BURNOUT, MYTH OR REALITY?

A structural and functional investigation using advanced MRI techniques

Alexia Van Goethem & Caroline Struijk

Faculty of Medicine and Health Sciences
University of Antwerp
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Promotor: prof. dr. Paul Parizel
Supervisor: Mr. Floris Vanhevel

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INTRODUCTION

"*In Belgium, a record number of working people is on sick leave because of burnout or other long-term mental illnesses!*" states an article published in the Belgian quality newspaper 'De Tijd' in December 2017 (33). Thirty percent of the Flemish working population experiences unacceptable levels of stress at work and 15% is on sick leave for 30 days or more each year because of these high levels of stress (34) "*…and numbers have increased with 30-40% in the past 5 years*" as reported on VRT news (35).

The incidence of burnout is rising in the working Western population. It is a 'hot topic' in the media and in the past decades numerous publications on burnout have been published in medical literature. Healthcare workers appear to be particularly susceptible to burnout because of high levels of stress and challenging working hours (1). A review article states that the prevalence of burnout among US physicians has risen rapidly to epidemic proportions, now exceeding 50% of all healthcare workers in the US. Especially physicians who had been in practice 11 to 20 years (middle career) appear to face a particularly challenging phase in their career and are more prone to burnout syndrome (3). Hence, patient safety is threatened since the rate of medical errors increases with rising burnout incidence (4).

Burnout syndrome, usually abbreviated to burnout, was first described by Maslach and Jackson in 1981 who defined burnout as "a syndrome of emotional exhaustion and cynicism that occurs frequently among individuals who do 'people work' of some kind" (5). Three subdimensions are derived from their assessment of a wide range of human services: emotional exhaustion (EE), feelings of depersonalization (DP) and reduced personal accomplishment (PA) (1). The Maslach Burnout Inventory (MBI) is based on these subdimensions (1).

Although "burnout" is common in popular speech, it is not incorporated in the 5th edition of the diagnostic and statistical manual of mental disorders (DSM-5). However, in the DSM-5 and the International Classification of Diseases (ICD) the adjustment disorder is registered and defined as: "The development of emotional or behavioral symptoms in response to an identifiable stressor(s) occurring within 3 months (…)" (6, 7). Therefore, burnout is linked to adjustment disorder with a defined stressor: work. However, we would like to point out that the duration of the stressor is of big importance. Burnout is preceded by a long-term work-related stress wherein emotional factors predominate. We believe that misconceptions about burnout will persist as long as no consensus about a universal definition as well as proper recognition, is reached.

The underlying pathophysiology of burnout is unclear. Inconclusive results were achieved studying the role of the hypothalamic-pituitary-adrenal-axis (hpa-axis) and cortisol levels in burnout subjects (8). However, several brain imaging studies showed that stress-processing limbic networks are affected in patients with clinical signs of burnout using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). Structural alterations such as cortical thinning of the medial prefrontal cortex (mPFC) and reduced gray matter volume in the dorsolateral prefrontal cortex (dlPFC) and anterior cingulate cortex (ACC) were found. Also, reduced connectivity between amygdala, mPFC and ACC were detected (9, 10). Another study presumed that subjects suffering from prolonged stress have an impaired ability to down-regulate negative emotions and used fMRI to assess amygdala functional connectivity (2). Their assumptions were based on a study that investigated the ability to cognitively down-regulate negative emotions and how this was disturbed after stress exposure (11). Also, numerous other research projects investigated extensively how the capability to cognitively regulate emotional responses is impaired across major neuropsychiatric disorders (12).

Burnout's core components are emotional exhaustion and depersonalization. Therefore, we suspect that neural mechanisms associated with emotional processing are disturbed in patients suffering from burnout. These regions are activated after the perception and interpretation of stressful stimuli, also called "cognitive appraisal" by Lazarus and Folkman (13). We took a closer look into the activity of emotion-processing-regions in the brain with the help of fMRI to allow us to understand the underlying mechanisms of burnout.

AIM OF STUDY

Based on literature findings we considered a dysregulation of the emotion- and stress-processing networks (2). Therefore, in this project, we aim to detect alterations in the activity of certain brain regions involved in the processing of emotions, using fMRI techniques. We performed fMRI in subjects while exposed to neutral and unpleasant visual stimuli and compared burnout patients with healthy volunteers. Regions of interest were the prefrontal cortex, the amygdala, the hippocampus, the caudate nucleus and the putamen. Hence, this project will cover the following research question:

'Can fMRI detect differences in emotion processing between patients with burnout and healthy subjects?'

MATERIALS AND METHODS

1. Study design

In this cross-sectional descriptive study, we observed the brain activity of two groups, i.e. individuals with burnout and healthy controls. Brain activity was measured using fMRI while patients watched a slideshow of images.

2. Subject selection

2.1 Subject population

All subjects were women, derived from a similar professional background (health care sector). The burnout subjects were recruited through the University Hospital of Antwerp and support groups. Healthy subjects were recruited through family, friends and acquaintances. Prior to MRI scanning, all subjects filled in the Maslach Burnout Inventory (MBI), the Patient Health Questionnaire-9 (PHQ-9) and a self-constructed questionnaire. The MBI is the leading measure of burnout and is used to evaluate the three dimensions of burnout: emotional exhaustion (EE), depersonalization (DP) and personal accomplishment (PA) (1,14). The PHQ-9 assesses whether depression is present and to what degree. Finally, items that explore personal life were covered in the self-constructed questionnaire, such as family life (marital status, children, etc.), social life and financial situation.

2.2 Inclusion criteria

- Right-handed women between 35- and 60-years old working in the health care sector
- Burnout subjects: diagnosis confirmed by a doctor AND moderate to high scores on the MBI (EE>=17, DP>=7, PA<=38)
- Control subjects: low scores on the MBI (EE<=16, DP<=6, PA>=39)

2.3 Exclusion criteria

- Major negative life event (loss of 1st relative family member)
- Somatization (fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome)
- Excessive alcohol and/or drug use
- Pregnancy
- Chronic neurologic disease such as history of epileptic seizures

- Severe impaired vision
- Other severe comorbidities
- MRI contraindications

3. Data acquisition and processing

The data is derived from blood oxygenation level dependent (BOLD) imaging. This signal is dependent on the level of deoxyhemoglobin (deoxyHb) in blood. DeoxyHb changes MR signal due to its paramagnetic properties. Brain activity will increase local blood flow and hence decrease the relative level of deoxyHb which in turn can be measured by fMRI. No administration of intravenous contrast is needed to obtain this information. We suspected a different BOLD signal in brain regions of burnout and healthy subjects, with regions of interest being the prefrontal cortex, the amygdala, the hippocampus, the caudate nucleus and the putamen.

3.1 MRI procedure and experimental fMRI design

Subjects were in the MRI scanner for approximately 20 minutes. First, we acquired high resolution anatomic 3D images of the brain (T1-weighted images). Then, brain activity was measured using fMRI. This activity was triggered while subjects were asked to simply perceive images presented on a slideshow. The functional MRI acquisition for this study was based on a block design (the most commonly used experimental design in fMRI) with interleaved blocks of neutral and unpleasant visual stimuli (Appendix I). In each block 10 images were shown, with a duration of 2.3 seconds per image. A total of 8 neutral and 8 unpleasant visual stimuli were shown to each subject (Figure 1). The images were collected with permission from the IAPS databank, consisting of stimuli standardized for the basic dimensions of emotion used to study both emotion and emotion regulation in adults (15). All MRI scans were acquired using a 3T Prisma fit scanner from Siemens at UZ Antwerpen. For each patient, T1 and fMRI data were collected. Table 1 summarizes further details of the MRI sequences used in this study. MRI exams were performed after working hours at the radiology department of Antwerp University Hospital. We performed the MRI procedures ourselves after completing a course and exam on MR-safety. Before scanning took place, subjects were asked to read and sign the consent form. Individuals could withdraw from the study at any time. The final version of this study protocol was reviewed and accepted by the Ethical Committee of the University of Antwerp on November 16th, 2017.

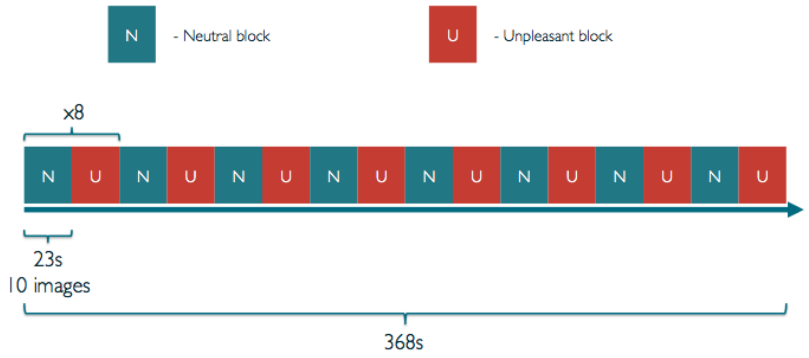


Figure 1 – fMRI block design

Table 1 – Details of the MRI sequences (TE – Echo Time, TR – Repetition Time, TI – Inversion Time)

Series	Sequence	Voxel size (mm)	TE (ms)	TR (ms)	TI (ms)	Flip angle	Nr. Volumes
T1	TurboFLASH 3D	1x1x1	3	2300	900	9°	1
fMRI	EPI-FID 2D	3x3x3.6	27	2300	-	70°	160

3.2 Data

MRI data of 20 subjects (10 burnout patients and 10 controls) was collected and analyzed. Burnout and control groups were equally balanced: All subjects were right-handed females with a mean age of 49 years (standard deviation of 7.1 years). There was no significant age difference between both groups (p=0.47).

3.3 Data processing

All data was processed using SPM12 (16). First, each subject's data was processed in order to produce individual activation maps or contrast images (first level processing). These maps or contrasts show for each subject which regions of the brain are activated during each task (neutral or unpleasant images), as well as the differences in activation between both tasks. In a second step, the activation maps from all subjects were analyzed and new contrasts were computed (second level processing). These second level contrasts show differences in 1st level contrasts between groups, as well as whole population activation maps.

First level processing

First level processing was performed as described in Figure 2. A description of each processing step is included below.

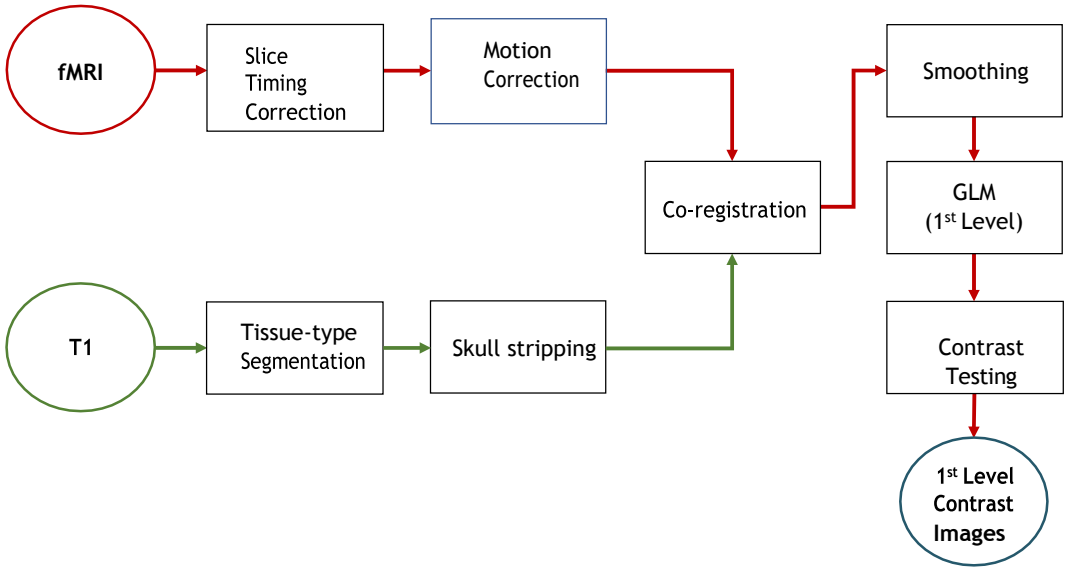


Figure 2 – First level processing pipeline

Slice timing correction

This pre-processing step corrects fMRI data for differences in acquisition time between slices of each volume. This correction is necessary to make the data of each slice correspond to the same point in time.

Motion correction

This step corrects for patient motion (head movement) during fMRI data acquisition.

Tissue-type segmentation

This function segments the T1-weighted images into the following 6 classes: grey matter (GM), white matter (WM), cerebral spinal fluid (CSF), bone, other soft tissues and background. This step is based on the unified segmentation paper (17).

Skull stripping

Combining the segmentation masks of GM, WM, and CSF a brain mask was created. The mask was then used for skull stripping the T1-weighted images, removing the information from all regions outside the brain. This

improves the co-registration between the fMRI data and the structural images, as well as the co-registration with a reference template (18).

Co-registration

After skull stripping, fMRI data and structural T1-weighted images were co-registered to each other (19).

Smoothing

The fMRI data was smoothed to suppress the spatial noise and enhance the signal to noise ratio (SNR) (20).

General Linear Model (GLM)

After pre-processing the data, statistical analysis of fMRI data was performed using a GLM based approach. This step allows retrieving the BOLD signal changes associated with the experimental design, dissociating it from other nuisance signal changes such as the ones caused by patient movement or scanner drift.

Contrast testing (first level)

After determining the different model parameters, 4 different contrast images were generated for each subject:

- Neutral > Unpleasant – contrast showing the regions that were significantly more activated during the Neutral blocks than the Unpleasant blocks.
- Unpleasant > Neutral – contrast showing the regions that were significantly more activated during the Unpleasant blocks than the Neutral blocks.
- Neutral – regions that were significantly activated during the Neutral blocks.
- Unpleasant – regions that were significantly activated during the Unpleasant blocks.

Thresholds of all contrast images defined considering a significance level of 0.05 and the family wise error (FWE) correction. The FWE correction reduces the probability of false positives in multiple testing, which is relevant in fMRI where thousands of voxels are tested simultaneously.

Second level processing

Second level processing was performed as described in Figure 3. A description of each processing step is included on the following page.

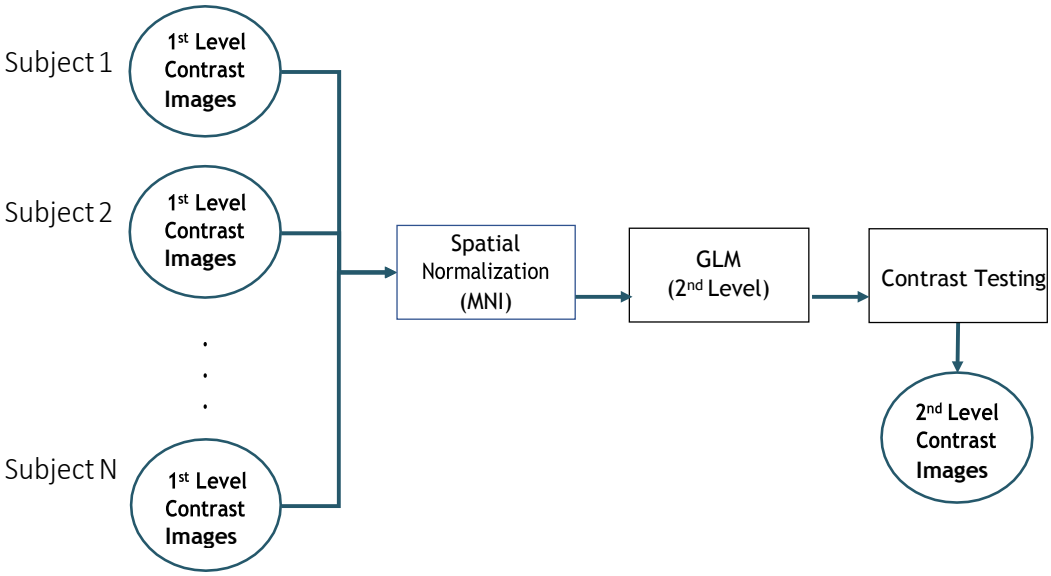


Figure 3 – Second level processing pipeline

Spatial normalization

All individual patient contrasts and structural images were warped to a common reference space (MNI space (21)). After spatial normalization of the different T1- weighted images, a structural template was created by averaging all normalized images (Figure 4).

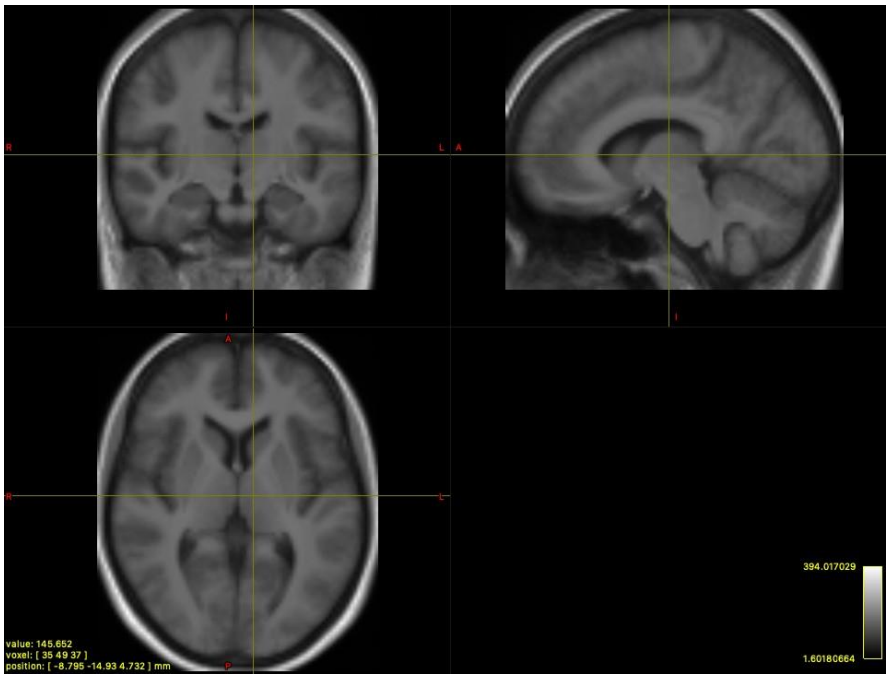


Figure 4 - Structural template created by averaging all normalized structural scans of this study. The high contrast between different structures shows the effectiveness of the spatial normalization step. Radiological view (left=right, right=left).

GLM second level and group contrasts

All spatially normalized contrasts were used as input for the second level GLM. For each first level contrast, 4 different GLM were used:

1. A two-sample t-test, to compare the Control versus the Burnout (BO) group. With following contrasts:
    a. BO > Control – this contrast shows the regions where a given first level contrast is higher in the BO group than in the Control group.
    b. Control > BO – this contrast shows the regions where a given first level contrast is higher in the Control group than in the BO group.
2. A one-sample t-test, to retrieve the general first-level contrasts ('Neutral>Unpleasant', 'Unpleasant>Neutral', 'Neutral', 'Unpleasant') from all subjects.
3. A one-sample t-test, to retrieve the general first-level contrasts ('Neutral>Unpleasant', 'Unpleasant>Neutral', 'Neutral', 'Unpleasant') from Control subjects.
4. A one-sample t-test, to retrieve the general first-level contrasts ('Neutral>Unpleasant', 'Unpleasant>Neutral', 'Neutral', 'Unpleasant') from BO subjects.

Thresholds of second level contrasts were defined using a less strict significance level than the first level ones. A significance level of 0.001 without correction for multiple comparisons was used.

RESULTS

1. Subject information results

When looking at the results of the MBI, following scores were acquired in the burnout group:

- Emotional Exhaustion (EE): 32 ± 7.6 (with EE 17 or more = moderate to high Emotional Exhaustion)
- Depersonalization (DP): 19.4 ± 7.2 (with DP 7 or more = moderate to high Depersonalization)
- Personal Accomplishment (PA): 30.2 ± 5.4 (with PA 38 or less = low to moderate Personal Accomplishment)

The mean duration of the active burnout these subjects were going through was 23.2 months, with a standard deviation of 22.1 months. Additionally, 6 burnout subjects were currently not working, 1 was partly working and 3 were still working.

MBI scores in the control group:

- Emotional Exhaustion (EE): 4.9 ± 6.3 (with EE 16 or less = low Emotional Exhaustion)
- Depersonalization (DP): 3 ± 1.9 (with DP 6 or less = low Depersonalization)
- Personal Accomplishment (PA): 44.9 ± 3.2 (with PA 39 or more = high Personal Accomplishment)

2. Data results

Given the complexity of processing fMRI data, the results below were obtained with the help of icometrix, an external center for diagnostic imaging in Leuven, Belgium.

First level analysis

An example of a first level analysis of one of the burnout subjects is given in Figure 5. For the results of the other subjects, see Appendix II with Figures 6 to 24.

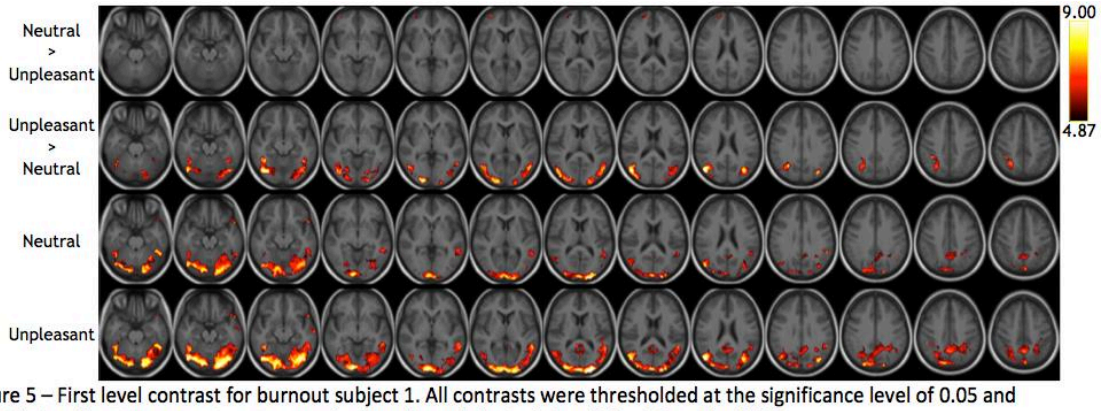


Figure 5 – First level contrast for burnout subject 1. All contrasts were thresholded at the significance level of 0.05 and considering the FWE correction. Images displayed in radiological view (left=right, right=left).

When looking at the first level contrasts (i.e. T-statistic maps) for every subject, it can be seen that considerable variability exists between different subjects. Besides this, there is a general trend showing higher brain activation in response to the unpleasant stimuli in the visual cortex in comparison with the response to the neutral stimuli. Seven out of the twenty cases showed significantly higher activation of the frontal cortex during the neutral block than during the unpleasant block. Nevertheless, the regions of the frontal cortex were different for these seven subjects. For one control subject, no significant brain activation was detected and in the case of another control subject only a very small region of the visual cortex showed significant values for the contrast Unpleasant>Neutral in a small region of the visual cortex. In contrast with these two subjects, one burnout subject showed a higher response to the visual stimuli than the remaining subjects. For this particular subject, brain activation is seen throughout the whole occipital lobe as well as in regions of the posterior parietal lobe and posterior temporal lobe.

Second level analysis

Figures 25 to 28 show the second level contrasts (i.e. at group level) associated with each first level (i.e. subject-level) contrast. A significance level of 0.001 with no correction for multiple comparisons was used. Contrasts comparing the burnout and control groups are not shown in these images since there were no significant differences between these two groups for none of the first level contrasts.

The results show that the contrast Unpleasant>Neutral showed significant values in several regions of the brain for both controls and burnout subjects (Figure 25). Looking at the combined analysis of all subjects we see significant values in the whole occipital lobe, in the posterior parietal lobe and posterior temporal lobe, in the genu of the internal capsule, in the right inferior frontal gyrus, in the orbital gyri and in both left and right hippocampi. The analysis of the same contrast for the two groups separately shows less significant differences. In both cases, significant values are seen throughout the occipital cortex. Significant values in the right inferior frontal gyrus are only seen for the control group.

In Figure 26, where the Neutral>Unpleasant group contrasts are shown, it is seen that almost no region showed significantly higher BOLD signal during the neutral stimuli than during the unpleasant stimuli. Only for the burnout group a small region of the medial frontal gyrus showed significantly higher activation during the neutral block compared with the unpleasant block. For the first level contrasts a few subjects showed significant

activation in the prefrontal cortex for this contrast (Neutral>Unpleasant). However, this was seen only in 7 out of the 20 subjects and the regions were different between subjects, which should explain the results of Figure 26.

Looking at the contrast for each of the stimuli separately, i.e. Neutral and Unpleasant (Figures 27 and 28), it becomes clear that overall more brain activation is seen in response to the Unpleasant stimuli than to the Neutral stimuli. However, looking at the contrasts of these stimuli separately does not allow to identify differences between them in terms of the regions that are activated. In both cases, we see activation in the occipital lobe.

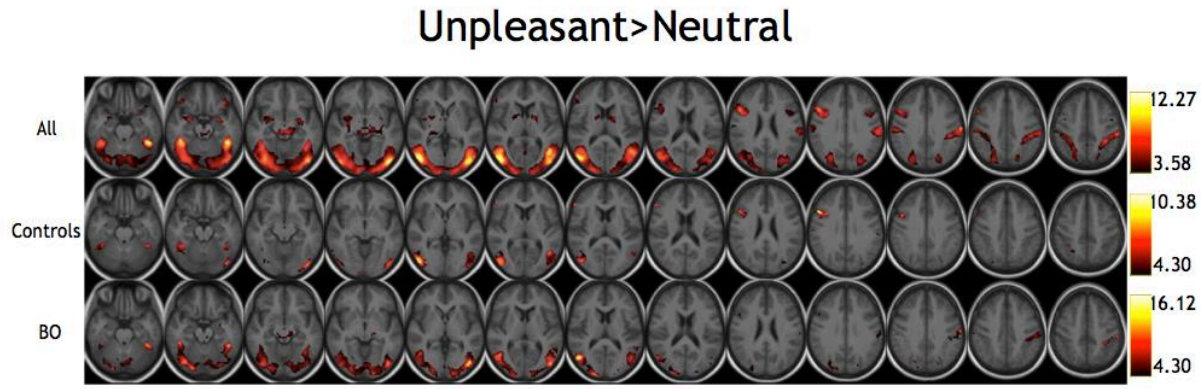


Figure 25 - Second level group contrasts based on first level contrast Unpleasant > Neutral. All contrasts were thresholded at the significance level of 0.001. Images displayed in radiological view (left=right, right=left).

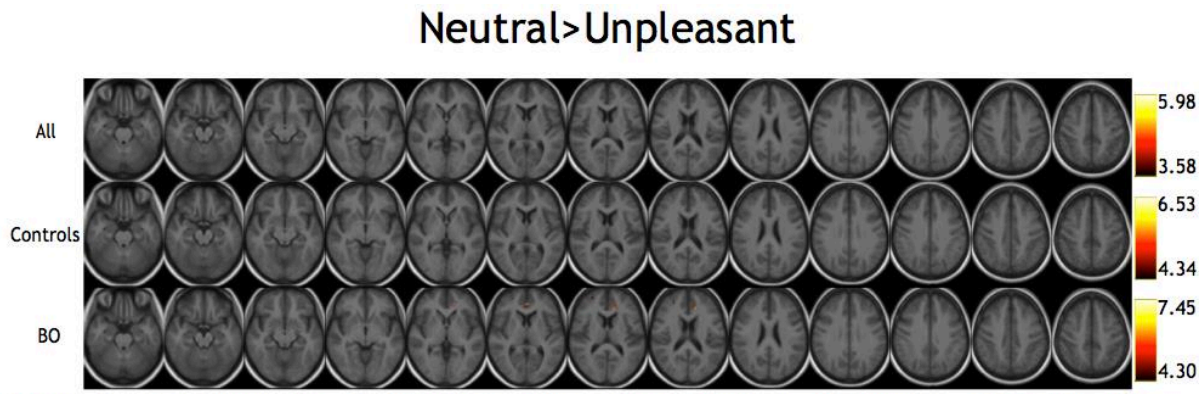


Figure 26 - Second level group contrasts based on first level contrast Neutral > Unpleasant. All contrasts were thresholded at the significance level of 0.001. Images displayed in radiological view (left=right, right=left).

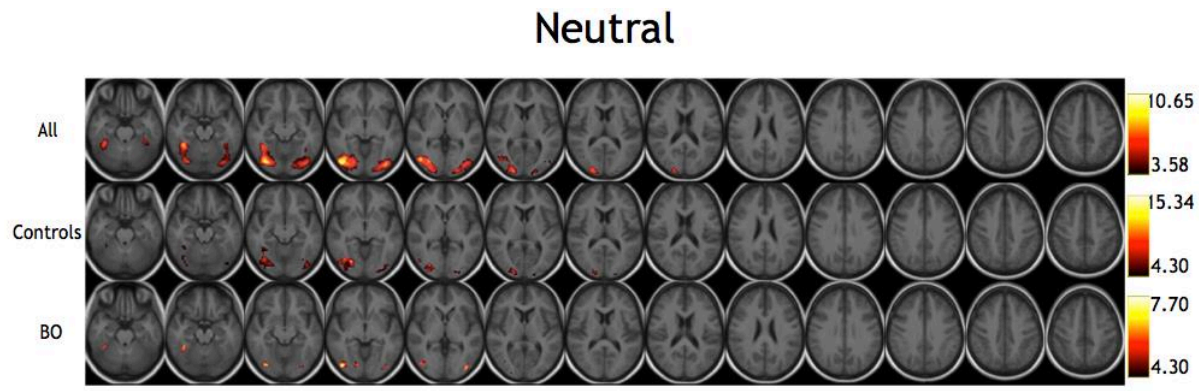


Figure 27 - Second level group contrasts based on first level contrast Neutral. All contrasts were thresholded at the significance level of 0.001. Images displayed in radiological view (left=right, right=left).

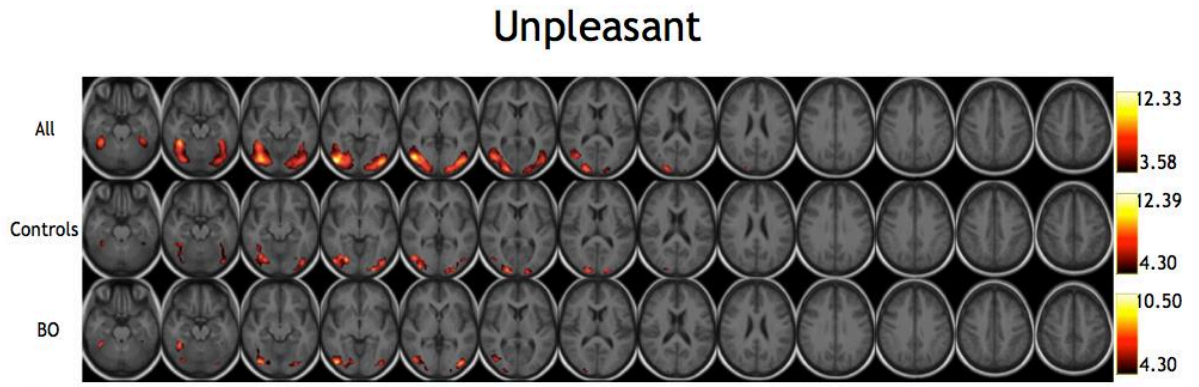


Figure 28 - Second level group contrasts based on first level contrast Unpleasant. All contrasts were thresholded at the significance level of 0.001. Images displayed in radiological view (left=right, right=left).

To understand which regions may potentially show significant activation differences between burnout and control groups if a similar study would be conducted using a larger population, we included Figures 29 to 32. These images show several brain regions where differences can be observed for some contrasts if a less strict significance level threshold is used. In these maps the colormap chosen goes from t-value=2.55, corresponding to p-value of 0.01, until t-value=3.60, corresponding to a p-value of 0.001. Given that in each map a large number of voxels is analyzed, these maps are expected to contain a certain number of false positives and need to be interpreted with caution.

Starting with the contrast Unpleasant>Neutral, Figure 29 indicates a tendency for higher values for this contrast in controls than in burnout subjects in the right inferior frontal gyrus. Figure 30, which shows the regions where the BOLD signal is higher in controls compared to burnout subjects during the Unpleasant stimuli, shows the same region. This tells us the brain activation during the Unpleasant images is the main driver of the referred differences seen between the two groups.

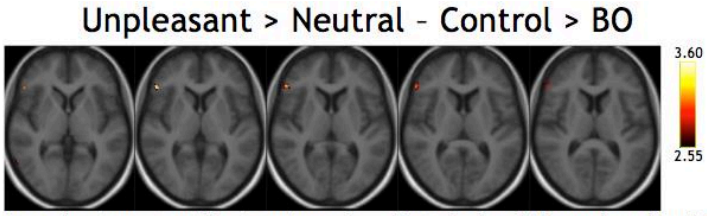


Figure 29 – Second level contrast showing *potential* brain regions where Controls show higher values than BO for the first level contrast Unpleasant>Neutral. This contrast is equivalent to the contrast BO>Control for Neutral>Unpleasant, however by looking at Figures 25 and 26 it is expected that the main differences between groups result from the first level contrast Unpleasant>Neutral. The t-value scale shown corresponds to p-values from 0.01 to 0.001. Images displayed in radiological view (left=right, left=right).

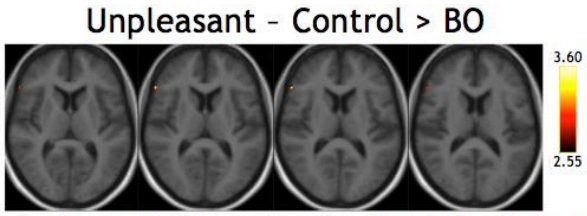


Figure 30 – Second level contrast showing *potential* brain regions where Controls show higher activation than BO for the first level contrast Unpleasant. The t-value scale shown corresponds to p- values from 0.01 to 0.001. Images displayed in radiological view (left=right, left=right).

In Figure 31, we see that the BO group showed a higher BOLD signal during the Neutral stimuli than the control group in a few regions: right hippocampus (uncus), right head of the caudate nucleus, right cuneus, right inferior frontal gyrus, and right thalamus.

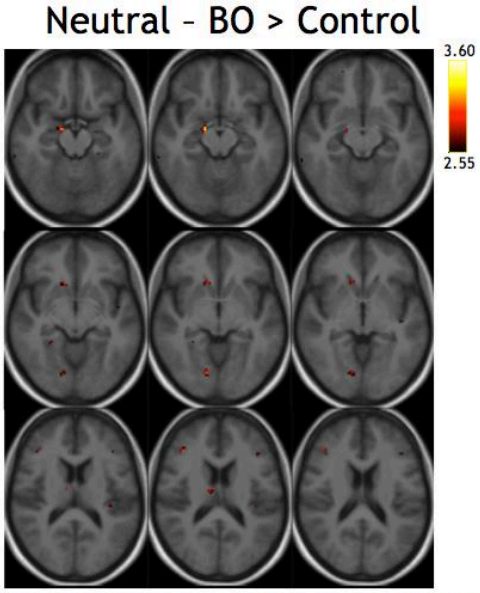


Figure 31 – Second level contrast showing *potential* brain regions where BO show higher activation than Controls for the first level contrast Neutral. The t-value scale shown corresponds to p-values from 0.01 to 0.001. Images displayed in radiological view (left=right, left=right).

Figure 32 shows regions where burnout subjects show higher BOLD signal during the Unpleasant visual stimuli than healthy controls. From all the contrasts comparing the two groups this seems to show the highest differences between groups, and from all the regions, the right inferior frontal gyrus shows the largest differences with a p- value of 0.002. In the left inferior frontal gyrus, the results show also greater activation for burnout subjects. Apart from this, a higher BOLD signal is also observed in the head of the right caudate nucleus and left inferior temporal lobe.

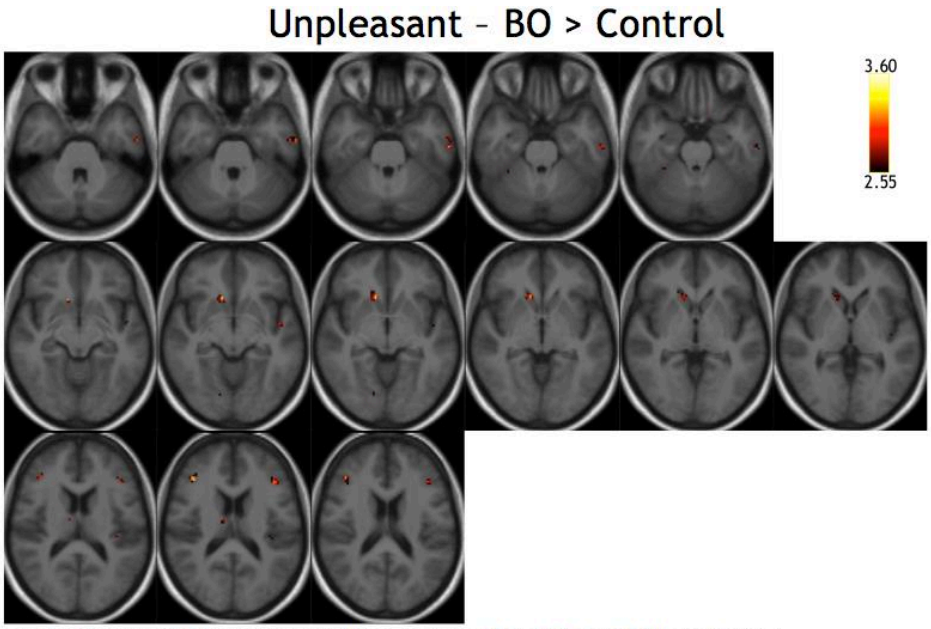


Figure 32 – Second level contrast showing *potential* brain regions where BO show higher activation than Controls for the first level contrast Unpleasant. The t-value scale shown corresponds to p-values from 0.01 to 0.001. Images displayed in radiological view (left=right, left=right).

3. Summary of results

The results of the fMRI analysis showed for the great majority of subjects higher BOLD signal during the Unpleasant visual stimuli than during the Neutral visual stimuli. Moreover, a few patients showed significantly higher activation in the frontal cortex during the Neutral stimuli than during the Unpleasant stimuli. However, since this effect was seen only for 7 of the 20 cases, and the involved regions were different for those cases, this effect was not seen in the group contrasts.

At the level of the whole group, the main differences between the BOLD signal for the Unpleasant and Neutral stimuli were seen in the occipital lobe, in the posterior parietal lobe and posterior temporal lobe, in the genu of the internal capsule, in the right inferior frontal gyrus, in the orbital gyri and in the left and right hippocampi.

The comparison between both groups showed no significant differences between groups. Despite this, an analysis of potential regions where differences between groups may be observed was conducted. In this case, a very relaxed significance level ($p=0.01$ for each voxel) was used and therefore some of the indicated regions may correspond to false positives. Taking this into account, the main results from the produced maps suggest that burnout subjects may show higher activation during the Unpleasant stimuli in the inferior frontal gyri and in the caudate nucleus.

DISCUSSION

Overall, the analysis of the fMRI results showed higher BOLD signal during the unpleasant visual stimuli than during the neutral visual stimuli for the majority of subjects. However, when we compare both groups, no significant differences in brain activity were detected. This might be explained from the small sample size of the study population as well as the inter-subject variability in both groups, partly related with differences in everyone's personal response to visual stimuli (i.e. one image can arouse different emotions based on everyone's personal experiences). It is important to point out that during the study set-up, extra attention was given to counterbalance these confounding factors by recruiting study subjects that formed as much as possible a homogeneous group with relation to age, gender, right-handedness, work environment (healthcare sector) and absence of other mental disorder.

However, the study suggests that burnout subjects may show higher activation during the Unpleasant stimuli in the caudate nucleus and in the inferior frontal gyri. A power analysis indicates that a sample size of 60 subjects (30 controls and 30 burn-out subjects) would be required to confirm these differences between both groups in 80% of the studies, or a sample size of 70 subjects (35 in each group) to achieve a power of 90%. These calculations assume a significance level of 0.001.

Processing of emotions has been a large topic of interest in neuroimaging research in the past decades. Images shown to our study subjects were derived from the IAPS database, including affect-related stimuli from varying faces, scenes and objects. A review about emotion face perception and fMRI states that complex processes are involved in the regulation of emotions derived from facial expressions and it cannot be related to a single neural event taking place in a single brain region (22). fMRI and EEG studies showed that emotions derived from facial expressions are processed in brain systems responsible for face recognition and memory such as the inferior occipital, fusiform cortex and hippocampus (22). Another study aimed to determine neural networks involved in emotion processing using scenic photographs from the IAPS (international affective picture system) using fMRI (23). The occipito-temporal cortex and amygdala-hippocampal complex showed a non-specific emotion-related activation. Important to emphasize is that activation was more marked in response to negative emotions (23). All of these findings could explain our first observations, that is, higher brain activity was measured during unpleasant stimuli in various regions of the brain, involving

occipito-temporal cortex, hippocampus and limbic structures. This confirms what is described in literature, namely complex pathways and interaction of various regions are involved in emotion processing (24).
The fact that our findings are in line with other neuro-imaging research confirms that our study set-up (selection of images, fMRI block design) was sound and that our fMRI examinations were performed well. Hence, expanding the present study with a larger sample size of 60 subjects could confirm differences in brain activity in potential regions such as the caudate nucleus and the inferior frontal gyri.

The caudate nucleus is part of the striatum and receives input from several other brain regions including three structures involved in affective assessment of the environment: the ventromedial prefrontal cortex, the insula and the amygdala (25-27). Additionally, dopaminergic neurons, a key modulator of emotional processes, are predominant in the striatum (28). The response of the striatum to negative visual stimuli was studied through fMRI and it demonstrated that the striatum showed greater activation in response to negative than in response to neutral images (29). Two additional regions showed significant activation associated with that in the caudate nucleus. One of them was the dorsal visual cortex, more specifically the inferior parietal lobule. Data in literature has shown activation of this region when negative (painful) stimuli were presented to human subjects. The other region was the ventral-lateral prefrontal cortex, which also shows significant responses to negative pictures and projects this information to the caudate nucleus (29). Previous findings about these interconnections are in agreement with models described in literature proposing that the striatum is the first station of the main subcortical output system of the emotional brain (30). Consequently, the striatum is able to activate motor functions such as emotional expressions or specific behaviors (31). The exact meaning of the fact that burn-out subjects may show higher activation during the Unpleasant stimuli in regions such as caudate nucleus and inferior frontal gyri is unclear.
Therefore, there is a need for more research that provides answers related to the neuronal mechanisms of burnout. However, the possibility that there is a significant difference in the pattern of brain activation in patients suffering from burnout might have important consequences. Both for patients and their environment it might be helpful to confirm their condition. Moreover, fMRI might not only be used in the diagnosis of burnout patients, but also in their follow-up and in monitoring treatment response.

Previous research on burnout mostly used subjective measure methods, maintaining unclarity about the underlying mechanisms of burnout symptoms. On the other hand, neuroimaging techniques such as MRI and fMRI are used more often in the recent decades increasing the understanding of the pathophysiology of burnout. Blix et al. compared cerebral gray and white matter volumes between burnout patients and healthy controls (10). Burnout subjects showed a significant reduction in gray matter volumes of the anterior cingulate cortex (ACC) and the dorsolateral prefrontal cortex (dlPFC). Even more important, the caudate nucleus and the putamen volumes were reduced and correlated inversely to the degree of perceived stress. To summarize, fronto-striatal morphology was affected in burnout subjects (10). Another study showed that burnout subjects had a significant mesial frontal cortical thinning and caudate nucleus volumes were reduced ($p=0.040$) while amygdala volumes were bilateral increased ($p=0.020$). The study showed that in burnout there was an association between cortical thinning as well as with selective changes of subcortical volumes and behavioral correlates (9). Golkar et al. analyzed the negative effects of long-term related stress on the individuals' ability to regulate emotional tension and cope with stressors. The burnout group showed reduced connectivity between the amygdala and the dlPFC. These findings suggest that burnout subjects have altered emotion- and stress-processing limbic networks associated with a reduced ability to down-regulate negative emotions (2).

Relating this literature to our findings illustrates that with the help of structural volumetry and voxel-based morphometry, this condition may be associated with structural alterations in the brain. In particular the limbic structures are affected as well as the prefrontal cortex, the striatum (caudate nucleus, putamen) and the amygdala. Yet, the exact role of each specific region and their interactions is unclear. Overall, this research project represents part of a larger effort to demystify burnout pathophysiology.

As stated before, considering the potential and the limitations of our project, the greatest strength is the technical design of our study. Factors such as the block paradigm set-up, IAPS databank and the professional equipment at the university hospital allowed us to acquire qualitative and reliable fMRI results. Next, the study population was very homogeneous (all right-handed females with a medical profession, no significant age differences …) and all burnout subjects had a moderate to high MBI score. In addition, burnout diagnosis was

confirmed by a doctor. Furthermore, confounding factors such as drinking coffee up to 4 hours before scanning and wearing make-up (some sort of make-up contain metal which can interfere with the results) were avoided.

Regarding the weaknesses of this study project, both a limited sample size as well as challenges to distinguish burnout from depression are worth mentioning. Clinical symptoms of these two mental disorders may resemble as these disorders may affect both mental and physical health of the patient. We have tried to gain insight into this by having the subjects fill in the PHQ-9, which assesses the possible presence and degree of depression. All controls scored low on the questionnaire (i.e. <10). In the burnout group we note significant higher scores, with only 2 burnout subjects scoring low and the mean score being 14.1 ± 5.8 out of 27. Based on these results, we cannot neglect that some burnout subjects may experience anhedonia. Finally, the use of medication in both groups was compared. None of the control subjects took central nervous system depressants while 7 out of 10 burnout subjects took anti-depressive agents or benzodiazepine(-like) agents. Considering their pharmacodynamical effects on the central nervous system, they may have affected the way these subjects experienced and processed their emotions during the fMRI experiment.
We believe that further research in this field could be promising, however, one of the most important challenges we faced was reaching the right sample size, preserving homogeneity between subjects. As an alternative, less strict in- and exclusion criteria could be used.

We believe that burnout research in general is of great clinical (and as a consequence economic) relevancy. Firstly, as stated in the introduction, burnout poses a substantial economic burden to the society. It has an important socio-economic impact of decreased productivity levels, increased rates of resignation and premature retirement. In 2017 a record number of Belgian people were at home with a burnout (33). IDEWE, a Belgian external service for prevention and protection at work, calculated that each employee with burnout symptoms costs an additional €7392 each year (36). From a clinical point of view it is the individual who suffers from burnout that is affected in the first place. However, with burnout in a person working in the healthcare sector, medical mistakes are made more often which has a direct negative impact on patient's safety and well-being (4).

Furthermore, our research could also be of relevance in burnout therapy. Taking a closer look into activity of emotion-processing-regions in the brain with the help of fMRI gives us more knowledge on some of the regions

involved. Consequently, new insights into treatment and prevention strategies can be developed. One possibility would be to look at the efficacy of deep brain stimulation, a field that is already been explored in depression (32).

To recap, this study points in the direction of an altered brain activity in burnout patients in the caudate nucleus and in the inferior frontal gyri. However, there is still much to discover and with this pilot study we contribute in paving the way into more burnout research.

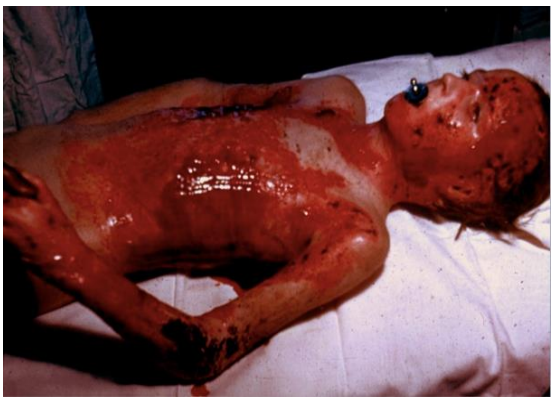
ACKNOWLEDGEMENTS

This research was supported by the Department of Radiology of the University Hospital of Antwerp, Belgium. Firstly, we would like to take the opportunity to thank our supervisor prof. dr. Paul Parizel for his guidance, suggestions and encouragement throughout the course of this study project. Secondly, we would like to show our gratitude to Floris Vanhevel who provided insights on the technical aspects of fMRI scanning and prof. dr. Johan Van Goethem for his expertise that greatly assisted our research. Next, we are very grateful for the collaboration with Wim Van Hecke, Nuno Barros, Thibo Billiet and Annemie Ribbens from icometrix. Their experience and insights on fMRI data analysis in particular was greatly appreciated. Finally, we would like to express our gratitude toward the study subjects: without their cooperation, this study was not possible.

APPENDIX I – Examples of used images

1. Neutral


2. Unpleasant

APPENDIX II – First level analysis

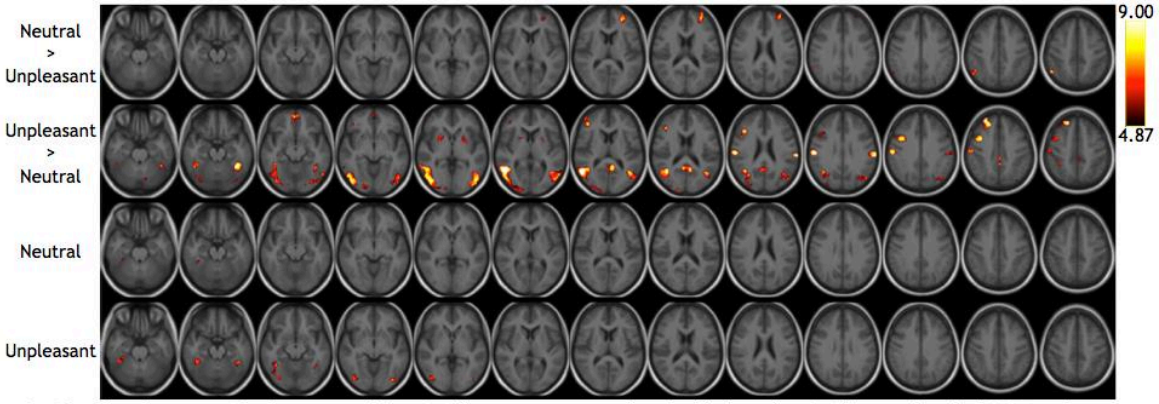


Figure 6 – First level contrast for burnout subject 2. All contrasts were thresholded at the significance level of 0.05 and considering the FWE correction. Images displayed in radiological view (left=right, right=left).

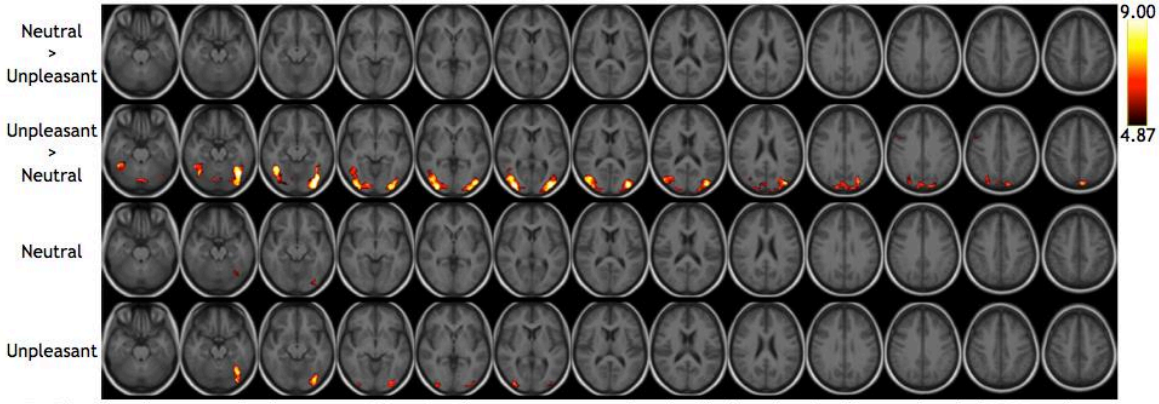


Figure 7 – First level contrast for burnout subject 3. All contrasts were thresholded at the significance level of 0.05 and considering the FWE correction. Images displayed in radiological view (left=right, right=left).

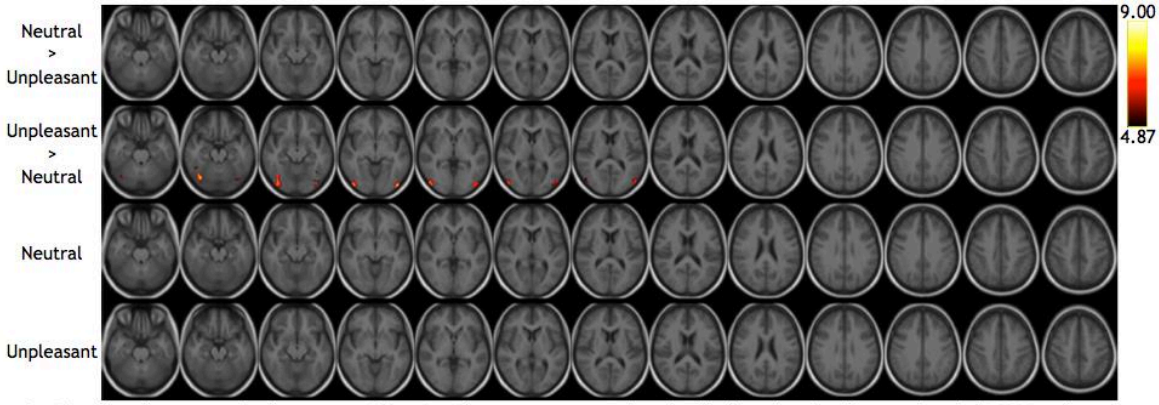


Figure 8 – First level contrast for burnout subject 4. All contrasts were thresholded at the significance level of 0.05 and considering the FWE correction. Images displayed in radiological view (left=right, right=left).

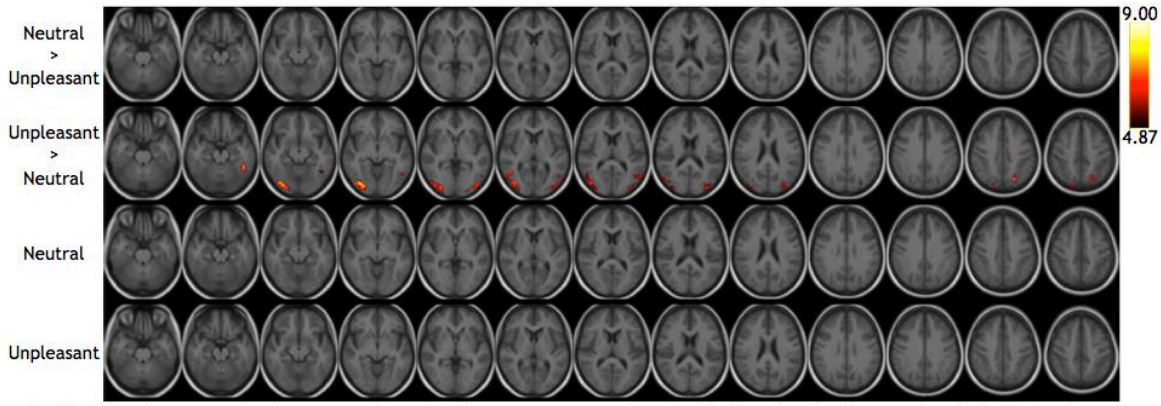


Figure 9 – First level contrast for burnout subject 5. All contrasts were thresholded at the significance level of 0.05 and considering the FWE correction. Images displayed in radiological view (left=right, right=left).

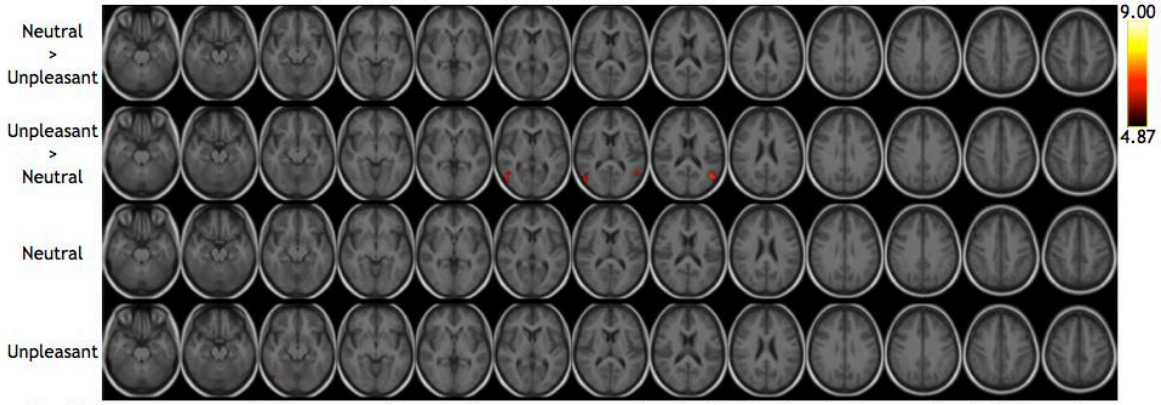


Figure 10 – First level contrast for burnout subject 6. All contrasts were thresholded at the significance level of 0.05 and considering the FWE correction. Images displayed in radiological view (left=right, right=left).

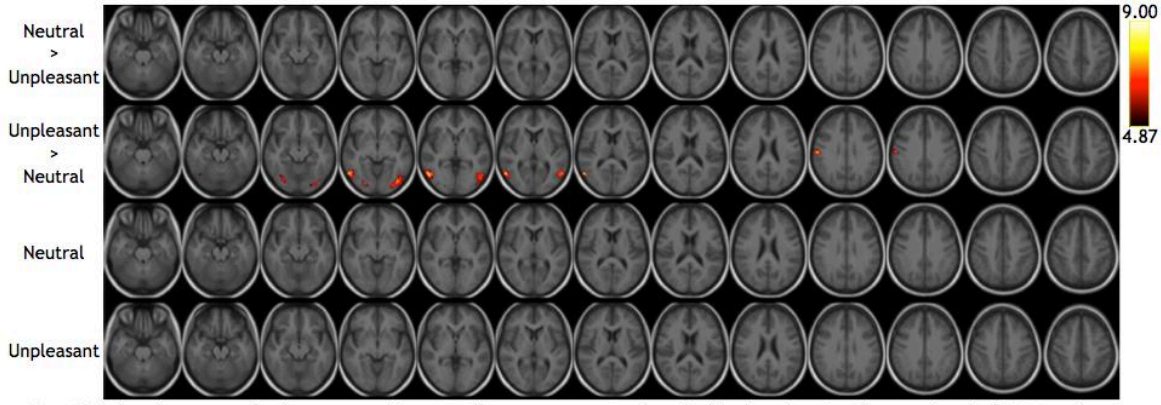


Figure 11 – First level contrast for burnout subject 7. All contrasts were thresholded at the significance level of 0.05 and considering the FWE correction. Images displayed in radiological view (left=right, right=left).

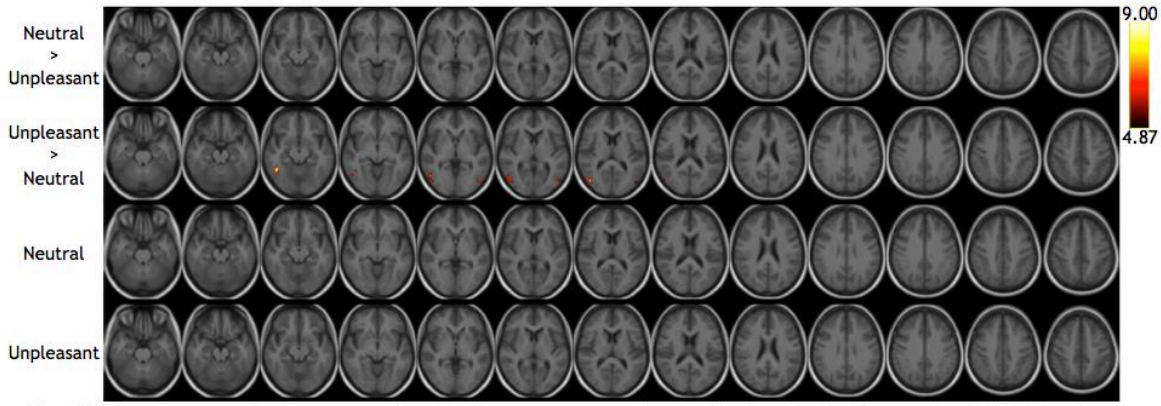


Figure 12 – First level contrast for burnout subject 8. All contrasts were thresholded at the significance level of 0.05 and considering the FWE correction. Images displayed in radiological view (left=right, right=left).

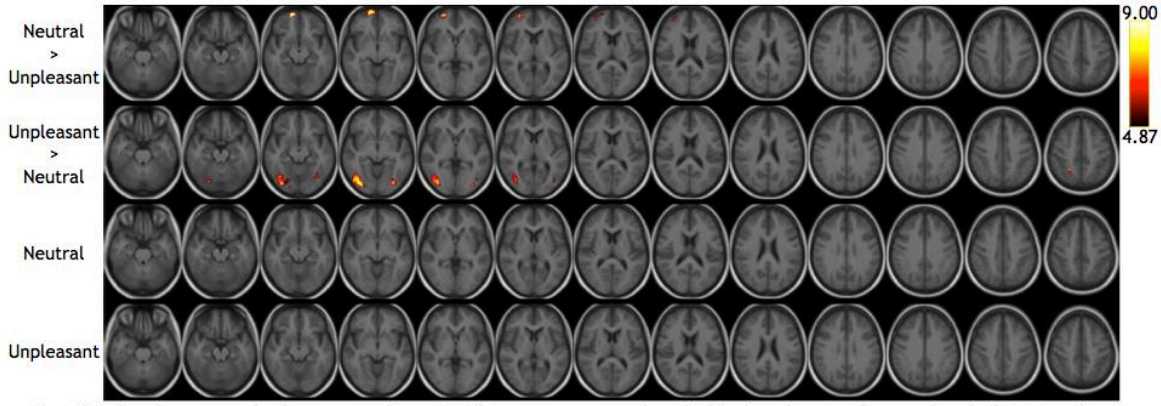


Figure 13 – First level contrast for burnout subject 9. All contrasts were thresholded at the significance level of 0.05 and considering the FWE correction. Images displayed in radiological view (left=right, right=left).

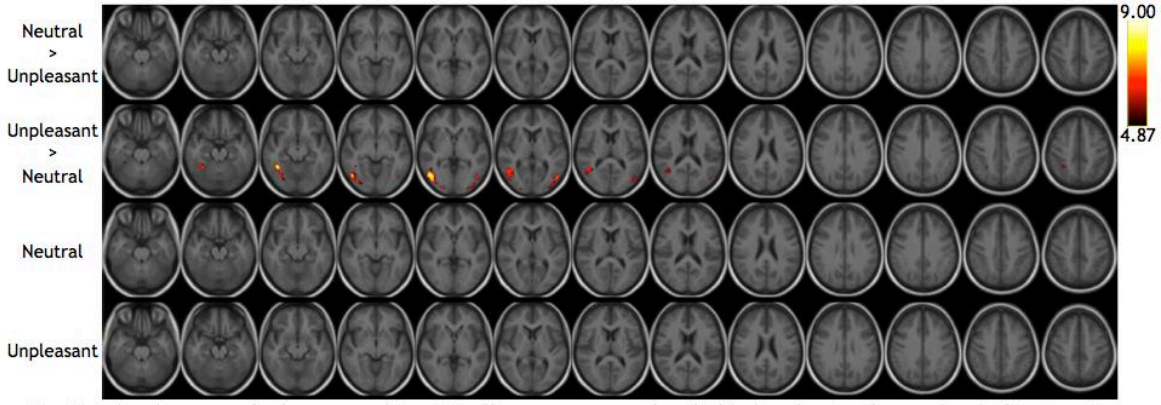


Figure 14 – First level contrast for burnout subject 10. All contrasts were thresholded at the significance level of 0.05 and considering the FWE correction. Images displayed in radiological view (left=right, right=left).

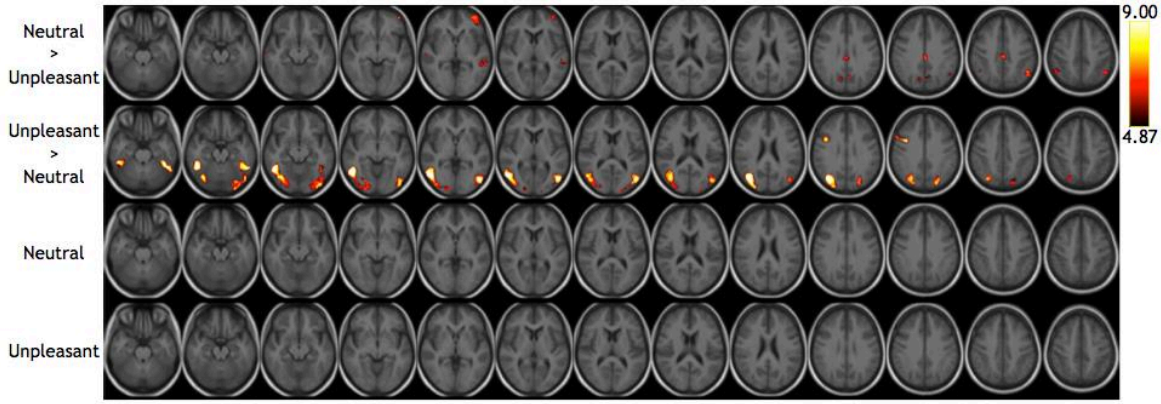


Figure 15 – First level contrast for control subject 1. All contrasts were thresholded at the significance level of 0.05 and considering the FWE correction. Images displayed in radiological view (left=right, right=left).

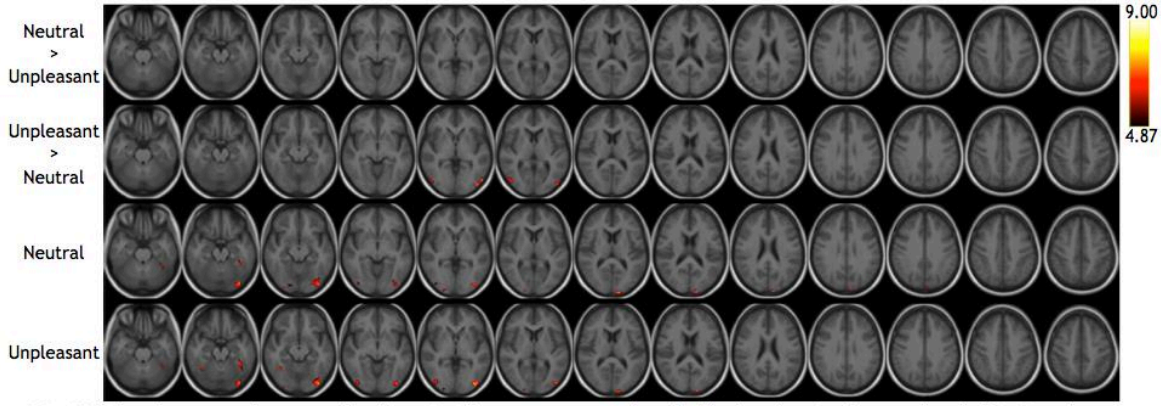


Figure 16 – First level contrast for control subject 2. All contrasts were thresholded at the significance level of 0.05 and considering the FWE correction. Images displayed in radiological view (left=right, right=left).

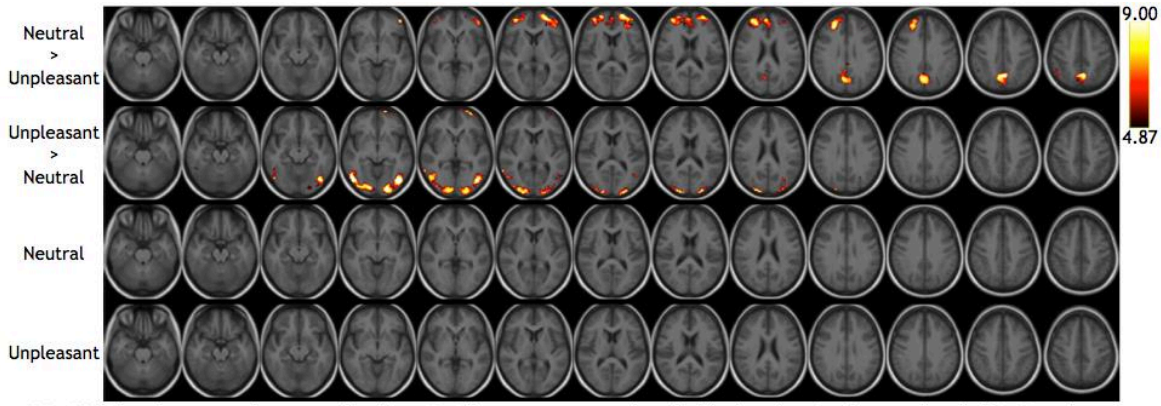


Figure 17 – First level contrast for control subject 3. All contrasts were thresholded at the significance level of 0.05 and considering the FWE correction. Images displayed in radiological view (left=right, right=left).

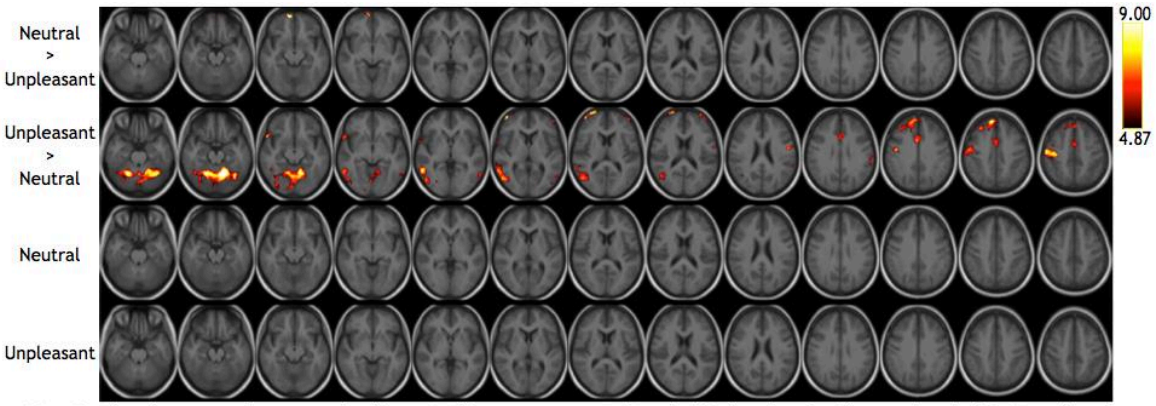


Figure 18 – First level contrast for control subject 4. All contrasts were thresholded at the significance level of 0.05 and considering the FWE correction. Images displayed in radiological view (left=right, right=left).

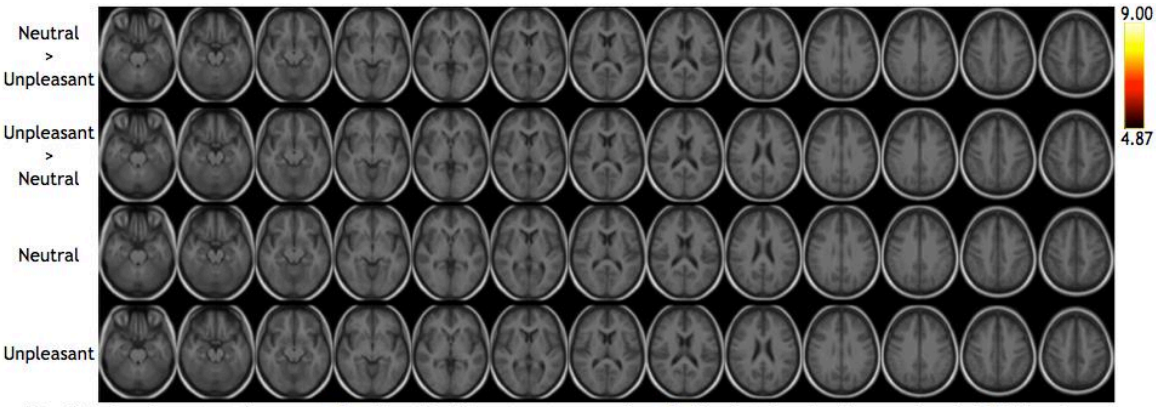


Figure 19 – First level contrast for control subject 5. All contrasts were thresholded at the significance level of 0.05 and considering the FWE correction. Images displayed in radiological view (left=right, right=left).

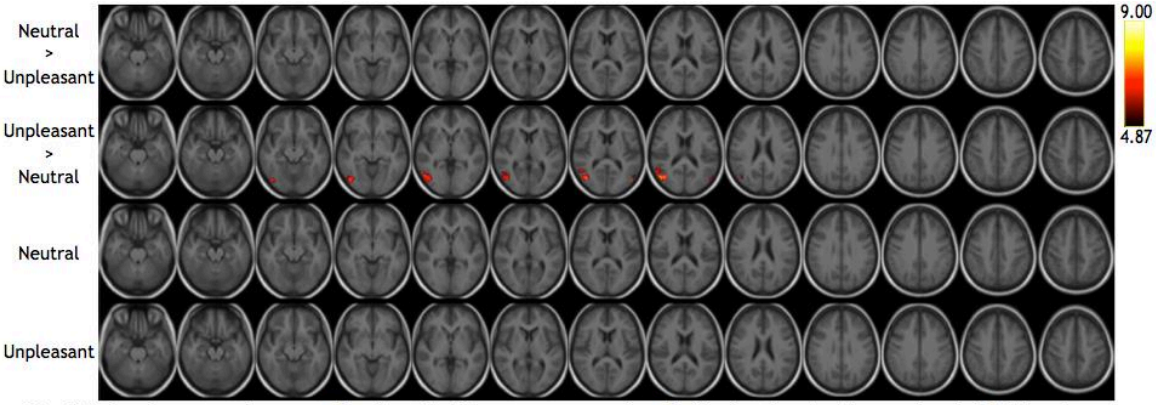


Figure 20 – First level contrast for control subject 6. All contrasts were thresholded at the significance level of 0.05 and considering the FWE correction. Images displayed in radiological view (left=right, right=left).

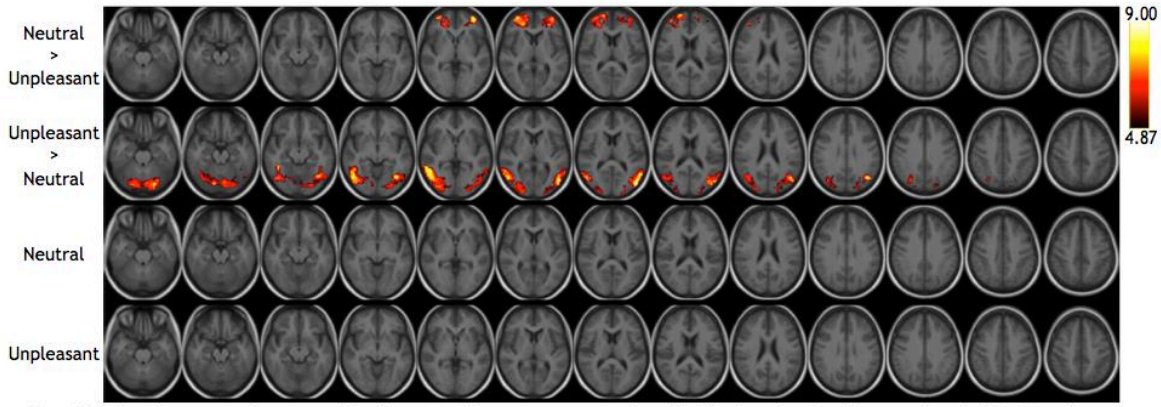


Figure 21 – First level contrast for control subject 7. All contrasts were thresholded at the significance level of 0.05 and considering the FWE correction. Images displayed in radiological view (left=right, right=left).

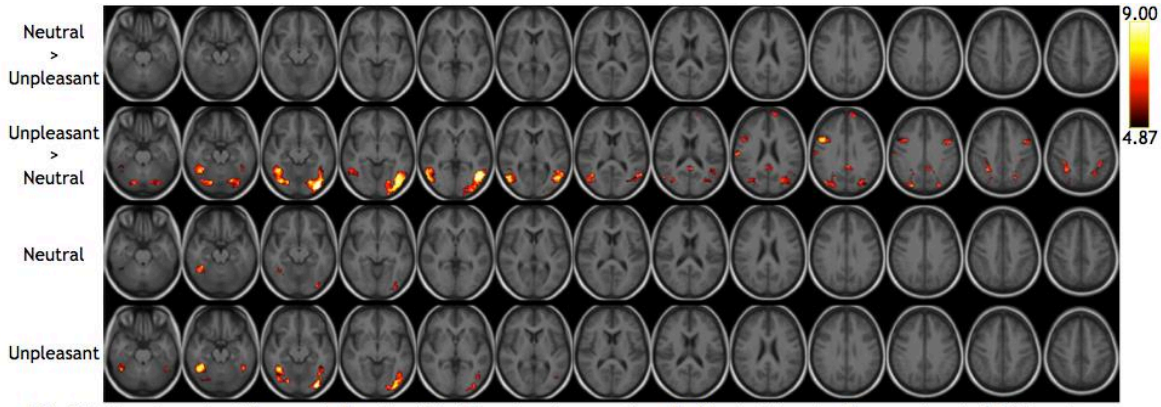


Figure 22 – First level contrast for control subject 8. All contrasts were thresholded at the significance level of 0.05 and considering the FWE correction. Images displayed in radiological view (left=right, right=left).

Figure 23 – First level contrast for control subject 9. All contrasts were thresholded at the significance level of 0.05 and considering the FWE correction. Images displayed in radiological view (left=right, right=left).

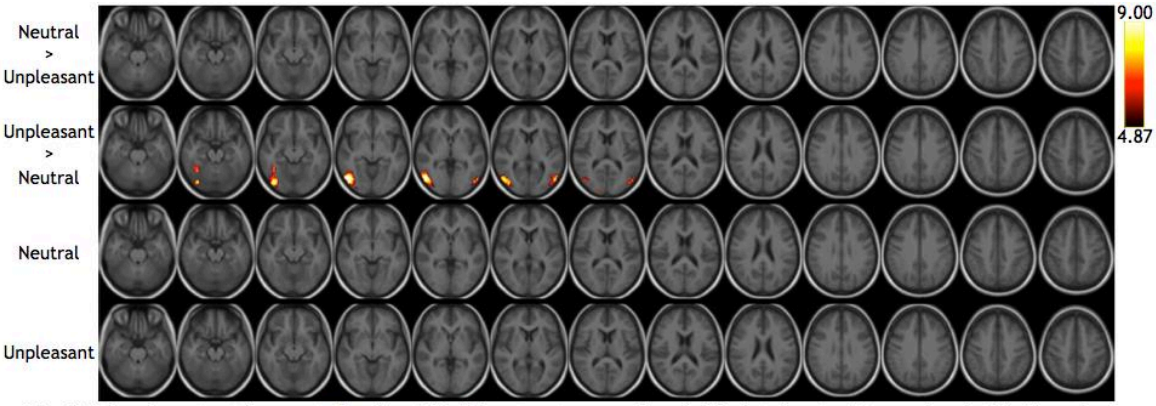


Figure 24 – First level contrast for control subject 10. All contrasts were thresholded at the significance level of 0.05 and considering the FWE correction. Images displayed in radiological view (left=right, right=left).

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