Human Chemosignals Modulate Interactions Between Social and Emotional Brain Areas

Saideh Ferdowsi¹, Dimitri Ognibene², Tom Foulsham², Vahid Abolghasemi¹, Wen Li³ and Luca Citi¹

Abstract—Chemosensory communication is known as an effective way to influence the human emotion system. Phenomena like food selection or motivation, based on chemical signals, present a unique pathway between chemosensory and emotion systems. Human chemosignals (i.e., sweat) which are produced during different emotional states contain associated distinctive odors and are able to induce same emotions in other people. For instance, sweat is known as a social chemosignal participating in social interaction. Chemosignal perception engages a distributed neural network which has not been well characterized yet. In this paper, we use functional magnetic resonance imaging (fMRI) to investigate the neural circuits underlying social emotional chemosignal processing. Chemosignals associated with disgust and neutral conditions were used to induce specific emotional states in fMRI participants during a healthy food judgement. We performed fMRI analysis with the aim of detecting active areas in the brain, followed by a dynamic causal modeling (DCM) analysis. fMRI analysis revealed functional activity in the fusiform face area (FFA), amygdala (AMG) and orbitofrontal cortex (OFC). In order to determine the effective connectivity among these regions as a result of emotional chemosignal processing, a set of dynamic causal models is proposed. Estimating parameters of the proposed models shows that social chemosignals modulate the connections between FFA, AMG and OFC. The results indicate that social chemosignals of disgust converge on orbitofrontal cortex - an area which is a critical region for object appraisal and valuation - after first influencing fusiform face area and amygdala.

Index Terms—Human Chemosignal, Dynamic Causal Modeling (DCM), Effective Connectivity, fMRI

I. INTRODUCTION

Chemosignals play an important role as social cues which are able to carry a wide range of information [1]–[3]. Many animals communicate with each other by changing the chemical secretions of their body and skin. Food selection and sexual interest are two well-known examples of situations where chemosignals have a significant role in social communication [4], [5]. Since there is a unique association between the olfactory system and feeding, mice use chemical secretion as an effective tool for food related communication [6]. Although the role of human chemosignal in social communication is well supported, our understanding of the function of human chemosignals and its underlying neurobiological changes is limited. Nevertheless, valuable studies have been performed in this context. Jasper et al. [2] conducted a study with the aim of investigating how people communicate with their body secretions. They collected sweat from a group of healthy males who were attending emotional videos. Two emotions were elicited by the videos: fear and disgust. Then, a group of females with normal sense of smell were asked to sniff the collected chemosignals. Facial electromyography (EMG) was used to measure the activity of face muscles representing emotions induced by sniffing chemosignals. Acquired EMGs revealed that facial muscle configurations changed in line with the emotion that was experienced by the sweat donor when he was watching the emotional video.

A recent fMRI study examined the role of human chemosignals of disgust in facilitating food judgment [7]. In this study, a factorial design including social and non-social odors was used to induce emotional states which in turn facilitated food judgement. Zheng et al. [7] reported that chemosignals of disgust (i.e. sweat collected during the watching of a disgusting video) improved outcomes of food healthiness judgement. This seemed to involve the recruiting of key social and emotional areas of the brain.

Krusemark et al. [8] explored changes in emotion processing neural circuits when anxiety was induced by olfactory stimuli. They used fMRI followed by DCM analysis to investigate connections between olfactory and emotion systems in the brain. Although they did not employ social chemosignals (i.e., sweat), the outcome of their research provides meaningful information about the function of networks underlying olfaction-emotion processing. A combined anxiety induction and odor detection (negative vs. neutral) task was utilized to describe effective connectivity among nodes in the olfaction-emotion processing network. Results of the fMRI analysis revealed activity in the olfactory cortical hierarchy (APC, PPC and OFC) and two key emotion regions (amygdala and pregenual ACC/pgACC). Krusemark et al. [8] specified sixteen dynamic causal models including the above five regions in the right hemisphere. Bidirectional endogenous connections between regions were considered, along with an initial input of odors/air into either both APC and AMG or APC alone. The result of estimating model parameters before and after anxiety induction indicated that neutral odors were detected as negative odors after inducing anxiety. Moreover, subjects needed more time to detect these odors. Exploring the model’s parameters after anxiety induction indicated that the olfactory sensory system adapted to increased anxiety. This was explained through the amygdala having effective connections with all levels of olfactory cortex.

In other research, Hummer et al. [9] investigated how human chemosignals influence frontolimbic activity in re-
sponse to emotional stimuli. The main aim was to investigate the neural network underlying chemosignal impact when subjects attend to emotional stimuli. Hummer et al. [9] used dynamic causal modelling to characterize how human chemosignals change connections within this network during perception of emotional images. They repeated their experiments in the presence and absence of human chemosignals. The specified dynamic model involved primary visual cortex (VC), amygdala, prefrontal cortex (PFC) and orbitofrontal cortex (OFC) for both hemispheres. They considered bidirectional connections between all nodes apart from VC and PFC. Image blocks (i.e. visual stimuli) stimulated VC which was connected to the amygdala. The emotion of the image acted to modulate the connection between VC and the amygdala. Their findings showed that, in the presence of chemosignals, emotional images decrease the input from VC to amygdala, leading to increased activity in OFC and PFC. On the other hand, chemosignals enhanced activity in the areas allocated to attentional resources and emotional information processing by modifying amygdala connectivity.

To the best of our knowledge, Hummer et al. [9] is the only study which has examined the role of chemosignals in modulating effective connectivity in neural networks when an emotion processing task is undertaken. However, they did not focus on the direct neural influence of smelling chemosignals. Therefore, in order to investigate how social-emotional signals directly influence brain activity and connectivity during healthy food judgement, we conducted a DCM study of the fMRI dataset recorded by Zheng et al. [7]. Their finding showed that human chemosignals of disgust outperform visual signals in helping people distinguish between healthy and unhealthy foods. So, a connectivity analysis for this dataset can reveal important information about the brain mechanisms involved in social emotional interaction.

In the next section, details of the fMRI data used in this study is provided. This data was previously described and reported by Zheng et al. [7], and for full details the reader should consult this work. Information about the procedure that we have used to analyse data and implement effective connectivity is provided in section II. Section III presents the experimental results and section IV concludes the paper.

II. MATERIAL AND METHODS

A. Subjects

Eighteen healthy female participants took part in this study. The reason for recruiting females was that, on average, they have higher sensitivity to sweat chemosignals than men [10]. Exclusion criteria included abnormal olfaction, abnormal vision, nasal infections, allergies and neuropsychological problems. Subjects were asked to avoid consuming food with a strong smell or flavor within thirty minutes of the experiment. All participants gave written informed consent that was approved by the University of Wisconsin Institutional Review Board. Data of two subjects who could not perform the task were removed from the dataset. Further details can be found in [7].

B. Stimuli

A factorial experimental design including two emotions (disgust and neutral) × two sources (social and primary) × two modalities (visual and olfactory) was employed as stimulation to help subjects discriminate healthy and unhealthy foods. Social olfactory stimuli (sweat) were collected from fourteen healthy heterosexual Caucasian males1 who provided informed consent similar to the female participants. All sweat donors were non-smokers who had been asked to avoid odorous food, alcohol, deodorants, scented products, strenuous activity and sexual activity [2]. In order to induce emotions, sweat donors watched video clips containing disgusting and neutral scenes. Primary (non-social) olfactory stimuli were synthetic chemical odors which have been used to induce disgust and neutral emotions. Face images representing neutral or disgust emotions were used as social visual stimuli. Animal images such as cockroaches and bugs were used as disgusting primary visual stimuli. In contrast, bird and fish images were used as neutral primary visual stimuli. As mentioned earlier, in this study social and primary stimuli were employed to induce disgust and as a consequence influence food healthiness judgement. Therefore, a set of food images including healthy foods (apple, juice and multigrain bread) and unhealthy foods (donuts, cakes and cookies) were selected from the Object Categories Set [12], Figure 1 illustrates the experimental design. The paradigm consists of eight experimental conditions and one control

---

1The authors of [7] took the conventional approach in human chemosensory research by recruiting female subjects and male donors in the study. While we understand this inclusion criteria serves to reduce the variance in the sample and increase the chance to detect subtle social chemosignaling, we also acknowledge the important problem of bias in scientific research, which has long been recognised [11]. For this reason, any results will need to be reproduced on a more diverse population to assess their external validity.
condition. To note, each experimental condition includes 12 trials. Participants performed a food judgement task at the end of each trial. A grey fixation crosshair was presented for 2000ms when each trial started. In olfactory trials, the cue “Sniff Now” was shown on the screen for 300ms followed by a sweat or odor delivery for 2000ms. The screen remained blank during the delivery of olfactory stimuli. In visual trials, the cue “Watch Now” was shown on the screen followed by a face or animal image for 2000ms. After stimulus delivery, a food picture was presented on the screen for 700ms and subjects were asked to make a two alternative forced choice (“healthy” or “unhealthy”) using a button box. The ninth condition is control condition which delivered clean air to subjects. The order of stimulus was pseudo-randomized to have repetitive conditions over trials. More details about the stimuli can be found in [7].

C. fMRI acquisition and analysis

fMRI images were acquired using a 3T GE MR750 MRI scanner by eight channel head coil with sagittal acquisition. For each run of each participant, 655 volumes were scanned, each one containing 48 slices. Pulse sequence parameters were TR/TE=2350/20ms; flip angle=60°; slice thickness: 2mm, in-plane resolution/voxel size: 1.72 × 1.72mm and matrix size: 128 × 128. A high resolution structural image was also scanned. The first six volumes were discarded to stabilize longitudinal magnetization. Moreover, field map data including phase and magnitude images were acquired using a gradient echo sequence to correct EPI distortion. In this study, spatial normalisation and smoothing was performed with the Diffeomorphic Anatomical Registration Trough Exponentiated Lie algebra (DARTEL) package implemented in SPM12. Smoothing was performed using a 6mm full-width half maximum Gaussian kernel. After preprocessing, the number of slices and voxel size were changed to 91 slices and 2×2×2mm³, respectively.

In the second step, we conducted first level analysis to detect the BOLD signal. A general linear model (GLM) comprising of 9 onset vectors including 8 experimental conditions and the clean air control condition was specified for each participant. Onset vectors were coded as delta functions and convolved with canonical hemodynamic response function (HRF) with temporal and dispersion derivatives to generate event-related regressors for fMRI analysis. Six movement-related vectors estimated during spatial realignment were also included in the model as nuisance regressors to consider motion-related variance. After designing the model, the parameters (β values) associated with each predefined regressor were estimated.

In the third step of the fMRI analysis, the estimated parameters were submitted to one-sample t-tests, resulting in second-level analysis. Based on the previous results by Zheng et al. [7], we focused on amygdala, orbitofrontal cortex and fusiform face area (FFA) as regions of interest (ROIs). For this purpose a set of anatomical masks were defined based on Neurosynth meta analysis maps [14]. We used the MarsBaR toolbox [15] to generate these anatomical masks by defining a 8mm sphere around the peak voxels reported in Neurosynth meta analysis maps. The main focus of this work is on the neural processing associated with social emotional signals. Therefore the contrast “Disgust Sweat – Neutral Sweat” was considered for further analysis. In second-level analysis, the effects of interest that reach a heuristic threshold (i.e. p < 0.001, 10 voxel extent) are corrected for multiple comparisons across small volumes of interest (SVC; p < 0.05FWE) based on the predefined anatomical masks. The results of this analysis is reported in section III(A). The BOLD signals which were estimated in regions of interest were then used to investigate effective connectivity between the social and emotional areas of the brain. In the next section, details of the DCM technique employed to explore effective connectivity will be given.

D. Dynamic Causal Modeling

Dynamic causal modeling is a Bayesian framework predominantly used for inferring effective connectivity between brain regions [16]. DCM considers the brain to be a deterministic dynamic system (i.e. a neural network). Experimental stimuli (i.e. inputs) lead to changes in neural activity and as a consequence perturb the state of this system. DCM models variations of brain states based on the inputs and measured brain activities. In particular, DCM estimates a set of parameters including intrinsic, driving and modulatory parameters. Intrinsic parameters characterise effective connectivity between active brain regions. Effective connectivity refers to direct causal influences among neural populations in the network. Driving parameters refer to direct influence of inputs to change activity in the brain regions. Modulatory parameters characterise changes in the activity of neural states resulting from experimental input manipulation.

In order to start a DCM process, neural populations are selected between those active in the task-based fMRI analyses of interest. These areas form the nodes of network models of interacting neural populations. Figure 2 represents
Fig. 2. Illustration of the concept underlying dynamic causal modeling. In our study, $z_1$, $z_2$ and $z_3$ are FFA, Amg and OFC respectively and $u_1$ and $u_2$ are driving and modulatory inputs respectively.

a general schematic illustration of causal dynamic model considered in this study. Nodes $z_1$, $z_2$ and $z_3$ represent FFA, Amg and OFC respectively. In principle, the intrinsic connections among these nodes which transfer influence of activity from one node to connected nodes could be bidirectional, one-directional, or null. $u_1$ is driving input which can have direct influence on single, multiple, or no node(s). And $u_2$ is the modulatory input that is either nonexistent or able to modulate one or multiple nodes. It should be noted that the mentioned nodes are outputs of the dynamic network and produce observed brain signals which are BOLD signals here. Different combinations of intrinsic, driving and modulatory connections lead to generating different dynamic models. After specifying dynamic models, parametrized differential equations describe the interaction and neuronal dynamics of the network models. Then, taking into account prior beliefs about the value the parameter can assume and using the observed data, BOLD time series in this case, the posterior distribution for each unknown parameter is estimated for each model using Bayesian optimization. Finally, Bayesian model comparison is performed to select the model that explains the data most accurately and has the fewest parameters.

Figure 3 presents our proposed dynamic models which were evaluated at the level of each subject. As can be seen, the specified models use bidirectional endogenous connections between all active regions during social-emotional olfactory processing. In general, based on figure 2 there are a large number of possible models with different combinations of active areas and inputs. We tested different configurations where the valence of social chemosignal directly affected the different areas involved. However, the obtained results were not consistent. Hence, following the literature [1], [7], we only report models that emphasize the role of the FFA in perceiving social chemosignals. Parameter estimation was then performed for each specified model and for each participant. In the last step, model comparison was implemented using random-effect (RFX) Bayesian model selection in SPM12 to find the best optimal model [17]. We computed exceedance and posterior probability to find the best model. Exceedance probability of a given model refers to the probability that the model is more likely to be valid than any other examined model for the given data.

III. RESULTS

A. BOLD Detection

Results of the group-level analysis of fMRI data are provided in this section. As mentioned, the main aim of this study is to examine networks involved in social and emotion processing. Therefore, the contrast image of brain activation based on “disgust sweat – neutral sweat” was estimated to determine the BOLD response to social chemosignals. Then, single subject contrasts were entered into a one-sample t-test resulting in a group level statistical parametric map of the T statistic. Sagittal, coronal and transversal views of detected active areas from this fMRI group analysis are shown in Figure 4. Consistent with previous literature, significant
responses were observed in the right FFA, right amygdala and right OFC. Table I presents more details, including the coordinates, the Z-score and the number of active voxels of each extracted BOLD signal. Active voxels are overlaid on the high resolution structural image of the figure. Our examined contrast between disgust and neutral sweat revealed that the brain will engage the FFA. This is in contrast to a primary olfactory processing task which would be expected to involve primary and higher order olfactory cortices and emotional networks (i.e. PPC, OFC and Amygdala). The FFA is a face processing area in the brain which is mainly responsive during facial recognition tasks. It is remarkable that this area is also engaged during human chemosignal processing, even though in the olfactory conditions no face stimuli were presented. We propose that this region is active because human chemosignals communicate social information in a similar way to faces. This implies that the FFA participates in social perception in an amodal manner. Moreover, as can be seen from the results presented in Table I, disgust sweat also selectively activates the Amygdala and OFC. In general, we were able to replicate the analysis of Zheng et al. [7] on the same data and we now move on to our most novel contribution which examines effective connectivity within this neural network.

### B. Effective Connectivity Analysis

The main aim of this research is to explore the effective connectivity between nodes of the neural network underpinning social-emotional processing. For this purpose, a subset of possible dynamic causal models which are shown in figure 2 were specified. Seven proposed dynamic models shown in figure 3 were specified using the time series of detected active areas for each subject. Then, parameters of these models were estimated. In the final stage, Bayesian model averaging (BMA) across all subjects and all models was implemented. Figure 5 represents results of Bayesian model averaging for specified models. The results of BMA averaging showed that model number 2 outperforms other models in terms of higher expected probability (0.2) and higher exceedance probability (0.26). This model contains a driving input from the social olfactory stimuli and bidirectional connections between the key regions of interest. Most importantly, it is distinguished by chemosignal modulation of the connection from Amygdala to OFC. Averaged intrinsic and input (includes driving and modulatory) parameters over all subjects for this model are presented in Table II and Table III.

#### TABLE I

<table>
<thead>
<tr>
<th>Region</th>
<th>Talairach Coordinates</th>
<th>Z</th>
<th>Cluster Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fusiform Face Area</td>
<td>(44,-44,-28)</td>
<td>2.60</td>
<td>105</td>
</tr>
<tr>
<td>Orbitofrontal Cortex</td>
<td>(30,38,18)</td>
<td>2.38</td>
<td>26</td>
</tr>
<tr>
<td>Amygdala</td>
<td>(26,0,-28)</td>
<td>2.81</td>
<td>15</td>
</tr>
</tbody>
</table>

**Bayesian Model Selection**

![Expected probability and exceedance probability for specified models.](image_url)
TABLE II
Average estimated parameters for the intrinsic connections in the winning DCM model (Model 2).

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFA → OFC</td>
<td>0.043</td>
</tr>
<tr>
<td>FFA → AMG</td>
<td>0.074</td>
</tr>
<tr>
<td>AMG → OFC</td>
<td>0.093</td>
</tr>
<tr>
<td>AMG → FFA</td>
<td>0.085</td>
</tr>
<tr>
<td>OFC → FFA</td>
<td>0.064</td>
</tr>
<tr>
<td>OFC → AMG</td>
<td>0.077</td>
</tr>
</tbody>
</table>

TABLE III
Average estimated parameters for driving and modulatory inputs in the winning DCM model.

<table>
<thead>
<tr>
<th>Chemosignal</th>
<th>Input Type</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disgust</td>
<td>Driving</td>
<td>0.035</td>
</tr>
<tr>
<td>Neutral</td>
<td>Driving</td>
<td>0.017</td>
</tr>
<tr>
<td>Disgust</td>
<td>Modulatory</td>
<td>0.026</td>
</tr>
</tbody>
</table>

III respectively. The results suggest that social chemosignals modulate the connection from AMG to OFC. The obtained results for intrinsic connections highlight the importance of connectivity between Amygdala and OFC (the main node of olfactory processing) and FFA as the main node of social information processing. Positive parameters show that activity in one region lead to increase activity in connected regions. Specifically, the estimated intrinsic projection parameters between Amygdala and FFA confirm the integrative role of these areas in chemosignal processing. The modulatory effect of disgust could have emerged at various different places in this network. However, the results showed that it was the pathway between the Amygdala and OFC which was being modulated (not, for example, connections involving FFA). This is interesting because it suggests an influence on activity of the OFC which is a critical region for object appraisal and evaluation, which would have been important in the food judgement task. The estimated parameters for driving input showed that disgust chemosignals increase the activity in the FFA region.

IV. CONCLUSION AND DISCUSSION

This paper presents an fMRI study exploring effective connectivity in a social-emotional task. After processing fMRI data at both subject and group levels, a set of dynamic causal models was implemented using extracted BOLD time series from FFA, AMG and OFC regions. The obtained results by fMRI and DCM analysis illustrated that FFA region is highly involved in social chemosignal processing, consistently with previous literature [1], [7]. More specifically, this region showed strong variation of activity in different emotional conditions (i.e. disgust and neutral). In contrast, lower level olfactory sensory brain regions showed minor direct response variation. This may be surprising as FFA is not as near to the sensory signal as the AMG. However, AMG may be involved in core processing for this task, which is common across conditions and thus unlikely to change its overall activation level on the basis of high level signals. On the other hand, the FFA is strongly involved in higher level social signal processing, e.g. faces, and so it is a good target for a discriminative activation in response to such signals. Social chemosignals also modulate on AMG connectivity to OFC. In our future work, a more comprehensive study with a higher number of possible models and contrasts is expected.

REFERENCES

[13] [https://www.fil.ion.ucl.ac.uk/spm/].
[14] [https://www.neurosynth.org/].
[15] [http://marsbar.sourceforge.net/].