivity. Although preliminary, our results highlighted a different behaviour of connectivity based on stimulus valence.

Group level analysis showed no modulation of the neutral odor on any connection of the network. On the other hand, both the pleasant and unpleasant stimuli had an effect on the backward connection from EC to PC. Accordingly, we may suggest that olfactory stimuli with emotional valence may

produce changes in connectivity otherwise not elicited with neutral stimuli. Moreover, we observed that both positive and negative odors had negative-valued effect size, indicating a inhibitory effect on such a connection. It is worthwhile mentioning that the pleasant odor induced a stronger modulation than the unpleasant odor.

We are aware that modeling the neural circuits of olfactory perception could include other regions, such as AM and hippocampus [1], [28]. Yet, measuring subcortical activity with EEG is still tricky. In particular, the EEG inversion may be not feasible. Hence, although these regions have bidirectional connections with the nodes of our network, we cannot exclude their contribution to the observed connectivity. While EC is the gateway to the emotional processing of odors, the role of EC back projection to PC have been recently linked to a top-down tuning of fine odor discrimination [7]. Here, we speculate that such tuning is more active when the odor is neutral rather than when it is clearly pleasant or unpleasant since in the first case a more precise discrimination is needed to evaluate potential meaning (e.g., threat, reward etc.) of the presented odor.

To the best of our knowledge this is the first study applying DCM for EEG to investigate the modulatory effects of valence on the effective connectivity among brain regions involved in olfactory processing. Although preliminary, our results highlighted a physiologically plausible modulation of valence on EC→PC group average connectivity. In this view, future analysis could include other types of stimuli, as well as provide other experimental paradigms. We also argue that inter-subject variability could be considered as well when investigating the neural processing of odors. In fact, the influence of odors may differ, based on subject-specific factors such as age, sex, or cultural background [29]. Accordingly, it would be of interest to study the effect of inter-subject variability in response to odor valence, as for instance by including regressors of subjects specific differences in the PEB analysis.

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