STUDY OF EFFECTIVE CONNECTIVITY FOR FACE PERCEPTION IN HEALTHY SUBJECTS AND PARKINSON'S DISEASE

Elvis Lira da Silva[1,4], Gabriela Castellano[1,4], João Ricardo Sato[2,3,4]
Ellison Fernando Cardoso[2,4] and Edson Amaro Jr.[2,4]
[1]*Institute of Physics "Gleb Wataghin", University of Campinas - UNICAMP, Campinas, Brazil*

[2]*NIF, LIM-44, Department of Radiology, University of São Paulo, São Paulo, Brazil*
[3]*Center of Mathematics, Computation and Cognition, Universidade Federal do ABC, Santo André, Brazil*

[4]*CInAPCe Program (Cooperação Interinstitucional de Apoio a Pesquisas sobre o Cérebro), São Paulo, Brazil*

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Abstract: Facial perception is a fundamental task in our daily life and plays a critical role in social interactions. Evidence from neuropsychological, neurophysiologic, and functional imaging studies indicated that face perception is mediated by a specialized system in the human brain. We investigated the neural connectivity induced by face presentation with different emotional valences in Parkinson's disease (PD) patients and a control group of healthy, drug-free volunteers, using event-related fMRI in a parametric design. In this study, we focused on applying Dynamic Causal Modelling (DCM), an approach that allows the assessment of effective connectivity within cortical networks (Friston et al. 2003), to the study of effective connectivity between maximally activated brain regions in response to passive viewing of facial stimuli. A connectivity model was built based on the literature and in our fMRI analyses, which included the fusiform gyrus, anterior cingulate gyrus, dorsolateral prefrontal cortex (DLPFC) and dorsomedial prefrontal cortex (DMPFC). The results showed differences in connectivity between the PD group and the control group. We found that the effective couplings among DLPFC/DMPFC and FG, DLPFC/DMPFC and ACG, were higher in PD patients than healthy subjects, while the effective coupling among FG and ACG was lower in PD patients.

1 INTRODUCTION

The branch of Neuroscience that studies functional integration between cerebral areas has recently shown a significant growth. Functional integration refers to the interactions among specialized neuronal populations, where the integration is mediated by the so called effective connectivity. Effective connectivity is defined as the influence that regions, which encompass given neuronal populations, exert on each other. It is important to study the effective connectivity to know how different areas, involved in a particular brain processing task, are related.

Facial perception is one of the fundamental tasks in our daily life and plays a critical role in social interactions. It is a highly developed visual ability in humans and it is mediated by activation in a distributed neural system that encompasses visual, limbic, and prefrontal regions (Fairhall and Ishai, 2007; Haxby et al., 2000). Facial perception with different emotional valences involves the emotional recognition that is related to the activity of amygdala, insula, orbitofrontal cortex and ventral striatum. The areas linked to emotional regulation include the anterior cingulate, dorsolateral and medial prefrontal cortices (Phillips et al., 2003a, b).

In this study we investigated the effective connectivity induced by face presentation with different emotional valences in Parkinson's disease (PD) patients and a control group of healthy, drug-free volunteers. Depression is the most common psychiatric disease in patients with Parkinson's disease (PD) (Cardoso et al., 2007). Although several studies have been performed to investigate the pathophysiology of depression in PD, many questions remain unanswered.

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To investigate effective connectivity within the distributed cortical network for face perception, we combined conventional Statistical Parametric Mapping (SPM) and the technique of Dynamic Causal Modelling (DCM) (Friston et al., 2003). DCM consists of a theoretical-experimental approach that treats the brain as a nonlinear deterministic dynamic system. DCM regards an experiment of fMRI as a designed perturbation of neuronal dynamics that is distributed throughout a system of coupled anatomical nodes to change region-specific neuronal activity (Friston et al., 2003). In practical terms, a reasonably realistic neuronal model of interacting cortical regions is built, with neuro-physiologically meaningful parameters. This model is supplemented with a forward model of how neuronal or synaptic activity is transformed into a measured response, and the parameters of this model can be estimated by attempting to match the predicted BOLD signal to the observed BOLD signal.

DCM has been previously used to investigate visual perception and visual imagery of faces (Mechelli et al., 2004) and face perception in healthy subjects (Fairhall and Ishai, 2007; Rotshtein et al.2007).

2 METHODS

Eckmann's faces were morphed to produce neutral, low and high intensities of sadness, as shown in Figure 1. An event-related fMRI paradigm, similar to Fu et al. (2004) was used. Facial stimuli and baseline trials (crosshair fixation) were presented in random order. Each trial and control condition was presented for 2 s, and the inter-trial interval was randomly varied according to a Poisson distribution (2–12 s; mean 5 s). All images were acquired in a 1.5 T GE scanner, equipped with a 33 mT/m gradient.

Figure 1: An example of stimuli set used. Eckmann's faces were morphed to produce neutral, low and high intensities of sadness. Facial stimuli and baseline trials (crosshair fixation) were presented in random order in the event related fMRI paradigm.

The images were oriented according to the AC–PC line; and 168 brain volumes were acquired, with 15 slices each (7 mm thickness, 0.7 gap), 64×64 pixels matrix, 20×20 mm FOV, 90° flip angle, 2.0 s TR, 40 ms TE, using a gradient echo EPI acquisition.

The fMRI statistical and DCM analyses were performed using the free software Statistical Parametric Mapping (SPM8, www.fil.ion.ucl.ac.uk /spm/). All volumes were slice time corrected, realigned to the middle volume, corrected for motion artifacts, mean-adjusted by proportional scaling, normalized into standard stereotactic space (template provided by SPM8), and smoothed using a 8 mm full-width at half-maximum (FWHM) Gaussian kernel. The time series were high-pass filtered to eliminate low-frequency components (filter width = 128 s) and adjusted for systematic differences across trials.

DCM is constructed by a bilinear approximation that allows the dynamics of the system to depend on three groups of parameters: parameters that mediate intrinsic coupling among the areas, parameters that mediate the influence of extrinsic inputs on the areas and (bilinear) parameters that allow the extrinsic inputs to modulate that coupling (Friston et al., 2003). The model depends on the experimental design, where the extrinsic inputs enter the model by two ways: directly influencing the areas (driving inputs) and/or influencing the coupling among the areas (contextual inputs).

All patients were recruited from the Movement Disorders Clinics of Hospital das Clínicas – University of São Paulo (São Paulo – Brazil) and all gave written informed consent. The study was approved by the ethics committee of the University of São Paulo (Project Approval number: 414/03).

2.1 Effective Connectivity Analysis

We studied 19 healthy subjects and 17 patients with Parkinson's disease. Initially, fMRI was used for locating brain responses to the experimental task (face perception with different emotional valences). Individual maps of activations were generated using voxel based analysis. Next, second-level analysis was used to generate maps of the group using one sample t-test, with corrected (FWE) p-value < 0.05.
Based on our analysis of the healthy group data and on the works of Phillips et al. (2003a,b), we determined which areas should enter in the model of DCM. The model included 3 areas: left and right Fusiform Gyri (FG), Anterior Cingulate Gyrus (ACG), and Dorsolateral Prefrontal Cortex (DLPFC)

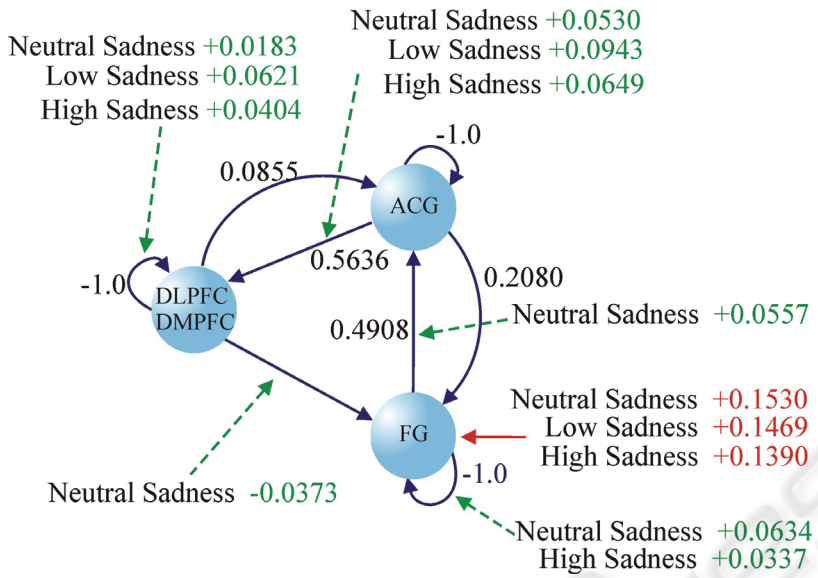

Figure 2: DCM results for healthy subjects. Black arrows (and values) are the results of intrinsic connections, green arrows (and values) are the results of modulatory connections, and red arrows (and values) are the results of direct influence of the stimuli on the FG area.

/ Dorsomedial Prefrontal Cortex (DMPFC). These regions of interest (ROIs) were defined using masks created with the WFU Pickatlas software (Maldjian et al., 2003 and Maldjian et al.,2004).

After delimiting the brain areas aforementioned in the individual brain activation map, time series of voxels limited by a sphere of 8 mm were extracted. These spheres were located in the local maxima of the activation map for each anatomical area included on the model. This procedure was performed for each of the subjects. These three volumes of interest (VOIs) were identified for each individual subject. Mean localization and t-values of these areas are shown in Table 1 for healthy subjects and PD patients. All three VOIs were reliably delineated in 16 of the 19 healthy subjects and 10 of the 17 PD patients (Table 1) ($p < 0.05$, uncorrected).

Initially the DCM model was estimated separately for each subject. In order to generalize our results to the population level, the estimated connection strengths from that analysis were then subjected to a second-level analysis (using Matlab functions) where the significance of inferred connections was tested using one-sample t-tests against the null hypothesis that the connection strength is equal to zero.

Table 1: Regions of the DCM model for healthy subjects and PD patients. The x, y, z, columns give the average coordinates across all subjects for the location of each region (with the standard deviation – SD – in parentheses). The T column shows the average T-statistics across subjects in the first-level analysis (and the SD in parentheses). "L" and "R" mean Left and Right, respectively.

Healthy subjects				
Regions	x	y	z	T
FG (R)	31.3(7.1)	-59.5(6.9)	-18.4(3.1)	4.0(1.5)
ACG (R)	3.7(4.0)	14.2(9.9)	20(16,9)	2.53(0.8)
DMPFC/ DLPFC(R)	21.8(13.8)	19.3(14.7)	56(18)	4.6(1.5)
FG (L)	-31.3(7.9)	-58(14.4)	-20(4.9)	3.8(1.1)
ACG (L)	-7(2)	22.3(8.2)	8.3(14.9)	2.5(0.5)
DMPFC/ DLPFC(L)	-30.1(13.1)	-2.5(8.7)	63.2(8.7)	4.0(1.4)
PD patients				
Regions	x	y	z	T
FG (R)	30(8.6)	48.6(16.5)	-21.1(7.9)	4.1(1.2)
ACG (R)	5.2(3.2)	20.3(5.6)	28.1(12,8)	2.9(0.6)
DMPFC/ DLPFC(R)	17(15.2)	9.0(8.3)	59.7(13,3)	4.1(1.0)
FG(L)	-22(0)	-67.5(10.6)	-16.0(0)	4.9(1.2)
ACG (L)	-11(0)	26.0(0)	28.0(0)	2.9(0)
DMPFC/ DLPFC(L)	-32(2.8)	-3.5(10.6)	63.0(4.2)	4.3(0.7)

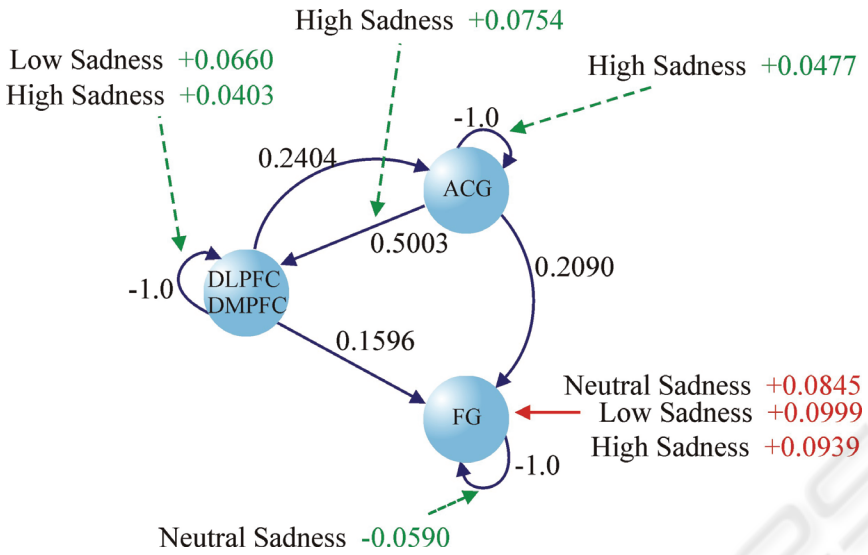

Figure 3: DCM results for PD patients. Black, green and red arrows represent the same as for Figure 2.

3 RESULTS

We found that emotion perception and recognition in faces involve activity in the FG, ACG, DLPFC and DMPFC brain areas. The activation of these areas was found through the fMRI analysis. A model that connects the different areas was defined; taking into account the FG, ACG and prefrontal cortex regions. As a first model we admitted that all regions interacted with one another; and that the face stimuli entered the model as driving inputs on FG only. The face stimuli also entered the model as contextual factors on all connections. From this model, the intrinsic connections between each of the components of the model were estimated using a DCM analysis.

The results of the groups are shown in Figure 2, for healthy subjects, and Figure 3, for PD patients. Only connections that were significant (non-zero mean) after the one-sample t-test ($p < 0.05$) are shown. Black arrows (and values) are the results of intrinsic connections, which do not depend on external stimuli. Green arrows (and values) are the results of modulatory connections given by contextual inputs; these values increase or decrease the influence of the intrinsic connections and depend on the external stimulus. Red arrows (and values) are results of direct influence of stimuli on the areas. Values are shown when significant (one-sample t-test) for each of the experimental conditions (neutral, low and high sadness).

In principle we can see, in control subjects (Figure 2), an increase in activity in the FG areas induced by modulation of connectivity by neutral and high sadness faces (FG → FG connection) and in the DLPFC/DMPFC areas induced by modulation of connectivity by all faces (DLPFC / DMPFC → DLPFC / DMPFC and ACG → DLPFC / DMPFC connections).

Neutral faces increase activity in ACG areas (FG → ACG connection) and decrease activity in FG (DLPFC / DMPFC → FG connection).

For PD patients (Figure 3), we can notice an increase in activity in the DLPFC and DMPFC areas induced by the modulation of connectivity by low sadness (DLPFC/DMPFC → DLPFC/DMPFC connection) and high sadness faces (DLPFC/DMPFC → DLPFC/DMPFC and ACG → DLPFC/DMPFC connections). We can also see an increase in activity in the ACG areas induced by the modulation of connectivity by high sadness faces (ACG → ACG connection). In addition, we see a decrease in activity of the FG area induced by the modulation of connectivity by neutral faces (FG → FG).

Using a two-sample t-test (through Matlab functions) we compared the connections of the two groups (healthy and PD) and found a significant difference among the intrinsic connections (black lines in Figures 2 and 3) DLPFC/DMPFC → ACG (p-value of 0.0345), DLPFC/DMPFC → FG (p-value of 0.0303) and FG → ACG (p-value of 0.0487).

We found that the effective coupling DLPFC/DMPFC → ACG and DLPFC/DMPFC → ACG were higher in PD patients than in healthy subjects, while the effective coupling FG → ACG was lower in PD patients. The results are shown in Table 2.

To compare the connectivity patterns between the stimuli of high sad and neutral faces, we used a paired t-test among these conditions within each group (PD patients and controls), for every connection (intrinsic, modulatory and direct influence) in every region. We found a significant difference between the connectivity for these two conditions in healthy subjects. The connectivity for the sad faces stimulus has greater modulation by prefrontal areas in the ACG and FG, which is in agreement to the article by Philips et al. (Phillips et al., 2003a). According to Phillips et al., the prefrontal areas are responsible for the regulation of the emotional state and the perception of emotion. Therefore, we may conclude that in healthy subjects, the prefrontal area regulated the emotional state due to the presentation of the sad faces stimulus. On the other hand, we did not observe this difference in the group of Parkinson's disease patients: the t-test did not show significant differences in connectivity between the different face conditions. In fact, many studies (Assogna et al. 2008; Dujardin et al 2004; Sprengelmeyer et al. 2003) have described the disability that Parkinson's patients have for the recognition and perception of emotion, suggesting that the decline in dopaminergic nigrostriatal leads not only to motor disorders but also to a deficit in processing facial emotions. This suggests that the connection between the prefrontal cortex areas and the other areas of the model is affected by Parkinson's disease, and causes this deficit in processing emotions.

Results about the comparison between different conditions for healthy subjects and PD patients are shown in Table 3. For clarity only the results for the comparison between the neutral and high sadness conditions are shown. The connection FG → DLPFC (intrinsic and modulatory) is not shown in the table because it was not included in the model.

Table 2: Comparison between healthy subjects and PD patients connections. Significant differences are marked with bold-face. Connections marked with asterisk are higher in PD patients than healthy subjects.

Comparison between groups			
Connections	Healthy Subjects	PD Patients	P-value
Intrinsic Connections			
FG→FG	-1.000	-1.000	-
FG→ACG	**0.4908**	**0.2620**	**0.0487**
ACG→FG	0.2080	0.2090	0.9850
ACG→ACG	-1.000	-1.000	-
ACG→DLPFC	0.5636	0.5003	0.6691
DLPFC→FG	**0.0361**	**0.1596**	**0.0303***
DLPFC→ACG	**0.0855**	**0.2404**	**0.0345***
DLPFC→DLPFC	-1.000	-1.000	-
Modulatory Connections (Neutral)			
FG→FG	0.0587	0.0590	0.9896
FG→ACG	**0.0557**	**-0.0820**	**0.0047**
ACG→FG	-0.0059	0.0017	0.6207
ACG→ACG	0.0014	0.0404	0.1135
ACG→DLPFC	0.0530	0.0390	0.6259
DLPFC→FG	**-0.0373**	**0.0128**	**0.0345***
DLPFC→ACG	-0.0300	-0.0055	0.3046
DLPFC→DLPFC	0.0183	0.0261	0.6131
Modulatory Connections (Low Sadness)			
FG→FG	-0.0192	0.0180	0.2513
FG→ACG	0.0102	0.0236	0.7676
FG → DLPFC			
ACG→FG	-0.0245	-0.0010	0.3873
ACG→ACG	0.0042	0.0387	0.1190
ACG→DLPFC	0.0943	0.0671	0.5274
DLPFC→FG	**-0.0246**	**0.0239**	**0.0324***
DLPFC→ACG	-0.0024	0.0011	0.8531
DLPFC→DLPFC	0.0621	0.0660	0.8996
Modulatory Connections (High Sadness)			
FG→FG	0.0337	0.0234	0.6424
FG→ACG	0.0047	0.0076	0.9513
ACG→FG	0.0226	0.0111	0.5818
ACG→ACG	**0.0087**	**0.0477**	**0.0344***
ACG→DLPFC	0.0649	0.0754	0.7691
DLPFC→FG	0.0179	0.0068	0.6267
DLPFC→ACG	0.0061	0.0095	0.8716
DLPFC→DLPFC	0.0404	0.0403	0.9974
Extrinsic Connections			
Stimulus → FG (All others connections not included in the model)			
Neutral	**0.1530**	**0.0845**	**0.0330**
Low Sadness	0.1469	0.0999	0.2165
High Sadness	0.1390	0.0939	0.2400

4 CONCLUSIONS

Using DCM, we explored the effective connectivity of the main cerebral regions involved in responses to facial stimuli with different intensities of sadness, for both PD patients and healthy subjects. The results showed differences in connectivity between the PD group and the control group, suggesting that these changes in connectivity can play an important role in Parkinson's disease and may thus provide insights on the underlying mechanisms of PD.

However, as the success of DCM is dependent on the experimental design and on the specified interacting regions model, other models involving those regions should be tested for a more definitive conclusion.

Table 3: Comparison between the neutral and high sadness faces conditions, for healthy subjects and PD patients connections. Significant differences are marked with bold-face. Connections marked with asterisk are higher in the high sadness than in the neutral condition. Healthy subjects show many more significant differences between high sadness and neutral faces than PD patients.

Healthy Subjects (Comparison between conditions)			
Modulatory Connections			
Connections	Neutral	High Sadness	P-value
FG→FG	0.0587	0.0337	0.2430
FG→ACG	0.0557	0.0047	0.1149
ACG→FG	**-0.0059**	**0.0226**	**0.0459***
ACG→ACG	0.0014	0.0087	0.6311
ACG→DLPFC	0.0530	0.0649	0.5454
DLPFC→FG	**-0.0373**	**0.0179**	**0.0100***
DLPFC→ACG	**-0.0300**	**0.0061**	**0.0346***
DLPFC→DLPFC	**0.0183**	**0.0404**	**0.0470***
Extrinsic Connections			
Stimulus → FG (All others extrinsic connections were not included in the model)	Neutral	High Sadness	P-value
	0.1530	**0.1390**	**0.0414**
PD Patients (Comparison between conditions)			
Modulatory Connections			
	Neutral	High Sadness	P-value
FG→FG	0.0590	0.0234	0.1538
FG→ACG	**-0.0820**	**0.0076**	**0.0427***
ACG→FG	0.0017	0.0111	0.5809
ACG→ACG	0.0404	0.0477	0.7515
ACG→DLPFC	0.0390	0.0754	0.2473
DLPFC→FG	0.0128	0.0068	0.7276
DLPFC→ACG	-0.0055	0.0095	0.6463
DLPFC→DLPFC	0.0261	0.0403	0.5526
Extrinsic Connections			
Stimulus →FG (All others extrinsic connections were not included in the model)	Neutral	High Sadness	P-value
	0.0845	0.0939	0.4041

REFERENCES

Assogna F. , Pontieri F., Caltagirone C., Spalletta G. 2008. The recognition of facial emotion expressions in Parkinson's disease. *European Neuropsychopharmacology* 18, 835–848.

Dujardin K., Blairy S., Defebvre L.,, Duhemb S., Noël Y, Hess U., Destée A. 2004. Deficits in decoding emotional facial expressions in Parkinson's disease. *Neuropsychologia* 42, 239–250

Cardoso, E., Fregni F., Maia F., Boggio, P., Myczkowski, M., Coracini K., Vieira A., Melo L., Sato, J., Marcolin M., Rigonatti S., Cruz A.,Barbosa, E. and Amaro, E., 2007. rTMS treatment for depression in Parkinson's disease increases BOLD responses in the left refrontal cortex. *International Journal of Neuropsychopharmacology*, 11(2), 173 – 183.

Fairhall, S. and Ishai, A., 2007. Effective Connectivity within the Distributed Cortical Network for Face Perception. *Cerebral Cortex*, 17(10), 2400–2406.

Friston, K., Harrison, L., Penny, W., 2003. Dynamic causal modeling. *NeuroImage* 19, 1273– 1302.

Fu C., Williams S., Cleare A., Brammer M., Walsh N., Kim J., Andrew C., Pich E., Williams P., Reed L., et al. 2004. Attenuation of the neural response to sad faces in major depression by antidepressant treatment: a prospective, event-related functional magnetic resonance imaging study. Archives of General Psychiatry 61, 877–889

Haxby, J., Hoffman, E., Gobbini, M., 2000. The distributed human neural system for face perception. *Trends in Cognitive Sciences,* 4(6), 223–233.

Mechelli A., Price C., Friston K., Ishai A., 2004. Where bottom-up meets top-down: neuronal interactions during perception and imagery. *Cerebral Cortex*. 14, 1256-1265.

Maldjian, J., Laurienti, P., Burdette, J., Kraft, R., 2003. An Automated Method for Neuroanatomic and Cytoarchitectonic Atlas-based Interrogation of fMRI Data Sets. *NeuroImage*, 19, 1233-1239.

Maldjian, J., Laurienti, P., Burdette, J., 2004. Precentral Gyrus Discrepancy in Electronic Versions of the Talairach Atlas. *Neuroimage*, 21(1), 450-455.

Phillips M., Drevets W., Rauch S., Lane R., 2003a. Neurobiology of emotion perception I: The neural basis of normal emotion perception. *Biological Psychiatry* 54, 504–514.

Phillips M., Drevets W., Rauch S., Lane R., 2003b. Neurobiology of emotion perception II: Implications for major psychiatric disorders. *Biological Psychiatry* 54, 515–528.

Rotshtein P., Vuilleumier P., Winston J., Driver J., Dolan R., 2007. Distinct and convergent visual processing of high and low spatial frequency information in faces. *Cerebral Cortex* 17, 2713–2724.

Sprengelmeyer R., Young A., Mahna K., Schroeder U. , Woitalla D., Büttner T. , Kuhn W. , Przuntek H. 2003. Facial expression recognition in people with medicated and unmedicated Parkinson's disease. *Neuropsychologia* 41, 1047–1057.