THE LOCALIZATION OF EMOTIONAL STROOP ACTIVATIONS IN HEALTHY AND MAJOR DEPRESSIVE DISORDER POPULATIONS USING fMRI

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ABSTRACT

THE LOCALIZATION OF EMOTIONAL STROOP ACTIVATIONS IN HEALTHY AND MAJOR DEPRESSIVE DISORDER POPULATIONS USING fMRI

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Among many tasks suggested to measure emotional conflict resolution, the Word-Face Stroop Task stands out since it specifically creates a conflict between two emotional items: Emotional words versus emotional faces. The Turkish valence-specific Word-Face Stroop Task is demonstrated to work as an effective tool to measure emotional conflict resolution and revealed different behavioral patterns between depressed and healthy groups. In this dissertation, using the functional magnetic resonance imaging (fMRI)-compatible Turkish Word-Face Stroop, it is aimed to show that the group differences in behavioral patterns will be reflected as different brain activation patterns. The behavioral results of this valence-specific Word-Face Stroop revealed that both group succeeded to show positive-negative asymmetry effect, i.e. slowing down towards negative cases; whereas patients were faster and more correct towards negative cases in contrast to healthy group. In line with these behavioral results, different patterns of brain activations are found between the groups: Compared to healthy group, patients showed higher activations in cognitive control centers of the brain, such as right Dorsolateral Prefrontal Cortex and Superior Frontal Gyrus towards negative stimuli; and they showed higher activations in Frontal Eye Field and Middle Frontal Gyrus that are crucial for attention regulation and reorientation, towards incongruent cases. These activations, along with the behavioral findings, lead to the conclusion that patients' allocation of attention is mostly biased toward negativity. Thus, rather than showing a specific emotional or cognitive deficits, patients seem to have a differently molded attentional mechanism that is negatively-biased.

Keywords: Emotional conflict resolution, Word-Face Stroop, major depression disorder, functional magnetic resonance imaging (fMRI), negative bias

ÖZ

SAĞLIKLI VE DEPRESİF POPÜLASYONLARDA DUYGUSAL STROOP AKTİVASYONLARININ fMRI İLE LOKALİZASYONU

Başgöze, Zeynep

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Duygusal çelişki çözümleme ölçümü için önerilen testler içinde Kelime-Yüz Stroop testi öne çıkmaktadır. Bunun sebebi çelişkiyi tam anlamıyla iki duygusal içerikli öğe, yani duygusal içerikli kelime ve duygusal içerikli yüz ifadeleri, arasında yaratabilmesidir. Özellikle yalnızca olumlu-olumsuz ekseninde değişiklik gösteren duygusal uyaranlar kullanılarak geliştirilmiş olan Türkçe Kelime-Yüz Stroop testinin duygusal çelişki çözümlemeyi başarılı şekilde ölçebildiği önceki çalışmalarda gösterilmiş, sağlıklı ve depresif gruplar arasında farklı davranışsal örüntüler gözlemlenmiştir. Bu tezde Türkçe Kelime-Yüz Stroop testinin fonksiyonel manyetik rezonans görüntülemeye (fMRG) uyarlanmış versiyonunu kullanarak hasta ve sağlıklı gruplar arasında gözlemlenen farklı davranışsal desenlerin beyin aktivasyonlarında da gözlemlenip gözlemlenemeyeceği araştırılmak istenmiştir. Kelime-Yüz Stroop testinin davranışşsal sonuçları iki grubun da pozitif-negatif asimetri, yani negative sözcüklere daha yavaş tepki verme etkisini göstermiş; ancak hastalar sağlıklı bireylerle karşılaştırıldıklarında negatif durumlara karşı daha hızlı ve doğru yanıt vermişlerdir. Bu davranışsal bulgularımızla uyumlu olarak gruplar arası beyin aktivasyonlarında da farklılıklar gözlemlenmiştir: Depresyon hastaları sağlıklı bireylere göre sağ Dorsolateral Prefrontal Korteks ve Süperiyör Frontal Girus gibi bilişsel kontrol merkezlerinde negatif durumlara karşı daha fazla aktivasyon göstermiş; uyumsuz durumlara ise özellikle dikkat yönelimini ayarladığı iddia edilen Ön Göz Alanı ve Orta Frontal Girusta daha fazla aktivasyon göstermişlerdir. Davranışsal bulgular ve bahsi geçen aktivasyon farklılıkları depresyondaki bireylerin dikkatlerinin ağırlıklı olarak negatif uyaranlara yöneldiğine işaret etmektedirler. Dolayısıyla depresif bireyler doğrudan duygusal veya bilişsel bir soruna sahip olmaktan ziyade negatif yönde yanlılık gösteren, farklı yapılanmış bir dikkat mekanizmasına sahipler gibi gözükmektedir.

Anahtar Kelimeler: Duygusal çelişki çözümleme, Kelime-Yüz Stroop, majör depresif bozukluk, fonksiyonel manyetik rezonans görüntüleme (fMRG), negatif yanlılık

To my little angels Arman & Ozan

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ACC	Anterior Cingulate Cortex
	cACC Caudal Anterior Cingulate Cortex
	dACC Dorsal Anterior Cingulate Cortex
	rACC Rostral Anterior Cingulate Cortex
BA	Brodmann Area
BDI	Beck Depression Inventory
CBF	Cerebro-Spinal Fluid
CGI	Clinical Global Impression Scale
CS	Congruency Score
DCM	Dynamical Causal Modeling
DICOM	Digital Imaging and COmmunications in Medicine
DLPFC	Dorsolateral Prefrontal Cortex
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (4^{th} version)
EPI	Echo-Planar Imaging
FEF	Frontal Eye Fields
fMRI	Functional Magnetic Resonance Imaging
FOV	Field of Vision
FWHM	Full Width at Half Maximum
GLM	General Linear Modeling
GM	Gray Matter
GP	Globus Pallidus
HAM-D	Hamilton Depression Scale
HRF	Hemodynamic Response Function
LPFC	Lateral Prefrontal Cortex
MDD	Major Depression Disorder
MEG	Magnetoencephalography
MFG	Middle Frontal Gyrus
MNI	Montreal Neurological Institute
OFC	Orbito-Frontal Cortex
PET	Positron Emission Tomography
RT	Reaction Time
SMA	Supplementary Motor Area
SNR	Signal to Noise ratio
SPS	Suicide Probability Scale
WFS	Word-Face Stroop

CHAPTER 1

INTRODUCTION

A free man thinks about death,
but his wisdom is in reflections about life, not death.

Baruch Spinoza

Among several deficits observed in Major Depression Disorder (MDD), the most frequently reported one is problems in conflict resolution (Paelecke-Habermann, Pohl, & Leplow, 2005; Holmes & Pizzagalli, 2007). The classical Stroop task measures cognitive aspects of conflict resolution by focusing on the dominant effect of word meaning over word color. While major depression patients are consistently reported to be slower than healthy controls in the Stroop task, they still exhibit the expected inhibitory slowdown in reaction times for incongruent cases (Markela-Lerenc, Kaiser, Fiedler, Weisbrod, & Mundt, 2006; Gohier et al., 2009). On the other hand, a task-irrelevant emotional load may also create conflicts. Furthermore real life conflicts that we face cannot be readily isolated from an emotional content. In order for our mental functioning to work efficiently, cognition must be protected from interference by irrelevant emotional stimuli (Etkin, Egner, Peraza, Kandel, & Hirsch, 2006).

There is an array of emotional Stroop paradigms, for which a general response characteristic emerges in the depressed patient populations. A meta-analysis of emotional Stroop tasks reveal that depressed populations exhibit longer response latencies in contrast to healthy controls, along with the finding that depressed individuals mostly show an emotional bias that favor negative stimuli (Epp, Dobson, Dozois, & Frewen, 2012). In order to investigate emotional aspects of conflict resolution, it is imperative to consider not only congruence, but also emotional conditions (i.e. happy/sad or positive/negative). Word-Face Stroop tasks that generate interference between affective words and affective faces allow for simultaneous investigation of both of these factors. Compared to the classical Stroop task, the Word-Face Stroop task is less frequently investigated. Nonetheless, in healthy and depressed populations, interference effects are consistently observed for conflicting emotional content in words and pictures (Stenberg, Wiking, & Dahl, 1998; Haas, Omura, Constable, & Canli, 2006; Etkin et al., 2006; Egner, Etkin, Gale, & Hirsch, 2008; Başgöze, 2008; Başgöze, Cullen, Gökçay, 2014; Başgöze, Gönül, Baskak, Gökçay, 2015; Zhu, Zhang, Wu, Lu, & Lu, 2010; Hu, Liu, Weng, & Northoff, 2012; Strand, Oram, & Hammar, 2013.; Chechko et al., 2013). A valence specific version of a Turkish Word-Face Stroop (WFS) Task, which was created during my master's thesis, is repeatedly shown to successfully work as an emotional conflict resolution task (Başgöze, 2008; Başgöze et al., 2014; Başgöze et al., 2015). The arousal level of all words were strictly controlled to be neutral so that this Word-Face Stroop task, unlike others (Hu et al., 2012; Haas et al., 2006), can exclusively measure the effect of positive and negative valence. Excluding the arousal level, we wanted to eliminate the effect of arousal in evaluation of emotional stimuli, which, we thought, is the reason why most of the previous researchers' results on emotional Stroop are incompatible with each other[1]. In classical Stroop tasks, which require more of a pure cognitive processing (isolated from emotional content), patients succeed in showing the basic interference effect, i.e. slowing down towards conflicting (incongruent) stimuli (Gohier et al., 2009; Başgöze, 2008; Başgöze et al., 2014). However, when the conflict is on an emotional level (using tasks with emotionally loaded stimuli), patients fail to show the "emotional" congruency effect, i.e. slowing down towards emotionally loaded conflicting stimuli compared to incongruent stimuli (Başgöze, 2008; Başgöze et al., 2014; Başgöze et al., 2015).

This dissertation's main motivation is not only to understand the underlying cognitive and emotional mechanisms that would cause the behavioral differences between the healthy and depressed groups, as mentioned above, but additionally and most importantly to propose a different kind of attentional networking in depressed brains via revealing group differences in brain functioning. This dissertation has another advantage compared to a purely clinical or psychological study: The way this manuscript examines depression and the mechanism in the brain that depression triggers is formulated in the light of cognitive sciences, which integrates psychology, neuroscience, computer science, and philosophy. The findings of this study are expected to shed light to new network models of attention and emotion. Such neuroscientific findings will help constructing more realistic neural network models, since the brain is currently seen as a network of neural networks (Tryon, 2014). The connectionist models can be modeled by using the networks studied in neuroscience such as attentional network, emotional network and even resting state network, "because the hardware is similar" (Hinton and Shallice, 1991, p. 74).

Therefore in this study, using a valence-specific Turkish fMRI-compatible WFS task, we expect to see opposite patterns in the brain activations when we contrast patient and control groups. Most of the previous studies claimed that the failure of emotional inhibition in patients could be caused by the hyperactivity of rostral Anterior Cingulate Cortex (rACC) as a result of an inability to deactivate this region when required (Wagner et al., 2008; Schlösser et al., 2008). On the other hand, it is also possible that this region can no longer play its crucial inhibitory role on amygdala

[1] There are different dimensional models trying to define emotions, which will be explained in the next section. Our task is designed to be specifically consistent with the Circumplex Model of Emotions that evaluates emotions with respect to different dimensions, such as valence and arousal (Russell, 1980).

(Mayberg et al., 1999), showing a decreased activation in patients (Pezawas et al., 2005) and hence amygdala activation of patients could be significantly more than controls, whereas the opposite pattern (increased activation of rACC and so inhibition of amygdala) could be perceived in the healthy group. However, the tasks and the patient groups these studies employed vary significantly (for example, most of them included emotional stimuli that have arousal value such as ‘anger’, which would produce amygdala activation). This valence-specific task is only conducted in newly diagnosed unmedicated depression population, or unmedicated patients who were diagnosed years ago and recently consulted the doctor right before their incoming depressive episode. Thus this study is expected to reveal more specific results and to clarify conflicting results found in the studies mentioned above.

According to the most recent studies about the underlying neural mechanisms of depression, there seems to be a reciprocal relationship between the regulatory cortical and emotionally expressive limbic system. Since patients are demonstrated to have a disrupted fronto-limbic circuitry in these studies (Stuhrmann, Suslow, & Dannlowski, 2011; Lu et al., 2012; Chechko et al., 2013), we specifically expect to see different activation patterns in the regulatory areas, such as Dorsolateral Prefrontal Cortex (DLPFC), Middle Frontal Gyrus, and Middle Cingulate Gyrus, reflecting themselves either as a hyperactivity of the regulatory system, which might be caused by a dysfunction or by a mood-biased attention mechanism (negative mood); or as a hyperactivity of the limbic system which cannot be inhibited and controlled by the regulatory mechanisms.

Various studies propose that an enhanced sensitivity to negative situations is what makes patients more prone to misinterpret emotionally conflicting situations (Zetsche & Joormann, 2011), which then result in a dysfunction in conscious perceptions and social interactions (Victor, Furey, Fromm, Öhman, & Drevets, 2010). This, in turn, increases the intensity of their depressive symptoms (Gotlib, Krasnoperova, Yue, & Joormann, 2004); thus creating the ‘negative’ vicious cycle in which the patients get stuck. Therefore, if the behavioral results yield a different pattern towards negative stimuli compared to positive stimuli between the groups, then we would also expect to see different patterns of brain activations for both of the groups when valence of the words is considered. Especially dorso-rostral ACC and DLPFC are thought to be activated while processing the valence of the words. Moreover, valence and arousal levels are demonstrated to be processed via different circuits in the brain (Colibazzi et al., 2010). Therefore, for example, since arousal level of the words is eliminated in this study, there is no expectation to see any significant activation difference between the groups in amygdala and hippocampus.

Depression seems to desensitize patients towards emotion identification and causes a misinterpretation of the affect in a negatively biased way (Bourke, Douglas, & Porter, 2010; Elliott, Zahn, Deakin, & Anderson, 2010). Therefore, this bias would be reflected as different behavioral and brain activation patterns for patients compared to healthy group, especially in response to incongruent cases. Face expressions are expected to create a conflicting case for healthy individuals towards incongruent cases. This would not work the same way for the patients, since the emotional faces do not always work as conflicting cases for the patients, because of their differently biased emotional processing, i.e. negatively biased.

The organization of this dissertation is as follows: In Chapter 2, an overview of the literature on the cognitive and emotional conflict resolution, brain mechanisms that are found responsible for these functions, major depression disorder and various theories behind understanding how these mechanisms are influenced in depression will be provided. Chapter 3 will outline both the behavioral and neuroimaging methods used in this study. In Chapter 4, the results of the experiment will be presented both for behavioral and fMRI analyses. In Chapter 5, the findings from the previous chapter will be discussed in a step by step basis. Finally, in Chapter 6, a brief conclusion regarding our research will be drawn.

CHAPTER 2

LITERATURE REVIEW

2.1. An evolutionary advantage: Resolving the conflicts

2.1.1. Cognitive conflict

When there is a conflict between a previous and a current thought or response, the brain seeks the most economical way—i.e. the fastest and most appropriate— to detect and resolve the conflict in hand to decide on the best option required to keep the survival in a constantly changing environment. Without the cognitive-emotional networking of the brain, human beings cannot adapt themselves to new situations and thus may simply be unable to survive. We certainly need our emotional system to detect the dangerous situations and warn our cognitive system in order to act on it accordingly, hence getting the famous response: fight or flight! We should know where and when to focus our attention from less relevant to more relevant situations. Therefore, the brain needs to resolve conflicts in order to monitor incessantly the distractors which cause incongruities with current tasks people face constantly in their daily lives. This important ability to suppress the conflicting case in order to perform better can be called as 'conflict resolution'.

Conflict resolution is generally measured by the classical Stroop task where participants need to suppress word meaning to be able to name the ink color (Stroop, 1935). When the ink color and meaning are the same the stimulus is called "congruent" (e.g. "red" printed in red); whereas the stimulus is "incongruent" when the ink color and the meaning do not match (e.g. "red" printed in green) (Figure 1). The well-known effect stemming from responding significantly later to incongruent cases than congruent cases is originally called "Stroop effect" (MacLeod, 1991) or sometimes called "interference effect" (Pardo, Pardo, Janer, & Raichle, 1990). This task is considered as a useful tool to investigate the condition of the cognitive processes that might be impaired because of a psychiatric disease (Williams, Mathews, & MacLeod, 1996). Among other types of cognitive processing, the classical Stroop Task seems to be prominent in detecting impairments especially in selective attention (Siegle, Stuart, Thase, 2004).

Figure 1: Classical Stroop Task (from "Studies of interference in serial verbal reactions" by Stroop, 1935, Journal of Experimental Psychology)

This task exclusively measures cognitive interference. During the conductance of this purely cognitive task, the brain areas which seem to have the most crucial roles are Anterior Cingulate Cortex (ACC) and Dorsolateral Prefrontal Cortex (DLPFC) – which will be explained in detail in the following subsections. ACC activity is demonstrated to increase while performing the incongruent task in which participants try to resolve a conflict between the word and the ink color (Pardo et al., 1990). Further studies show that the conflict is detected and evaluated in ACC which thus alerts DLPFC that in turn tries to reduce the conflict, eventually providing the conflict adaptation (Egner & Hirsch, 2005). It is still not well known whether the conflict occurs while responding or during semantic (or conceptual) encoding. On the other hand, numerous studies showed that both response and semantic levels of processing seem to contribute to the Stroop effect, whereas distinct areas in the brain (such as ACC and DLPFC) work in a parallel way in case of cognitive interference (van Veen & Carter, 2005).

2.1.2 Emotional Conflict

Conflicts in life usually bear emotional content. These emotional conflicts are the ones that actually complicate decision processes needed to provide the ultimate conditions for our survival. Although quantifying a concept involving emotions might seem highly improbable, various studies measure cognitive processes to mirror the effects of emotion. Since these tasks measure the interference effect of two conflicting emotional conditions that can be observed in a cognitive level, it is preferred to use the term "emotional interference" for these measurements. Therefore whereas classical Stroop task measures cognitive conflict resolution (or cognitive interference), revealing the inhibitory effect of the word meaning over the word color, emotional conflict resolution (or emotional interference) is measured by tasks revealing the inhibitory effect of an affective stimulus over another affective stimulus.

2.1.2.1. Emotions

The ‘Basic Emotions’ theory, which state that there were six basic universal emotions (happiness, sadness, anger, fear, surprise and disgust), was mostly accepted in the field in the past (Ekman, Friesen, & Ellsworth, 1972). However, with the help of new technologies and especially after the neuroimaging studies burst, the scientific community started to prefer dimensional theories of emotion, since emotions turned out to be not as clear cut as it was once thought. Therefore, various two dimensional emotion theories were suggested, although those two dimensions vary; sometimes it was ‘positive and negative’ affect (Watson, Wiese, Vaidya, & Tellegen, 1999), sometimes ‘tension and energy’ (Thayer, 1989), or ‘approach and withdrawal’ (Lang, Bradley, & Cuthbert, 1998), or ‘valence and arousal’ (Russell, 1980). The Circumplex Model of Affect is largely accepted for many years, since this model has been showed to be more consistent with recent emotion studies (behavioral, neuroimaging or genetic) and with recent research on mental disorders (Posner, Russell, & Peterson, 2005).

According to this model, there are two basic emotional dimensions: valence and arousal. Valence is the dimension which ranges from pleasant to unpleasant (e.g. “peace” is mostly regarded as pleasant, while “cancer” is regarded as unpleasant). Arousal is the dimension which is related to the intensity of the excitement (e.g. “peace” has a very low arousal value, whereas “cancer” creates a great deal of excitement and hence has a high arousal value).

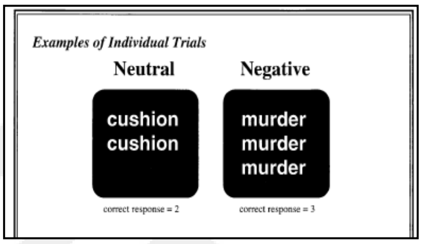
Studies conducting different kinds of tasks (subsequent detection, word recognition, lexical decision etc.) reveal that people tend to have longer response latencies in response to negatively valenced words than the positively valenced ones (Pratto & John, 1991; White, 1996; Stenberg et al., 1998). This asymmetry is especially perceived when the tasks have an affective orientation (such as making participants evaluate the emotional value of the stimuli), but not when a non-affective orienting task (e.g. just reading or detecting the stimuli) is conducted (Dahl, 2001), which might have occurred because of the different organization of the emotional material in memory. It is claimed that the networks getting activated for negative and positive stimuli might be distinct and the positive stimuli are probably more easily processed than negative ones, because they are more detailed in the cognitive-emotional network in the brain (Ashby et al., 1999; Isen, 1985; Ruiz-Caballero & Gonzalez, 1994 in Kuchinke, et al., 2005).

2.1.2.2. Conflicts with emotions involved

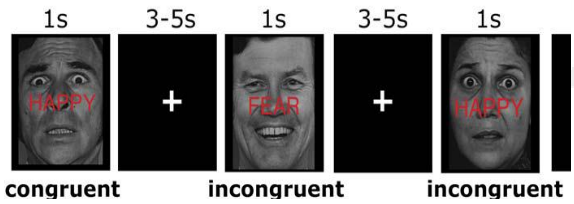
Earlier studies that aimed at measuring emotional interference mostly used tasks that generate conflict between emotional words and their color, where subjects are expected to read out the color of the words that are either neutral or emotionally loaded (Emotional Stroop--Gotlib and McCann, 1984, Figure 2a) or between emotional words and the number of their occurrences in a given trial, where subjects are expected to say the number of the words that are either neutral or emotionally loaded (Emotional Counting Stroop--Whalen et al., 1998, Figure 2b). However, these designs failed to generate emotional conflict consistently due to the occurrence of the conflict between two distinct domains: emotion and cognition. Therefore, researchers attempted to further generate conflict between emotional words versus emotional pictures in other tasks (Stenberg et al., 1998; Anes & Kruer, 2004; Etkin et al., 2006; Haas et al., 2006). However, these studies had limitations related to the isolation of the emotional dimensions of the words (i.e. valence and arousal) or the standardization of the basic properties of the words, such as frequency, length and concreteness. For example, in Etkin et al.'s study (2006) names of the emotions were used as targets without separating arousal from valence (Figure 2c); therefore, anger and fear were counted as negative emotions just as 'sad' which are actually processed distinctively in the brain (Dahl, 2001; Lewis, Critchley, Rotshtein, & Dolan, 2008).

a. Emotional Stroop with color naming (Gotlib and McCann, 1984)

b.Counting Emotional Stroop (Whalen et al., 1998)



c. Emotional Stroop with faces and emotions (Etkin et al., 2006)



d.Emotional Stroop with faces and emotional words (Haas et al., 2006)

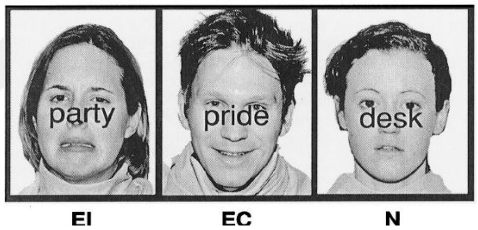


Figure 2: Different types of Emotional Stroop Tasks

The cognitive conflict and emotional conflict appear to activate different networks in the brain (to be explained in subsection 2.3.). The emotional Stroop task that seems to succeed more in creating an emotional conflict occurring in the emotional network specifically was Haas et al.'s design (2006). However, the words in their fMRI compatible Word-Face Stroop were not neutral in arousal level; moreover, they included neutral cases in their study. These are important factors, because, for example, the fact that they failed to show rACC activation towards incongruent cases in their results might be the result of the difference in processing arousing stimuli while trying to solve an emotional conflict. Including the neutral cases might also have distorted their results, because neutral stimuli are actually harder to process, since human brain is mostly automatized, thus processes faster, in evaluating emotionally loaded stimuli (Roesch et al., 2010). Consequently, 'neutral', according to dimensional emotion models, according to which these experiments are designed, is not purely neutral; but is just the least emotionally salient part of a U-shaped valence curve (Lewis et al. 2008) (Figure 3).

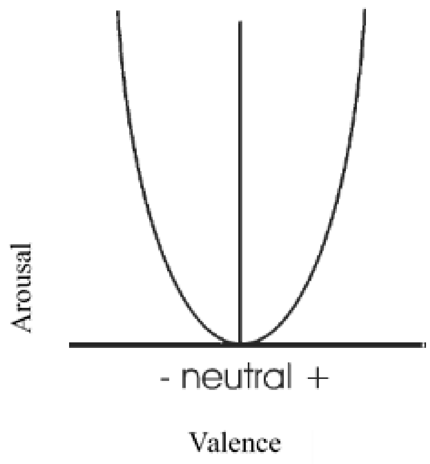


Figure 3 U-shaped distribution of emotional valence (from Lewis et al., 2008, p.742)

During the conductance of these emotional tasks mostly increased caudal ACC activation is detected especially for the emotionally incongruent trials, where the “conflict monitoring” is thought to occur (Haas, et al., 2006). However, it might be problematic to rely on the results from various neuroimaging studies using emotional Stroop tasks because of the huge variance among the experimental designs, variables, hypotheses and neuroimaging techniques.

Therefore, to satisfy the need for a valence-specific version of emotional Stroop task (a.k.a. e-Stroop), in my masters’ thesis, a Word-Face Stroop task is designed to accurately measure reaction times during emotional conflict (Başgöze, 2008).

2.2. The valence-specific Turkish Word-Face Stroop Task

In our Word-Face Stroop task created in my master’s thesis (Başgöze, 2008) the emotional state of the given word was asked to participants on a valence scale (positive, neutral, negative); while the words were displayed on emotionally affective faces. In congruent situations, words with positive valence were shown on faces with positive affect, and words with negative valence were shown on faces with negative affect; whereas in incongruent situations positive words were shown on faces with negative affect and vice versa. There was also an additional condition where words with neutral valence were shown on neutral faces, which was assumed to constitute a baseline at that time. This task differs from Haas et al.’s task (2006) with respect to the fact that the stimuli are controlled according to all emotional axes (while keeping arousal levels neutral), as well as word frequency, length and concreteness.

Since most of the neuroimaging e-Stroop studies do not exclude the arousal dimension, they usually find dysfunctional amygdala activations. For example, in an emotional interference task comparing fearful and neutral face processing, depressed individuals showed higher activities of amygdala and failed to show necessary DLPFC activation as control group showed (Fales et al., 2007). In order to specify our behavioral task’s role in creating a pure emotional conflict, we decided to include only emotionally loaded words (no verbs, adjectives and adverbs; but only nouns in order to control the stimuli as much as possible) that vary only in the valence dimension. The reason to eliminate the arousal dimension from our stimuli is supported by the study by Collibazzi and colleagues (2010) which revealed that there are distinct networks that subserve the valence and arousal dimensions of emotions. In this fMRI study, midline and medial temporal lobe structures, such as amygdala, hippocampus, thalamus and caudate were found to mediate arousal; whereas dorsal cortical areas and meso-limbic pathways, such as dorsolateral prefrontal cortex and rostro-dorsal Anterior Cingulate Cortex, were associated with valence (Colibazzi, et al., 2010). Thus, one of the reasons why previous studies on emotional conflict (Whalen, et al., 1998; Bush, et al., 1998; Stenberg et.al., 1998; Anes & Kruer, 2004; Etkin, et al., 2006) reported diverse results was the fact that arousal dimension was not neutralized in their versions of emotional Stroop.

Apart from the fact that this task is in Turkish, the main methodological differences of it from other Word-Face Stroop tasks were that:

1) The participants were expected to evaluate the words on the foreground, rather than the pictures on the background (different from Etkin et al., 2006; Egner et al., 2008; Hu et al., 2012; Chechko et al., 2013)
2) The words are strictly controlled according to valence and arousal axes (keeping arousal levels as neutral), as well as word frequency, length and concreteness and were kept as nouns only (different from Stenberg et al., 1998; Haas et al., 2006; Zhu et al., 2010, and Strand et al., 2013)
3) The words are not emotion names (e.g. ‘happy’ ‘anger’ ‘fear’); but emotionally loaded words (different from Etkin et al., 2006; Egner et al., 2008; Zhu et al., 2010 and Chechko et al., 2013).

The reasons behind these differences were that the arousal dimension is entirely eliminated, the valence of the words are more strictly controlled and participants can elaborate on words more, rather than quickly process the emotion verbally/phonetically from that emotion’s name. We wanted to make the participants elaborate on the emotional value of the words as much as of the faces and to use the faces as distractors; since emotional faces are shown to be more readily processed than emotional words (De Houwer et al., 1994; Bradley et al., 2010; Strand et al., 2012; Isaac et al., 2012).

The behavioral valence-specific Word-Face Stroop task that was created during my Master’s thesis repeatedly succeeded in creating the emotional conflict and revealed behavioral differences between healthy controls and depression patients, where patients failed to display emotional congruency effect, i.e. reacting slower to incongruent cases compared to congruent cases (Başgöze, 2008; Başgöze et al., 2015). However, since this doctoral thesis aims to probe the neural correlates of this behavioral difference between depressive patients and healthy people, the former behavioral Turkish Word-Face Stroop task needed to be revised to become a functional magnetic resonance imaging (fMRI) - compatible task. As previously mentioned, neutral stimuli may create a problematic case especially regarding brain activities, because they do not actually create a baseline case, rather they themselves create a conflicting case since human beings process emotionally loaded stimuli faster and tend to get confused when faced with neutral stimuli (Lewis et al., 2008; Roesch et al., 2010).

Moreover, concreteness of the words did not show any significant behavioral differences in our previous studies (Başgöze, 2008; Başgöze et al., 2015). Therefore, to keep the fMRI-compatible version of the task as simple and as effective as possible neutral cases and abstract words are removed from the task.

Another important difference of this study from the others is that specifically unmedicated (and also no psychotherapy) major depression patients are selected as participants, who were very recently diagnosed and started medication and/or psychotherapy right after participating in our study. The effects of all these will be explained in detail in the Methods section.

2.3. The bridge between emotion and cognition: The Anterior Cingulate Cortex (ACC)

Anterior Cingulate Cortex (ACC) is a crucial part of the limbic lobe that works like a bridge connecting the limbic system and the neocortex. In the last ten years, studies on ACC functioning revealed that its anatomical sub-partitions have different roles in cognition and emotion regulation: the anterior partition is thought to be responsible for execution, the posterior for evaluation, the dorsal (BA[2] 24 b′-c′, 32) for cognition and the ventral (BA 25, 33) for emotions (Bush, Luu, & Posner, 2000) (Figure 4). It is also demonstrated by Hirayasu et al. (1999) that subgenual ACC (BA25) is associated with emotions, while dorsal ACC with attention-related processes.

When there is a lesion in ACC (in humans and in cats), attention and kinetic states are found to be impaired (Cohen, Kaplan, Moser, Jenkins, & Wilkinson, 1999). Imaging studies indicated that the ‘cognitive part’ of ACC (dorsal) is crucial for attention and has reciprocal interconnections between Lateral Prefrontal Cortex (LPFC), parietal cortex, premotor and supplementary motor areas. On the other hand, ‘emotion part’ (rostral-ventral part, BA 24 a-c, 32, 25) has connections with amygdala, periaqueductal gray, nucleus accumbens, hypothalamus, anterior insula, hippocampus and orbito-frontal cortex (Devinsky, Morrell, & Vogt, 1995). This suggests that the cognitive part has access to sensory association cortices, whereas the emotion part has access to limbic structures.

[2] BA: Brodmann Area (Areas defined by German anatomist Korbinian Brodmann according to cytoarchitectural organization of neurons in the brain via cell staining) (Garey, 2006).

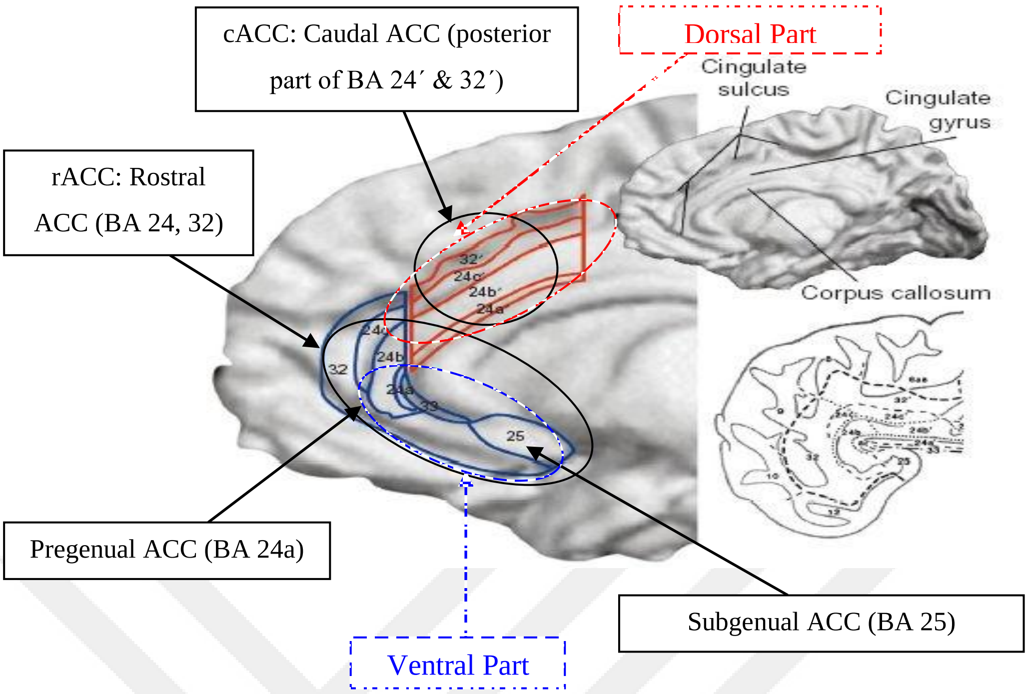


Figure 4: Anterior Cingulate Cortex (Adapted from "Cognitive and emotional influences in anterior cingulate cortex" by Bush, Luu, & Posner, 2000, Trends in Cognitive Science, 4(6), p. 216)

Interestingly, it has also been demonstrated that the region responsible for emotion regulation and the cognitive regions in ACC counteract. Bush et al. (2000) found that during an e-Stroop task[3], ACC's ventral part's activation decreases during cognitive information processing, while it increases during display of emotionally valenced words. Another study done by Davis et al. (2005), which monitored the single cell activity in ACC neurons, showed that in cognitively demanding tasks, neurons in the caudal ACC (cACC) were responding to the highly conflicting tasks (inhibitory or exhibitory) only for the emotionally loaded words, but not for non-emotional words. According to Davis, et al. (2005), different parts of ACC might not function in a counteracting way, rather ACC neurons might be showing an inhibitory effect in response to conflicting conditions. This could easily be the reason that led Bush et al (2000) to presume that there was no activation in rostral ACC (rACC). Hence, it is highly probable that what Bush et al. (2000) saw was not a deactivation, but rather an inhibitory effect of ACC neurons.

In order to elucidate the interaction between emotion and cognition, Mayberg, et al., (1999) constructed a model that examined the reason why depression causes cognitive impairments (particularly in the form of attentional deficits). They demonstrated that there is a functional reciprocal relationship between cortical and limbic pathways and that these pathways do not work independently. They found that negative mood increased the activation of limbic structures (more specifically the

[3] The version Bush et al. used was a "counting" e-Stroop, as shown in Figure 2b.

subgenual cingulate, BA25) while it decreased the activation of frontal cortices (more specifically the right prefrontal, BA9). This opposite pattern could actually be the explanation of how negative mood (emotion) can significantly and negatively influence attention (cognition) (Figure 5).

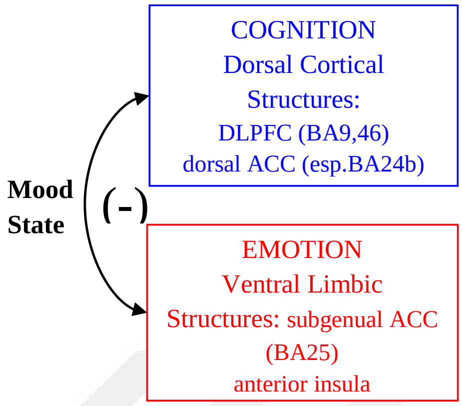


Figure 5: Simplified model of emotion-cognition interaction from “Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness.” by Mayberg et al., 1999, American Journal of Psychiatry, 156(5), p. 680.

It can be postulated that ACC plays in important role for alerting different parts of the brain in response to the situation. Both dorsal ACC (dACC: BA24b’,c’ and BA32) and rACC contribute to the error responses’ evaluation (Polli, et al., 2005), through the connectivity proposed by Mayberg in Figure 4. Observations of error related negativity (ERN), a component of event related potential, uniquely generated on ACC when errors occur, showed that ACC is responsible for error “detection”, which then leads to error correction via ACC’s connections to frontal cortices (Bush, et al., 2000), this has also been claimed by Botvinick et al. (2001).
While ACC is mostly involved in error-detection and also in modulation of emotional responses, it is speculated that it also subserves learning and behavior. Animal studies demonstrated that ACC appears to have an important role in early learning (Bussey et al., 1996). As Posner and Rothbart (1998) claimed, ACC may be in charge of maturation of our behaviors and self-regulation while growing up. This is facilitated by the migration of spindle neurons into ACC in early childhood. Additionally, the interaction between amygdala and ACC helps infants to learn how to control their emotions providing a kind of early self-regulation (Posner & Rothbart, 1998). Therefore, ACC seems to be involved in modulating self-confidence, emotional self-regulation, and learning through the consequences of our behaviors; in sum, many capabilities that are highly relevant to the deficits observed in Major Depressive Disorder patients.

2.4. Major Depressive Disorder

According to World Health Organization (WHO), currently more than 350 million people suffer from Major Depression Disorder (MDD) worldwide, also known as clinical or unipolar depression. WHO announced this mental disorder as the leading cause of disability worldwide and estimated it will generate the second largest disease burden by 2020. Although mild depression can be treated even without medicine, moderate and severe depression requires immediate medical care; since especially severe depression can easily lead to suicidal attempts. The cause of this illness is usually defined by a combination of genetic and environmental factors (aan het Rot, Matthew, & Charney, 2009).

The characteristics of a major depressive episode are abnormal depressed mood, feeling hopeless, worthless and guilty, loss of interest or abnormal irritability (for children and adolescents), all of which persist at least two weeks. These mostly psychological symptoms are usually accompanied by physical ones, such as abnormal appetite (eating too much or not eating at all), abnormal sleep (insomnia or hypersomnia), fatigue, loss of energy, slowing of speech, movement and thinking, or agitation. In addition, the patients' self-esteem is very much lowered, followed by an extreme pessimism, which usually leads to frequent thoughts about death and eventually makes them seriously suicidal (American Psychiatric Association [APA], 2013).

2.4.1. MDD and Cognition

The effects of MDD on human cognition are worth mentioning in order to understand the underlying mechanism of this disease. Diminished ability to think or concentrate and indecisiveness are among the diagnostic criteria of a depressive episode (American Psychiatric Association, 1994). These patients become mentally fatigued when they are asked to read, study or solve complex problems. Memory losses occur, which may even lead to dementia. The tasks measuring cognitive functions, in which depression patients fail, are Go/No-Go (requires attention), WCST (Wisconsin Card Sorting Task that requires decision-making) and Stroop tasks (requires conflict resolution, interference inhibition) (Markela-Lerenc, Kesier, Fiedler, Weisbrod, & Mundt, 2006). It is now well known that depression affects patients' performance for a wide spectrum of cognitive processes involving intelligence, problem solving, learning and speed (Christensen, Griffiths, Mackinnon, & Jacomb, 1997). Memory, attention, visuomotor speed and language stand out as the most affected cognitive functions in MDD (Ravnkilde, et al., 2002).

In MDD patients, conflict resolution is impaired similar to all the other cognitive processes. PET imaging studies show that depressed patients have blunted activation of ACC during performance of the incongruent cases in a classical Stroop task, compared to controls (George, et al., 1997). The rumination about continuous negative thoughts almost becomes a habit for MDD patients; and this rumination is so dominant and consuming that it impairs their ability to participate in daily life events (Jonides, 2004). Therefore, for these patients conflict appears to be between their constant negative thoughts and the thoughts that they actually need to process to pursue their daily activities.

2.4.2. MDD and Emotion

Although normative emotional state is characterized by a positive bias in the healthy population (Erickson et al., 2005), this bias is thought to be skewed for the depressed population (Beck, Rush, Shaw, & Emery, 1979; Weingartner, Cohen, Murphy, Martello, & Gerdt, 1981; Mathews, 1996; Mayberg et al., 1999). A series of experiments conducted on patients with depression, which included rapid visual information, pattern recognition memory test, spatial working memory test and affective Go/No-Go task, showed that patients made more omission errors when responding to happy words in contrast to sad words (Erickson et al., 2005). Therefore, researchers claimed that patients have a reduced hedonic state and their positive information processing is affected accordingly (Clark et al., 1991; Schotte et al., 1997; Loas, 1996). However, there might be an alternative explanation for patients' lack of positive bias. While the patients have an overall reduced success rate for all types of stimuli, they have displayed enhanced processing towards negative information. It is supported by various recent studies of attentional bias in depressive populations that having an attentional bias towards negative emotional stimuli results in the facilitation of the persistence of patients' negative mood, rather than an impairment in positive information processing (Clasen, Wells, Ellis, & Beevers, 2013).

For instance, in the study conducted by Erickson et al. (2005), although the error rates of the patients were higher for happy words, they responded quicker to sad targets than happy targets. Healthy subjects exhibited the opposite pattern for both error and response time. Thus, these results support the idea that unmedicated patients' performance failures stem from a differently working attentional mechanism, rather than a general cognitive impairment, which could explain the observed mood-congruent bias (Erickson et al., 2005).

Most of the recent emotional tasks are inclined to study depression involving affective faces, since emotion processing biases are usually found to be pronounced in response to affective faces (Stuhrmann et al., 2011). Moreover, understanding the face expressions is crucial from an evolutionary point of view. When there is an impairment in face processing, problems with social environment will inevitably follow, which seems to be the case for depressed individuals. Depression is claimed to desensitize individuals towards emotion identification; furthermore, it is also claimed that depression causes a misinterpretation of the affect in a negatively biased way (e.g. to evaluate the neutral faces as negative and positive faces as neutral) (Bourke et al., 2010; Elliott et al., 2010). There seems to be a deficit in interpreting the positively affective faces or a hypervigilance (i.e. being over-attentive) towards negatively affective faces (Stuhrmann et al., 2011). The misinterpretation of affective faces might create problems in misinterpreting the ongoing situation. For instance, the tendency of depressed individuals to interpret almost all expressions as negatively skewed might cause them to evaluate their current situation as threatening although it is actually not.

The brain regions mostly associated with the face processing problems in depression are amygdala, insula, parahippocampal gyrus, ACC and Orbitofrontal Cortex (OFC). Although amygdala is the first to mention when there is a mood-congruent bias and it usually demonstrates hyperactivity towards negative stimuli –being either pictures or words (Siegle, Thompson, Carter, Steinhauer, & Thase, 2007); not all neuroimaging studies tend to find amgydala activation in emotion processing of depressed population. The most plausible explanation for this is the differences in tasks used (mostly the stimuli); as well as the dependence of the results on the involvement of arousal dimension of the emotion. Depressed populations are shown to have an attentional bias towards negatively valenced information with less arousal (e.g. sad) in comparison to negatively valenced information with high arousal (e.g. angry) (Hill & Dutton, 1989; Gotlib et al., 2004; Hu et al., 2012). Therefore, the way that the negative mood affects patients' performance might be better observed involving only the valence dimension of the emotionally loaded information, preventing arousal dimension to interfere with their evaluation. In addition, this theory was recently supported by a particular fMRI study (Arnone et al., 2012), which showed that amygdala activation abnormally increases specifically in response to negatively valenced stimuli with low arousal (e.g. sad), rather than negatively valenced stimuli with high arousal (e.g. fear) in depressed populations. Such dissociation in the processing of information with respect to valence and arousal axes is supported by the dimensional theories of emotion (Osgood, Suci, & Tannenbaum, 1957; Lewis et al., 2008) as well. Contrary to the Arnone et al.'s study (2012), previous neuroimaging research on emotional conflict (Whalen et al., 1998; Anes and Kruer, 2004; Etkin et al., 2006) reported diverse results probably because these dimensions were not targeted exclusively. We now know that there are distinct networks that subserve valence (e.g. DLPFC, rostro-dorsal ACC, postcentral gyrus, inferior parietal and also precuneus) and arousal (e.g. amygdala, hippocampus, thalamus and caudate) (Colibazzi et al., 2010; Diener et al., 2012). This is the main reason why one need to be very careful in selecting the emotional stimuli that are going to be used in emotional tasks.

2.4.3. MDD and ACC

In MDD patients, ACC volume is reported to be significantly reduced compared to healthy population. Bilateral grey matter reduction is observed in ACC, especially for elderly depressed patients (Ballmaier, et al., 2004). Additionally, neuronal soma size in prefrontal cortex, including ACC, is also found to be decreased, meaning that neuronal activity is 9% diminished in the 5th layer of ACC (Chana, Landau, Beasley, Everall, & Cotter, 2003). In recent studies, glia cells (especially fibrous astrocytes) around BA24 (rACC) are shown to have larger cell bodies in suicidal MDD patients, compared to healthy controls (Torres-Platas et al., 2011). A portion of the cingulate cortex contains the highest density of 5HTT (serotonin transporter) terminals in a region where ACC gets dense projections from amygdala, supporting the fact that amygdala and ACC are significantly functionally connected (Pezawas et al., 2005). In literature amygdala is generally associated with fear conditioning, fear memory and negatively charged emotions (LeDoux, 2000). According to Pezawas et al. (2005), ACC and amygdala seem to function together in a feedback loop, where rACC inhibits amygdala activation (and thus the negativity of amygdala) with the help of medial prefrontal cortex neurons. Compatible with this view, rACC volume in depressed participants is found to be reduced (Drevets, 2000) which could cause the fact that rACC can no longer successfully inhibit amygdala's negativity. This connection between amygdala and ACC seems to be very crucial in MDD patients; because if ACC volume is low in patients and thus the neuronal activity of ACC is lowered, the amygdala-ACC connection weakens and will, in turn, diminish ACC's inhibition. This vicious cycle might be the reason why the patients become dysphoric (i.e. unhappy, dissatisfied, restless etc.).

The fronto-limbic circuitry which has been discussed before is crucial in MDD, because the impaired connection between ACC and DLPFC might be another underlying cause for dysphoria in patients. In different kinds of neuroimaging studies (such as PET and fMRI) healthy participants are showed to have increased subgenual ACC activation towards stimuli inducing sadness; whereas depression patients failed to show such activity (Drevets, 2000), which suggests that patients' ACCs fail to react properly to sad stimuli (i.e. it cannot warn the necessary parts of neocortex, such as DLPFC to act on it). If the connection between mood and attention, as mentioned in Mayberg et al.'s model (1999 & 2003), is in some way impaired, it could easily cause the cognitive functioning to break down, probably causing misevaluations of feelings, leading to depression. Therefore, ACC fails, causing DLPFC to fail, and a failed DLPFC cannot send a proper feedback to limbic structures and thus the vicious cycle is created causing constant anhedonia (i.e. inability to feel pleasure). By looking at the changes in brain glucose metabolism after a paroxetine[4] therapy, Kennedy et al. (2001) also showed that depressed patients have a deficit in cortical-limbic circuitry which is compensated by paroxetine intake.

An fMRI study, where affective facial processing in depressive patients is inquired, (Frodl et al., 2007) demonstrated deactivations in ACC, right DLPFC and right superior frontal cortex in healthy subjects, whereas MDD patients failed to show this deactivation in these areas; contrary to the findings mentioned above. This could occur because of the use of different neuronal strategies in face recognition or because of the impaired inhibition of the activation in these areas during emotional tasks.

To sum up, it seems that ACC performs error detection and alerts prefrontal or limbic circuits depending on the nature of the conflict. Cognitive conflicts require involvement of prefrontal circuits and emotional conflicts require the involvement of limbic circuits, which are both known to be affected in MDD. However the exact reason and the exact impaired location within this complicated circuitry still stays to be a mystery, especially regarding the contradictory findings of various researches mentioned in this section.

The reasons behind these contradictory outcomes probably stem from the differences in the neuroimaging techniques, task designs, subjects, analyses, the variables used and examined divisions of ACC. For instance, if the dependent variable is cerebral blood flow, which is measured from a region of interest (ROI), a hyperactivity might be found; however, if the variable is gray matter volume decreased number of neurons might be found in the very same region. Even decrease in gray matter

[4] Paroxetine is an antidepressant of the selective serotonin reuptake inhibitor (SSRI) type.

volume is problematic to interpret, since it might be caused by decrease in glia or neuropil (i.e. pile of dendrites and axons of neurons), but not by the decrease of somas (i.e. bodies of the neurons) (Drevets, 2000). The activities of brain regions measured by fMRI or PET can only tell us about the blood rush towards that region, not exactly which cells needed it. So for example, as Drevets (2000) stated:

> Although baseline CBF and metabolism appear abnormally decreased in PET images during MDEs [Major Depressive Episodes], computer simulations that correct PET data for the partial volume effect of reduced gray matter volume conclude the "actual" metabolic activity in the remaining subgenual PFC tissue is *increased* in depressives relative to control subjects (Drevets, 1999). (p.817).

While comparing fMRI results the tasks also create a huge difference especially if one tries to use a task involving emotional stimuli. Moreover the ACC division that is examined is also crucial because a counteracting relation (reciprocal inhibition) between ACC and DLPFC mentioned above exists also within the ACC compartments, i.e. between the cognitive (dorsal ACC) and emotion (ventral ACC) divisions. Even ventral part of ACC has various different layers that are connected to different areas of the brain, either limbic or cortical (e.g. BA24a,b,c, BA25). Therefore while trying to interpret the results of the neuroimaging studies using emotional tasks one should be very cautious and take the techniques, the task designs, the regions of interests of those studies into account.

2.5. Neuroimaging of MDD on cognitive and emotional processing

In order to understand the neural mechanism of cognitive and emotional conflict resolution in psychiatric diseases; and to clarify the specific regions impaired within the networks involved in emotion regulation and cognitive processes various types of emotional and classical Stroop tasks were tried using numerous neuroimaging techniques, such as fMRI, PET, resting state, connectivity analyses (Figure 6).

Bush et al. (2000) and Whalen et al. (1998) are the ones who elucidated the distinction between cognitive and emotional divisions of ACC conducting fMRI studies using an emotional counting Stroop task (Figure 7). It is then understood that resolving emotional conflicts activates rACC, whereas resolving cognitive conflicts activates dACC. However, lately researchers realized that the functional compartmentalization of ACC was not that simple. For example, a recent study claimed that dACC is actually crucial to process not only negative affect; but also pain (Shackman et.al., 2011), thus dACC was also processing emotional stimuli.

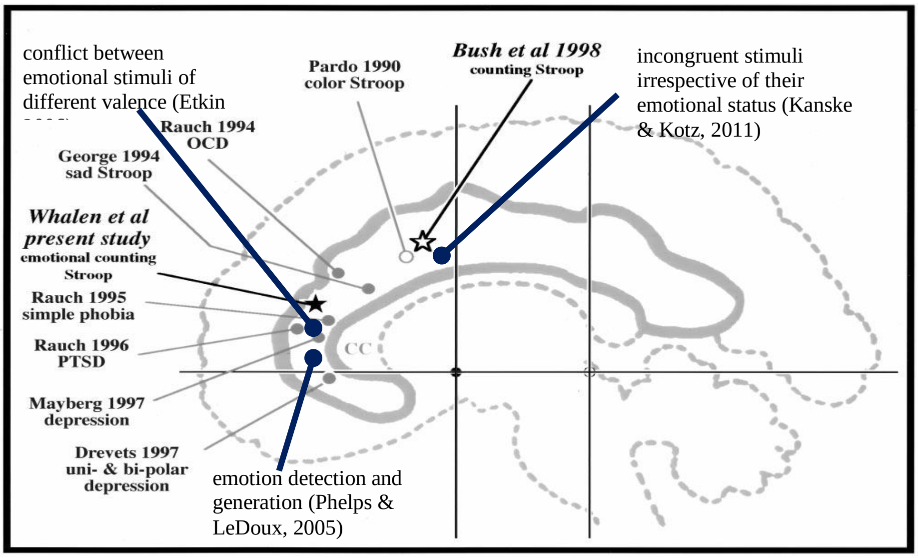


Figure 6: Stroop Tasks and ACC on psychiatric diseases (adapted from "The emotional counting Stroop paradigm: a functional magnetic resonance imaging probe of the anterior cingulate affective division" by Whalen et.al, 1998, Biological Psychiatry, 44(12), p. 1225).

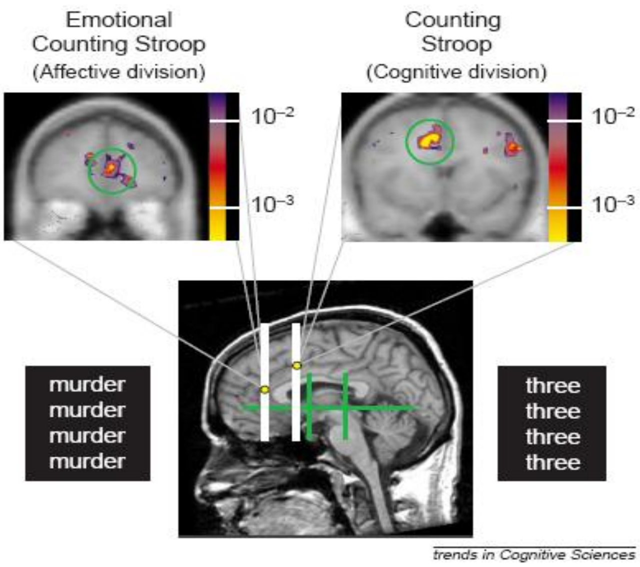


Figure 7: Comparison of emotional counting and counting stroops on ACC compartments (from "Cognitive and emotional influences in anterior cingulate cortex" by Bush, Luu, & Posner, 2000, Trends in Cognitive Science, 4(6), p. 218).

Wagner et al. (2008) and Schlösser et al. (2008) demonstrated an interesting activation pattern for conflict resolution tasks in depressed patients. Wagner et al. (2008) did not only measure the volume of rACC but they also conducted an fMRI study with a color-word (classical) stroop task to 16 female unmedicated depression patients. Their study revealed grey matter (GM) decrease in the orbito-frontal cortex (OFC) and subgenual ACC (BA25). Moreover, they found relative hyperactivation of rACC in response to incongruent cases, which they interpreted as patients' inability to deactivate rACC. They also found an inverse correlation between rACC activity and the GM reduction in OFC ($r = –0.62, p = 0.013$) (Figure 8).

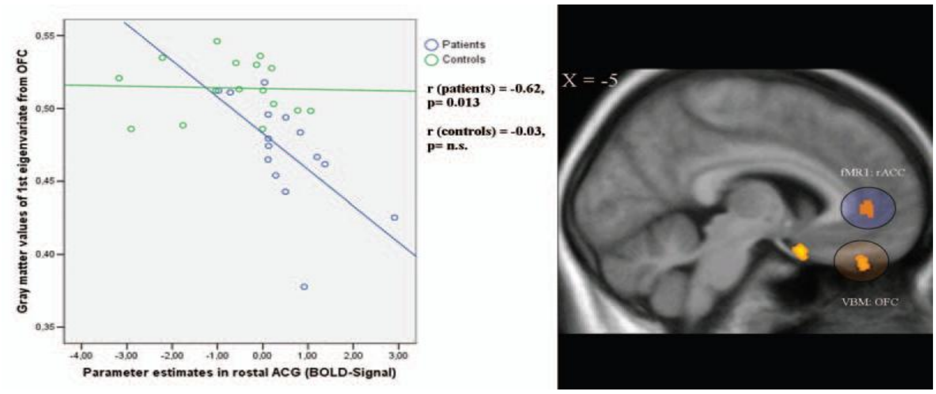


Figure 8: Negative correlation between rACC activation and GM reduction in OFC; from "Enhanced rostral anterior cingulate cortex activation during cognitive control is related to orbitofrontal volume reduction in unipolar depression." by Wagner et al., 2008, Journal of Psychiatry & Neuroscience, 33 (3), p.204.

Similarly Schlösser et al. (2008) found a significant difference for dorsal-to-rostral ACC connectivity between depressive patients and controls in terms of *higher connectivity* in patients, which meant that patients failed to down-regulate their rACC activation. Towards incongruent cases, control group showed deactivation in their rACC, whereas MDD patients showed hyperactivity in their rACC.

When the emotions are involved, most of the mechanisms and networks mentioned above start to vary drastically. Even if most of the studies involving emotional tasks (Table 1) find similar dysfunctional rACC and DLPFC in depressive individuals; the tasks they are using, the expected response from the participants and the type of the emotional stimuli researchers prefer to use show great variability and thus pose conflicting results and explanations about how depression influence the neural processing.

Table 1: Various fMRI studies using emotional tasks in MDD.

Study No as cited in text	Reference	No of Control particip ants	No of MDD Patients	Task	Stimuli / Evaluation	Medication
[1]	Mitterschif fthaler et al., 2008	14F/3M (17)	14F/3M (17)	Emotional Color Stroop	Colorful negative and neutral words / Name the color	Unmedicated
[2]	Elliott et al., 2002	8F/3M (11)	7F/3M (10)	Emotional go/no-go	Happy-sad-neutral words/button press for targets	All medicated
[3]	Grimm et al., 2008	11F/8M	21F/8M	Emotional judgment and Picture viewing	IAPS pictures/judge the valence of the pictures	Medicated and Unmedicated together, but unmedicated for the week of scanning
[4]	Chechko et al., 2013	13F/5M (18)	13F/5M (18)	Emotional and Non-emotional Word-Face Stroop Task	Emotional faces and emotion or age related names (e.g. sadness-fear-happiness and younger-middle aged-older) / Emotion of the faces are judged	Medicated and unmedicated together
[5]	Fales et al., 2007	12F/12M (24)	17F/10M (27)	Emotional interference task	House and face pairs (fearful and	Unmedicated (free for 4 weeks)

					neutral) /target and item matching	
[6]	Kaiser et al., 2015	-	53F/ 39M (92)	Emotion-Word Stroop Task (e-Stroop) & Color-Word Stroop Task (c-Stroop)	Positive or Negative Emotion words (e-Stroop) & Congruent or Incongruent Words /Name the Color	Unmedicated subclinical depression

Mitterschiffthaler et al. (2008) [1] showed sad versus neutral colorful words to 17 unmedicated MDD patients and expected them to evaluate the colors of the words. Behaviorally, reaction times were found to be significantly slower in patients compared to control group, certainly expected as a conclusion of an interference task. As for the imaging results; patients' left rACC (BA32) and their right precuneus were found to be more active relative to controls, during the exhibition of sad targets. Moreover, patients' rACC activation was positively correlated with their latencies caused by negative words.

Another fMRI study, conducted by Elliot, Rubinsztein, Sahakian and Dolan (2002) [2], with an emotional go/no-go task shows that depressed patients' response towards negative stimuli is enhanced in ventral ACC relative to control subjects, just as found in most of the behavioral studies (Figure 9).

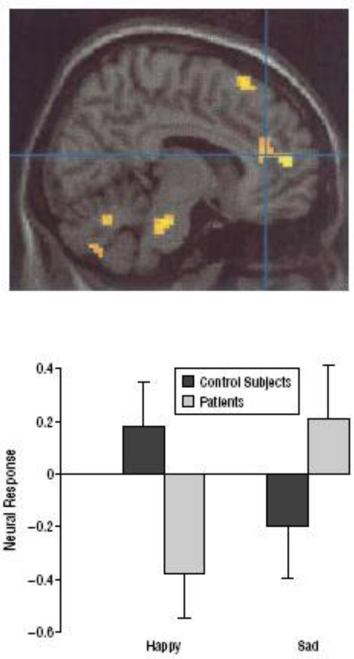


Figure 9: Opposite rACC activation pattern of healthy and MDD groups responding to sad and happy stimuli (from "The Neural Basis of Mood-Congruent Processing Biases in Depression" by Elliott, Rubinsztein, Sahakian, & Dolan, 2002, Archives in General Psychiatry, 59, p. 601).

Although ACC is a crucial brain region examined in depressed individuals using interference tasks; DLPFC and its connections with limbic system via ACC are also essential to understand the underlying cognitive and emotional mechanisms in depression. The pioneers of the neuroimaging research in depression, using resting state PET, revealed that there is an inverse relationship within DLPFC, just as in ACC. Apparently left DLPFC is demonstrated to have decreased cerebral blood flow (CBF) whereas right DLPFC shows increased CBF in depressed individuals (Mayberg, 2003; Grimm et al., 2008). Interestingly in an fMRI study, Grimm et al. (2008) [3] found that for the healthy population left DLPFC hypoactivity was significantly correlated with judgment of emotions rather than perception of emotions or attention; whereas right DLPFC was correlated with modulation of attention. This pattern was found to be altered in MDD patients, interpreted as an impaired modulation of neural activity by the authors (Grimm et al., 2008).

The idea of a hemispheric asymmetry in emotional processing actually can be traced back in emotion literature. Early research suggested that greater left hemispheric activity is associated mostly with positive emotions; whereas greater right hemispheric activity is mostly associated with negative emotions (Terzian & Cecotto, 1959; Alema et al., 1961, Perria et al., 1961 in Harmon-Jones, Gable, & Peterson, 2010). Later scientists realized that the lateralization of emotion in frontal and parietal regions differs from each other with respect to processing of emotion: Parietal asymmetries were linked with perception of emotion; while frontal asymmetries were mostly linked with the direction of motivation (high or low arousal) (Harmon-Jones et al., 2010). Therefore the importance of the distinction between valence and arousal in an emotional task reemerges: Apparently, processing emotional valence and expressions of emotions have functional differences in the brain compared to processing motivational intensity (arousal) and direction (valence).

A recent fMRI study using an emotional word-face Stroop also supported the theory that depressed individuals fail at activating the cortical structures adequately while showing hyperactivity in limbic structures (Chechko et al., 2013) [4]. However, group differences were not reported in behavioral analyses and an activity difference between congruent and incongruent trials was not demonstrated. The reason behind this result might as well be because of the task design and the selected stimuli: For example in that study, participants were expected to evaluate the emotional value of the faces, not the words. Moreover, they did not design their stimuli varying specifically in one axis only (solely valence or solely arousal). Since most of the studies don't exclude the arousal dimension from their tasks dysfunctional amygdala activations are usually found. In an emotional interference task comparing fearful (fear is highly arousing) and neutral face processing, depressed individuals showed higher activities of amygdala and failed to show necessary DLPFC activation as control group showed (Fales et al., 2007) [5]. Thus it is crucial to select valence- or arousal-specific stimuli in order to be more specific about where to expect task-relevant significant activations in the brain.

Kaiser et al. (2015) designed a study where they can compare emotional and cognitive Stroop performances and brain functions of unmedicated subclinically depressed patients. They showed that depressed individuals exhibited higher activations to negative distractors in areas responsible for cognitive control and attention orientation such as dACC and Posterior Cingulate Gyrus (PCC). Thus they claimed in the face of negative stimuli depression patients' attention is highly involved in internal negative thoughts and they hardly reorient their attention to the external world from their own negativity (Kaiser et al., 2015) [6].

The new trend in neuroimaging studies is to conduct effective[5] connectivity analyses in order to pinpoint the exact pathway that might be impaired in mental disorders. Dynamical Causal Modeling (DCM) is one of the preferred methods to understand more about brain connectivity. This is a model based approach, including 'intrinsic' and 'modulation' parameters. Intrinsic (or endogenous) connectivity refers to the baseline synchrony between various brain regions; whereas modulatory connectivity refers to a synchrony between regions that stems from performing a task (Friston, Harrison, & Penny, 2003). This method needs a hypothesis to test and eventually finds the best model that fits the imaging data.

[5] Effective connectivity is about the influence of a neural system over another in a causative way. This one is different from functional connectivity, which stands for a correlational approach (Friston, 1994).

A study that applied DCM on MEG[6] data demonstrated that the fronto-limbic effective connectivity in MDD patients is dysfunctioning, which supported previous theories mentioned above. Apparently, in patients, there was impairment in the intrinsic connectivity from DLPFC to the amygdala (top-down); whereas the intrinsic connectivity from amygdala to ACC, in addition to the modulatory connectivity from ACC to DLPFC (bottom-up) was significantly enhanced (Figure 10). The impaired DLPFC seems to fail to sway up the amygdala, a condition that causes an increase in amygdala-ACC and ACC-DLPFC bottom-up influence. Therefore, the dysfunctioning of this cortico-limbic connectivity might easily lead MDD patients to fail in dealing with emotional stimuli (Lu et al., 2012).

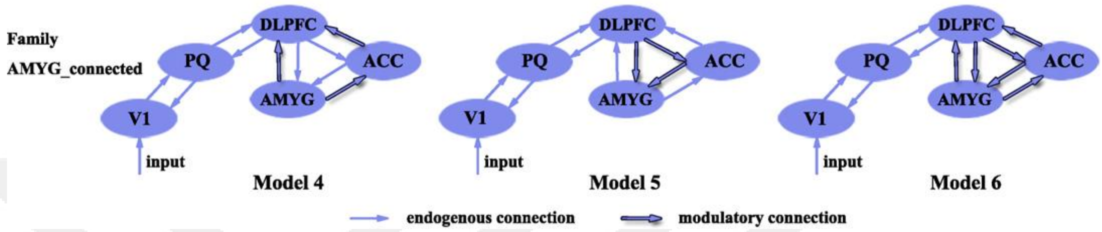


Figure 10: Connectivity models involving the primary visual cortex (V1), precuneus (PQ), DLPFC, ACC and Amygdala. In this study, Model 4 was found to be the best fit (from "Impaired prefrontal–amygdala effective connectivity is responsible for the dysfunction of emotion process in major depressive disorder: A dynamic causal modeling study on MEG" by Lu et al., 2012, Neuroscience Letters, 523, p.127).

A recent meta-analysis study, involving many different cognitive and emotional tasks with depressed individuals, brings to light that there is hypoactivity around anterior insula and rACC that is mostly related to a mood congruent bias in processing emotional stimuli and to impaired cognitive control (Diener et al., 2012). This means that depressed individuals have an emotional bias and therefore enhanced attention towards negative stimuli and weakened control over these stimuli. Moreover same emotional bias is also perceived in the subcortical level, involving thalamus and striatum (Figure 11) (Diener et al., 2012). Therefore, it seems that most of the studies in the literature about cognitive and emotional processing problems in depression reveal that patients have a hypersensitivity towards negative stimuli, which is linked with a poor cognitive control mechanism over this immense negative bias, perceived as hypoactivities especially in left prefrontal areas. More interestingly, the hyperactivities found in left Middle Frontal (BA9) and superior prefrontal regions (BA6)—although claimed to be an attempt of the patients to compensate more towards executive functions compared to healthy individuals— could not be explained as clearly as about the other regions' hypoactivities.

[6] MagnetoEncephaloGraphy: A neuroimaging technique that records the magnetic fields produced by electric currents of the cortical neurons.

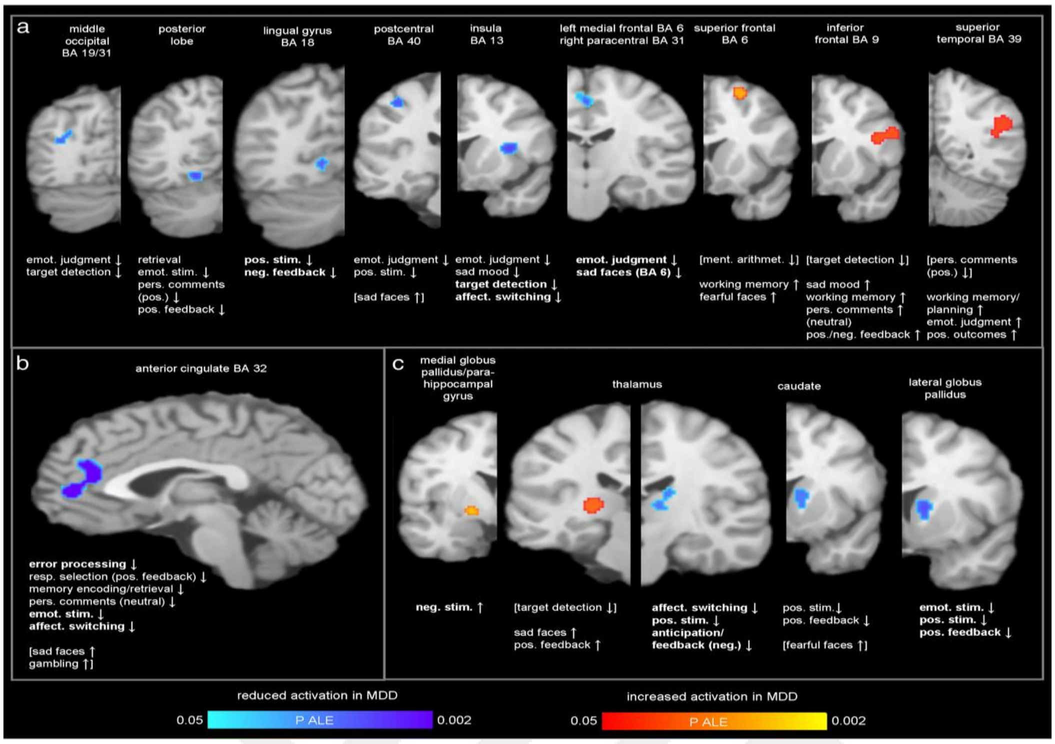


Figure 11: Various studies using many cognitive and emotional tasks conducted on MDD patients that are analyzed via Activation Likelihood Estimation (ALE) for a meta-analysis study (from “A meta-analysis of neurofunctional imaging studies of emotion and cognition in major depression” by Diener et al., 2012, NeuroImage, p.679)

Furthermore especially in the early stages of depression, the whole brain is claimed to display an abnormal pattern of cognitive processing, i.e. a disrupted cognitive connection network (CCN), which is associated with increased functional connectivity between left DLPFC, MFG, precuneus, BA6, BA7, BA22, BA40, BA43 and cingulate gyrus (Shen et al., 2015).

2.6. Attention-based theories and attentional networks in the brain

Although the sections for cognition and emotion were separated for the sake of brevity, it is virtually almost impossible to dissociate cognition/attention and emotion. Especially in order to understand more about the mechanisms affected by MDD, one should always keep in mind that detecting and interpreting something that has emotional load will always require some degree of attention. One particular reason why most of the studies mentioned so far reveal conflicting results is the large amount of fluctuation in the difficulty and attentional demands of these tasks. For example, tasks using attention manipulations (e.g. using cues, distracters etc.) demonstrated that amygdala activation does not only rely on negative emotions but also on attention (Brassen et al., 2010, in Pessoa, 2013). However, what is important here is the motivation of the agent, because selective attention is actually driven by our motives (Pessoa, 2013). Thus different motives and goals might cause the differences between patients and healthy group. Moreover, this attentional system does not always have to be consciously controlled. Initially, we all have different goals, over which we do not always have a conscious control. Having a strategy that we are not even aware of, we automatically compensate for the thoughts, feelings and behaviors that we do not actually intend to have (Glaser & Kihlstrom, 2005). Both consciously and unconsciously controlled thoughts have large effects on our behavior. For a depressed individual, a negatively skewed attention mechanism which is overtaxing might actually be the sign of an overly working unconscious control mechanism. Hence, in this dissertation I assert that depressed individuals' allocation of attention might be different from healthy individuals. For example, a healthy individual sees a positive face and a negative word superimposed on it, and she was asked to evaluate the word. Her attention is drawn by the positive face at first, but then realizing her goal, i.e. to evaluate the word, moves her attention from the positive face towards the negative word. This would of course cost her brain to process more, revealing itself as a longer reaction time. However when a depressed individual tries to do the same task, her attention would be drawn by the negative word immediately, because her motive was to attend to negative stimuli for a long time that it became automatized. Therefore, she evaluates the negative word easily, without any time cost. Consequently, the baseline emotional load that patients and controls try to compensate might be different, so that the attentional selection mechanisms are shaped accordingly.

For many years, depression has been proposed to be a mental disorder that specifically impairs cognitive functioning as mentioned in the previous sections. However, another point of view towards depression states that depression might actually have functional benefits to adapt to new situations (Oatley & Johnson Laird, 1987; Hecker & Meiser, 2005), and it might even be considered as "an evolved stress response mechanism" (Andrews & Thomson, 2009). There are two main attention-based theories which claim that depression should not be considered as a disease that causes cognitive deficits; rather it should be inquired as a case where the individuals' attentional mechanisms are differently allocated compared to a 'healthy' individual (being 'healthy': showing no symptoms as the 'patients' show): Defocused Attention Theory and Analytical Rumination Theory. These theories mainly differ in where patients allocate their attentional resources.

According to Defocused Attention Theory, patients are claimed to have a bias towards task irrelevant stimuli, in order to protect themselves from task-relevant state (which is the negative emotion state in which they are stuck) (Hecker & Meiser, 2005). Hence, their attention is defocused from the task at hand, and allocated towards irrelevant stimuli around. In contrast, Analytical Rumination Theory states the opposite, asserting that patients' attention is deeply focused in their continuous negative state in the search of solving the problems they ruminate about, so they cannot attend well to irrelevant stimuli, such as a task they are expected to do in a laboratory environment (Andrews & Thomson, 2009). Since the Word-Face Stroop task does not involve any obvious irrelevant stimulus, as used in Defocused Attention studies, I will not be able to directly discuss or falsify Defocused Attention Theory; however I will be able to support Analytical Rumination Theory, showing how depressed group deeply focus on their negative thoughts, disregarding positive stimuli, even if when they are targets.

Recent neuroimaging studies on visual attentional networks in the brain point out to a two-way system of attention: A top-down system (referred to as Dorsal Attention Network (DAN), covering bilateral frontal eye fields (FEF), superior parietal lobule and intraparietal sulcus) that is consciously goal-oriented; and a bottom-up system (referred to as Ventral Attention Network (VAN), covering mostly right hemisphere's middle frontal gyrus (MFG), inferior frontal gyrus, frontal operculum and insula) that is more automatic and stimulus-oriented (Japee, Holiday, Satyshur, Mukai, and Ungerleider, 2015). Although left MFG is considered as a part of the VAN, right MFG seems to be a crucial region where both systems are orchestrated, which gives the entire attentional system its flexibility (Corbetta, Patel, and Shulman, 2008) (Figure 12).

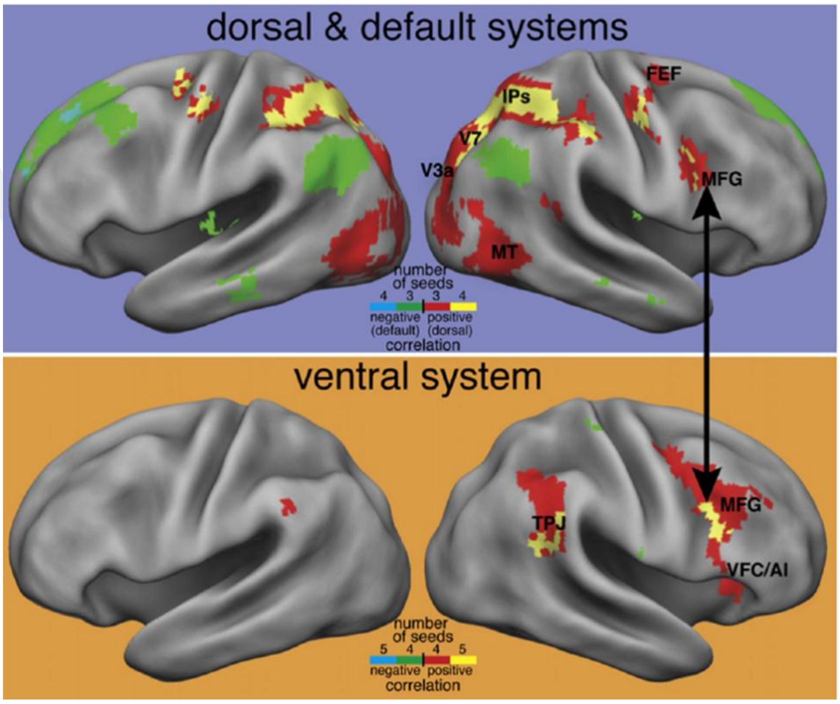


Figure 12 Dorsal & Ventral Attention Networks from "The reorienting system of the human brain: from environment to theory of mind." by Corbetta et al., 2008, p. 29

These VAN and DAN systems might comprise the different parts of the unconscious control mechanism of the patients, DAN making up for the top-down control mechanism, whilst VAN making up for the bottom-up unconscious mechanism. Both might be crucial to examine in order to understand how patients react differently than controls towards differently valenced congruent or incongruent cases.

One of the aims of this dissertation is to link these attentional systems with the networks that are repeatedly shown by the literature to be disrupted in depression, as mentioned in this section. Via establishing this link, I would like to assert that depression might not be interpreted as a disease that disrupts emotional or cognitive networks; rather it might be interpreted as a condition that leads to a differently molded network system depending on the alterations in the attentional network mechanisms mentioned above.

In sum, this dissertation suggests that depressed individuals' allocation of attention is different from healthy individuals. The baseline emotional load of patients and controls is different, i.e. former being negatively skewed, later being positively skewed; so that both groups' attentional selection mechanisms are shaped according to these different emotional baselines. Moreover, in order to strengthen my hypothesis about the different attention mechanism of the patients, I will emphasize on the attention reorientation studies, which most of the studies mentioned so far did not clearly mention linking it to depression directly. Therefore, depressed individuals, especially when they are faced with negative stimuli, might have a hyperactive control of these attentional systems to ruminate on and thus solve the negative situation, just as the Analytical Rumination theory suggests.

In the light of the background mentioned so far, this study attempts to emphasize the enhanced attention of the patients towards negative stimuli and would like to claim that the cognitive control mechanism of the patients is not physiologically impaired, but just reprogrammed differently because of their automatized attention allocation towards negative cases. So, if a patient can learn to reallocate her attention, her cognitive control mechanism and therefore her emotional processing mechanism which is closely linked to cognitive mechanism as shown by many researchers, such as Mayberg (1999 & 2003), would recover themselves, thus the patient would be recovered too. This is probably why mindfulness-based cognitive therapies (MBCT)[7] are very helpful for depressive patients; because the key point of mindfulness exercises is to teach the patient how to relocate their attention. Hence, patients let their thoughts come and go without judging them, but just watching them; and meanwhile they return their attention towards whatever they are doing in the present time (it could be breathing, washing the dishes, taking a shower etc.). "We are the editors, not the authors of our thoughts", reports Tryon (2014, p. 176). So, via this dissertation, let's reexamine our previous thoughts about depression.

2.7. Motivation behind the study and Hypotheses

Apart from the fact that our valence-based Word-Face Stroop task might have clinical relevance, our findings from this study might also shed a light into the understanding of a flexible human cognitive mechanism that seems to be able to be reprogrammed, hence get adapted in accordance with endogenous and exogenous factors. Furthermore, the way that it adapts itself and the context in which it adapts itself might be important factors in order to understand and investigate not only depression but also other mood disorders much better.

My hypotheses on the behavioral data are listed in the following:

- **H1** Depressed individuals fail to slow down towards incongruent cases, whereas controls succeed in doing so in WFS Task.

[7] A newer version of Cognitive Behavioral Therapy (CBT), involving mindfulness meditation, where individuals try to accept their thoughts compassionately but they don't get attached to them or act on them (Hofmann, Sawyer, & Fang, 2010).

H2 a. Patients' speed of reaction is no different than controls in a cognitive conflict resolution task (Classical Stroop Task).
b. Since patients' attentional mechanism is reshaped, their rate of correct responses towards interference case might show a different pattern than healthy controls.

H3 Both groups show positive-negative asymmetry effect, i.e. slowing down more towards negative cases in contrast to positive cases in WFS Task.

H4 There exists an interaction between valence (positive-negative) and group (healthy-depressed) in WFS Task, meaning that valence of the stimuli affect the behavioral pattern of healthy and depressed groups differently (patients showing a bias towards negative cases in contrast to controls).

H5 There exists a positive correlation between the severity of depression and the performance in resolving an emotional conflict through our valence-specific WFS Task.

As for the functional neuroimaging part of this study, I anticipate to see different activation patterns in patients compared to controls, which are relevant to our behavioral findings.

In brain activity patterns I expect to observe that:

H6 Both groups exhibit differential activations within ACC's sub-compartments.

H7 Patients exhibit more fusiform activity towards negative cases (both words and faces), since they are vigilant to process negativite stimuli.

H8 Patients exhibit right lateral prefrontal cortex (e.g. DLPFC, superior and middle frontal gyri) hyperactivity, associated with higher regulation and reorientation of attention towards negative and incongruent cases. Especially, right MFG is expected to show hyperactivity in patients towards incongruent and negative cases since they will try hard to reorient their attention.

H9 Patients' brain activation patterns exhibit VAN & DAN-dependent differences as follows:

- DAN hyperactivities are expected towards negative cases, because patients are expected to highly use their top-down system, since their goals are inherently driven in a negatively biased way (implicit goal).

- VAN hyperactivities are expected mostly towards positive cases, because these are salient and distracting to patients' continuous negative state (explicit goal)

CHAPTER 3

METHODOLOGY

Our study is approved by Ethical Review Boards of both Middle East Technical University and Ankara University School of Medicine abiding by Helsinki declaration.

3.1. Participants

1.1.1. Participants with Depression:

20 patients (12F, 8M; mean age: 32.85±10.32; mean education: 12±3.36; mean HAM-D: 23.35±3.45; mean BDI: 40.43±5.32) who are in a major depressive episode according to the DSM-IV criteria are invited to participate in the study on their first admissions to Ankara University Psychiatry Department Outpatient Service. The patients are diagnosed by the assigned clinician. They are enrolled after having signed written informed consent (See Appendix A).

Inclusion criteria: Age 20-55 years, right handed, male or female, Turkish as native language, 5 years or more education, having a 17 or higher point of score on HAM-D and having a 30 or higher point of score on BDI, having a major depression diagnosis according to DSM-IV, being right handed.

Exclusion criteria: Currently being under any mood-altering medication[8], inability to speak and read in Turkish, being unable or unwilling to consent or assent to remain relatively motionless within the MRI scanner for a period of 55 minutes, having a general health problem which could prevent participants to conduct the task, having a neurological disorder, having a head trauma which caused at least 30 minutes of unconsciousness, having a psychotic disorder, having a bi-polar diagnosis, having high anxiety, loss of a loved one in 2 months, alcoholism and/or drug abuse, having a visual defect, any medical condition which can prevent the participants from getting into an MR scanner (e.g. having a pacemaker, a metal implant or claustrophobia) and being actively suicidal.

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[8] If the patients have a history of MDD episode before, they are expected to be drug-free for at least 3 months; however our patient group mostly consists of newly diagnosed MDD patients who started their medication and/or therapy sessions shortly after scanning.

Diagnostic Procedures: Participants are asked to complete an initial screening/assessment battery, which includes the following assessments to determine eligibility for the study:

- Beck Depression Inventory (BDI; this self-report questionnaire assesses depressive symptoms in adults) (Beck, 1961)
- Beck Anxiety Inventory (BAI; this self-report questionnaire assesses anxiety symptoms in adults) (Beck, 1988)
- Edinburgh Handedness Inventory (this is used to document the participant's hand preference for 10 activities) (Oldfield, 1971)
- Hamilton Depression Rating Scale (HAM-D assesses the severity of symptoms observed in depression by interviewing the patient) (Hamilton, 1960)
- Clinical Global Impression Scale (CGI; this is used to measure symptom severity and also treatment response of patients to be able to compare the participants to typical patients with respect to clinician's experiences)
- Suicide Probability Scale (SPS; this is used to understand how probable a participant is suicidal) (Cull & Gill, 1988)

1.1.2. Healthy participants:

20 students and employees of Middle East Technical University (10F, 10M; mean age: 32.95±8.71; mean education: 14±4.32; mean BDI: 5.5) participated in this study to be a part of the control group. They also signed a written informed consent.

Inclusion criteria: Age 20-55 years, right handed, male or female, Turkish as native language, 5 years or more education, having a 15 or lower point of score on BDI, being right handed.

Exclusion criteria: Being under any mood-altering medication, inability to speak and read in Turkish, being unable or unwilling to consent or assent to remain relatively motionless within the MRI scanner for a period of 55 minutes, having a general health problem which could prevent participants to conduct the task, having a neurological disorder, having a head trauma which caused at least 30 minutes of unconsciousness, having any kind of mental disorder, loss of a loved one in 2 months, alcoholism and/or drug abuse, having a visual defect, any medical condition which can prevent the participants from getting into an MR scanner (e.g. having a pacemaker, a metal implant or claustrophobia).

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- Edinburgh Handedness Inventory (this is used to document the participant's hand preference for 10 activities) (Oldfield, 1971)

3.2. Stimuli

3.2.1. Affective Words:

Words are selected from a Turkish word database (TUDADEN) which was produced by METUNEURO LAB and Bilkent University (Gokcay & Smith, 2011). 64 emotionally valenced words (32 negative and 32 positive) are used in this experiment. Words' frequencies (M = 97.4±80.3) and lengths (M = 5.41±1.4) are controlled. All of the words are concrete nouns. The emotional valence scores varied across positive words (M = 7.29±0.49) and negative words (M = 2.89±0.79). It is important to note that the SD of emotional words within each category was low, indicating that the categories did not overlap. The valence levels differed significantly from each other F (2, 93) = 369,690, MSe= 157.528 (See Appendix B for the word list). The words are manipulated on the valence axis, but were neutral and standardized on the arousal axis (Figure 13).

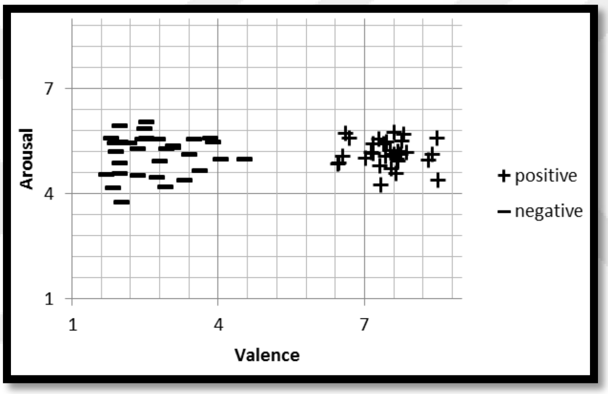

Figure 13: Valence and Arousal levels of the affective words used in the task

Neutral cases were eliminated in this fMRI study because our previous behavioral studies showed that the neutral case that was initially planned to work as a baseline does not qualify to be so, since both controls and patients had more difficulty in classifying such words, i.e. participants were automatically assigning an emotional content to the neutral word (Başgöze, 2008 & 2015). This result is compatible with previous studies providing evidence that emotional stimuli have processing priority regardless of their valence (Roesch et al., 2010).

3.2.2. Affective Faces

Faces in the background were chosen from The Productive Aging Lab Face Database (Minear & Park, 2004). 4 happy and 4 sad human face pictures, each having 2 male and 2 female samples, were selected. These pictures are resized to be compatible with E-Prime, the program we used to design the experiment; and in order to maintain coherence among the pictures their color values were rearranged with GIMP, an open source image editing program (See Appendix C for the faces).

3.3. Procedure

All participants who attend the fMRI experiment are first asked to conduct a paper-pencil Turkish *classical Stroop Task* right before the fMRI task, in order to have a classical conflict resolution/interference effect data to compare with the emotional conflict resolution/emotional interference effect, since emotional content creates a prominent difference in the behavioral and functional results in depressed patients. In this task, participants try to read out as rapid as possible first the color of the colored bars, then the color names, and then the color of the printed color names. When the print color and the name of the color are the same, it is called "congruent" (For example "red" is written in red). When the print color and the name of the color are different it is called "incongruent" (For example "red" is written in green).

Analysis for Classical Stroop Task: A 3x2x2 mixed design ANOVA with repeated measures on Stroop (color naming, word reading, interference) as a within subject factor and "depression" (healthy and depressed) and gender (female and male) as between-subject factors on reaction times and on correct response rates are conducted via SPSS.

The participants performed *the Word-Face Stroop* in a Magnetic Resonance scanner, where they are presented with a keypad that consists of two buttons, representing negative (left/blue) and positive (right/yellow). Subjects performed the task with only their right hand's thumb.

Participants are asked to judge the emotional valence of the words (positive or negative) which appear on a background consisting of affective faces (happy or sad). Each subject is expected to respond to two types of trials: congruent and incongruent. In congruent situations, positive words are shown on positively affective faces and negative words are shown on negatively affective faces; whereas in incongruent situations positive words are shown on negatively affective faces or negative words are shown on positively affective faces.

In order not to bore the subjects and let them take a breath and relax, this task is split to 4 different runs, each containing 16 words (8 positive and 8 negative) recurring as congruent and incongruent (e.g. the word "bulut" - "cloud" - shows up on a positive face as congruent and also on a negative face as incongruent). Therefore they respond to 32 words in each run and to 128 words in total.

The stimuli are shown on a gray background at the center on a personal laptop; however they see the stimuli from a mirror located on the head coil which reflects the image from the laptop screen, through a projector, to a curtain behind the scanner. The software program E-Prime was used to design the experiment.

At the beginning, participants are instructed to focus on a fixation point. When they see a word-face pair, they are supposed to answer using the keypad indicating their judgment of the word's valence. It is emphasized that they should answer according to the words' affect not the faces' affect. The flow of an experiment session is summarized in Figure 14. According to picture superiority effect, the emotion of the picture is expected to be prominent while the emotion of the word is faint (Paivio, 1971; Rajaram, 1993). Hence the subjects are supposed to inhibit the prominent emotion as induced by the face and respond to the emotion carried by the word.

The task is designed as an event related fMRI task design. The participants initially see a fixation point for 6000ms, and then observe the stimuli during 2000 ms (congruent or incongruent, showing up randomly). In order to catch the BOLD response from different time points, the stimuli stay 2000 ms on the screen, whereas fixation points stay on the screen during 2000 ms, 4000 ms or 6000 ms interchangeably. Both patients and controls are expected to evaluate the valence of the words as fast and as correctly as possible. Slides that consist of words on faces remain on the screen during 2000ms even if the subjects press the response buttons earlier than 2000ms.

Analysis for fMRI behavioral results: A 2x2x2x2 mixed design ANOVA with repeated measures on congruency (congruent and incongruent) and valence (positive and negative) as within-subject factors; depression (healthy and depressed) and gender (female and male) as between-subject factors on Reaction Times and on Correct Response Rates are conducted via SPSS.

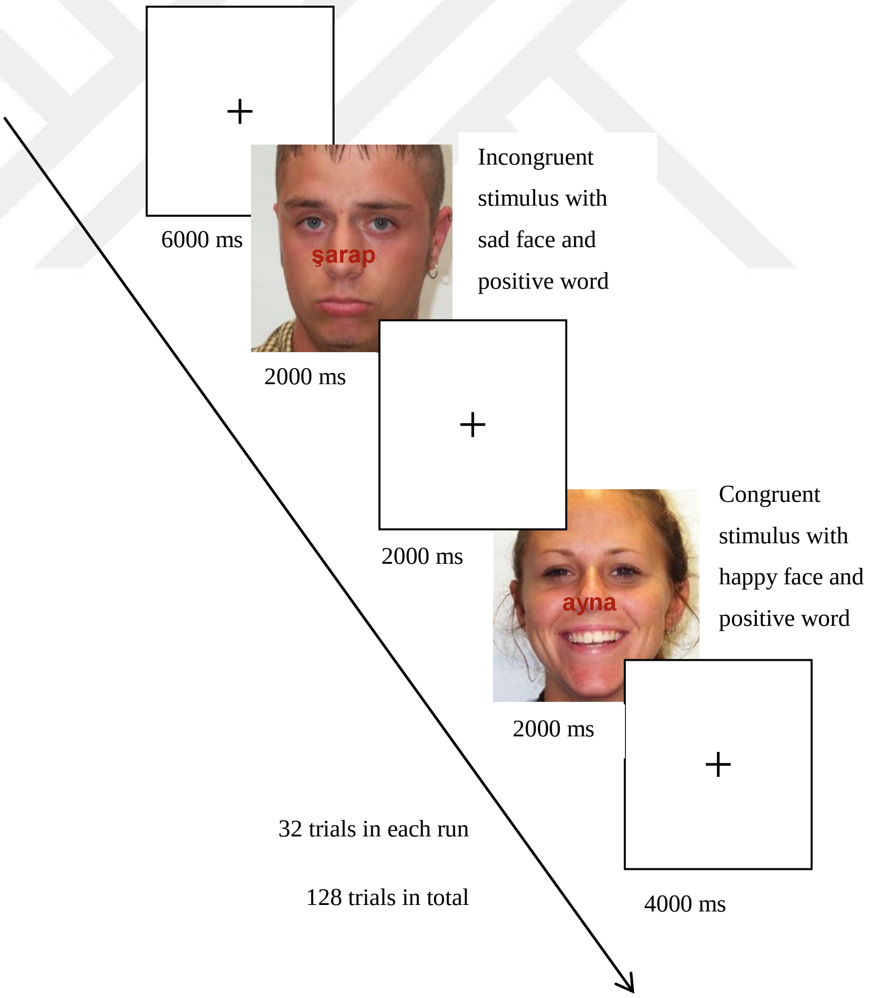

Figure 14: fMRI Experiment Flow

3.4. Neuroimaging Procedures

All participants are scanned with a 3T Siemens MR system at the National Magnetic Resonance Research Center (UMRAM) at Bilkent University, Cyber Park. Participants are given the opportunity to practice the task before getting into the scanner in order to orient the task. When the participants enter the scanner, they first have a resting state scan[9], then the 1st run of the Word-Face Stroop task fMRI scan, followed by the 2nd run of the fMRI scan, then the structural scan was performed, succeeded by the 3rd and the 4th fMRI scans respectively (26.5 minutes in total). **3 plane localizer**: This is a scout sequence used for orienting the 3D volume scan (1 min.). **Structural scan**: 3D T1 MPRAGE: TR=2500ms, TE= 3.03ms, 1mm slices, FOV 256, 1x1 voxel size, 224 slices in total (6 minutes). **Resting fMRI** data are collected with eyes closed and awake: 200 echo planar imaging volumes, FOV 192, TR=2s, TE=30ms, 34 contiguous AC-PC aligned axial slices, 4 mm slices, 3x3 voxel size, with 0.8mm gap (6.5 minutes). **Word-Face Stroop Task fMRI** data (for each of the 4 runs): 100 echo planar imaging volumes, FOV 192, TR=2000ms, TE=30ms, 34 contiguous AC-PC aligned axial slices, 4 mm slices, 3x3 voxel size (3.5 minutes X 4 runs = 14 minutes).

3.4.1. Data analysis

The data is analyzed using AFNI (Analysis of Functional NeuroImaging) software (Cox, 1996). Individual analyses for each subject are conducted in the first place. DICOManage software is used in the Windows environment to reorder and rename the DICOM[10] files. After transferring the data to the Linux environment, DICOM files are converted into the native BRIK[11] format over AFNI. After preparing the raw data, preprocessing steps are performed in order to obtain clean and noiseless fMRI data for further GLM (General Linear Model) analysis which was planned to be used to extract statistical functional activation maps related to our task (Figure 15).

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[9] Resting state analysis is out of the scope of this thesis.
[10] Digital Imaging and COmmunications in Medicine (DICOM) is a standard file format for medical imaging.
[11] An electronic medical imaging file format used by AFNI.

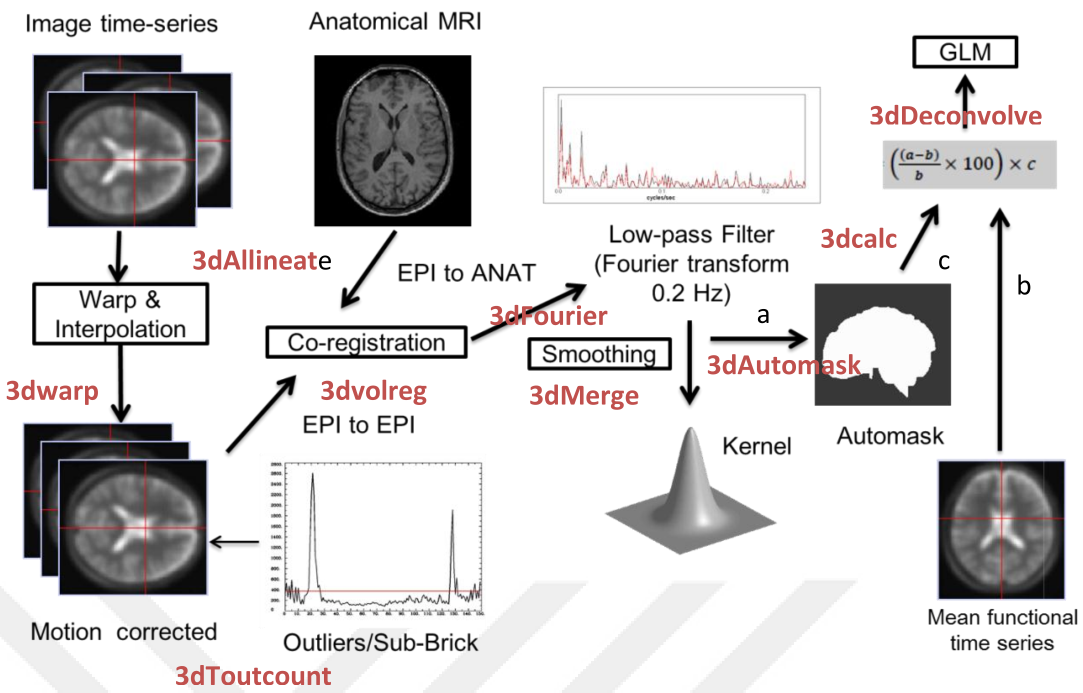


Figure 15 Preprocessing Flowchart and the correspondant AFNI codes

3.4.2. Preprocessing steps

To adjust Field of View (FOV) efficiently during data acquisition, we acquired oblique anatomical and functional images that needed to be warped and interpolated using **3dwarp** command of AFNI, in order for these images to correspond to a cardinal orientation.

To collect data faster, functional images are collected in low-resolution space; whereas the anatomical image is acquired in high-resolution space. These differently spaced functional and anatomical images must be registered in the same space so that a location in one could correspond to the same location in the other. For this purpose, the **3dAllineate** command is utilized.

While analyzing fMRI data, even a small head motion can create artifacts in activation maps, especially if the motion is correlated with the activation paradigm (Field et al., 2000; Hajnal et al., 1994). Therefore motion correction is crucial to maximize sensitivity to true activations related to the task in hand; while minimizing false activations related to motion (Johnstone et al., 2006). For motion correction, after checking for the outliers using **3dToutcount** command, a sub-brick (a representative reference brain volume) without a significant head motion for every run is determined to register all other whole brain functional MR images. For this purpose, **3dvolreg** command is used (Steger and Jackson, 2004). An iterative linear least squares rigid-body motion correction is usually adequate when the size and shape of the registered images are the same (Oakes et al., 2005). After co-registration 3dToutcount command is again applied to check whether the motion correction provided a decrease in signal amplitudes as expected.

3dFourier command is applied for temporal filtering. We have used low pass filtering that smoothes out the changes with frequencies higher than the hemodynamic response caused by the task (this threshold is defined as 0.2 Hz) (Sabuncu et al., 2010). Thus we get rid of the high frequency noises.

The next step is spatial smoothing that improves signal-to-noise ratio (SNR) and causes exploitation of the obtained activity profiles to voxels nearby, which eventually causes blurred localizations with respect to regular anatomical variability. Even though this procedure deteriorates the data, this averaging provides greater sensitivity in statistical analyses that are going to be performed later. So, by applying **3dmerge** command, data is convoluted with a 6 mm Full Width at Half Maximum (FWHM) Gaussian kernel. After reducing the noise with spatial blurring with the commands mentioned above, non-brain areas are removed using **3dAutomask** command, which created a mask keeping only the largest connected component of the threshold voxels (‘1’ for inside the mask; ‘0’ for outside of the mask).

To eliminate the variability among the baseline signal values which vary not only from voxel to voxel; but also from subject to subject, it is necessary to convert each subject’s fMRI time series into a common scale before conjoining the results for further statistical analyses. This scaling is performed using **3dTstat** and **3dcalc** commands; the former, to calculate mean values per voxel and latter, to scale the functional volumes and calculate the percent signal change voxel by voxel, thus simply to normalize. The formula we have used in 3dcalc to normalize the data is:

$$Percent\ Signal\ Change = \left(\frac{(a-b)}{b} \times 100\right) \times c$$

where, ‘a’ is the smoothed data, ‘b’ is the mean intensity value and ‘c’ is the masked brain (See Appendix D1 for the Pre-processing codes).

3.4.2.1. 1st Level GLM Analysis

General Linear Modeling analysis uses the sum of scaled and time-delayed versions of stimulus time series to extract statistical functional maps for individual subjects. Therefore ideal stimulus task waveform files should be created for GLM in order to compare them with the actual time series of subjects performing the task.

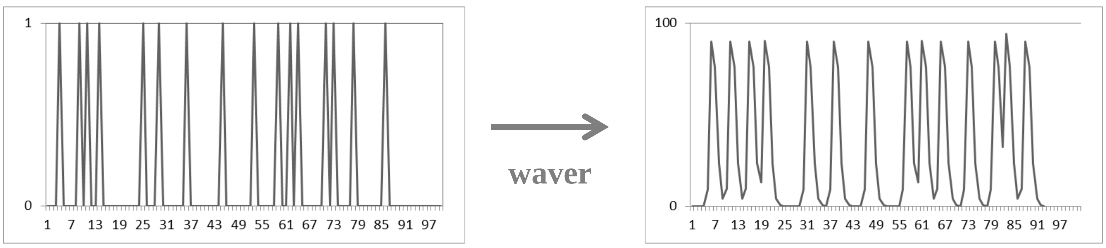
The individual GLM analyses for Word-Face Stroop Task fMRI results can be analyzed via looking at the significant activations for the contrasts for congruent-positive vs. congruent-negative and incongruent-positive vs. incongruent-negative so that fMRI’s ANOVA resembles more to the statistical design used for the behavioral analysis (a mixed design repeated measures ANOVA).

In our WFS task there are 100 samples in a run, and 4 different factor-couples: congpos (congruent-positive), congneg (congruent-negative), incongpos (incongruent-positive), and incongneg (incongruent-negative). Therefore there are going to be 8 ‘on states’ (indicated with ‘1’), and 92 ‘off states’ (indicated with ’0’) for each factor (Figure 16).

	sample no	congpos	congneg	incongpos	incongneg
	1	0	0	0	0
	2	0	0	0	0
	3	0	0	0	0
	4	1	0	0	0
	5	0	0	0	0
	6	0	0	1	0
	7	0	0	0	0
	8	0	0	0	0
	9	0	1	0	0
	10	0	0	0	0
	11	1	0	0	0
	12	0	0	0	0
	13	0	0	0	0
	14	0	1	0	0
	15	0	0	0	0
	16	0	0	1	0
	17	0	0	0	0
	18	0	0	0	1
	19	0	0	0	0
	20	0	0	0	0
	⋮	⋮	⋮	⋮	⋮
extra off states	98	0	0	0	0
	99	0	0	0	0
	100	0	0	0	0
		8 on states			

Figure 16: Content of ideal task file

After generating the ideal task file, ideal hemodynamic response functions are created out of these ideal task files by using **waver** command. This command creates an ideal waveform time series file by convolving the content of ideal task file with theoretical hemodynamic response function using Gamma variety function as a model of the shape of the hemodynamic response (Figure 17). Gamma degree was selected as 2, because our TR (sampling rate) is 2 sec.



Ideal stimuli

Theoretical HRF

Figure 17: Visual representation of estimated hemodynamic response function (HRF)

GLM analysis is conducted via **3dDeconvolve** command that is used to create a statistical map of voxels with signal patterns correlated with the task by filtering the relevant voxels which have β coefficients that pass the null hypothesis. A GLM equation simply is:

$$Signal = (\beta_1 x\ F_1)+(\beta_2 x\ F_2)+(\beta_3 x\ F_3)+(\beta_4 x\ F_4)+C+Err$$

where, F_1, F_2, F_3, and F_4 are the predictor functions or ideal hemodynamic response functions as presented in Figure 16 and β_1, β_2, β_3, and β_4 are regressor coefficients; C is the constant and Err is the error (Friston et al., 1995).

The resulting files obtained after preprocessing steps for four runs are concatenated within 3dconvolve command.

Using **3dConvolve** I obtained 4 main T-statistic maps for congpos, congneg, inconpos and incongneg; and 4 contrasts: congpos vs. incongpos; congneg vs. incongneg; congpos vs. congneg; incongpos vs. incongneg (See Appendix D2 for the code). Contrasts are simply the substractions of different conditions. Thus, for example the contrast of "congpos vs. incongpos" indicates the activation difference between congruent-positive and incongruent-positive cases, substracting the activation map of incongruent-positive case from congruent-positive case; more spesifically it is the difference in congruency when only positive cases are considered.

Furthermore, to be able to understand the effect of face expressions only, one more 3dConvolve is conducted after creating task waveforms for face stimuli. So, this time I only have one valence factor for the faces consisting of positive-face and negative-face levels (See Appendix D3).

Before proceeding to the 2nd level group analysis, *talairach transformation* is needed to be performed in order to control for the variability of brains' physical properties such as size and shape, so that inter-subject comparisons of the data can be performed in a more efficient way. For this purpose, each subject's anatomical brain images are needed to be transformed into a standard template so that we will know where in the atlas the exact location of a voxel is. Coordinates are standardized by mapping the images to Talairach (stereotaxic) format. I therefore transformed T1-weighted structural MRI volumes of all subjects into Talairach space manually via marking anterior commissure, posterior commissure and 6 extreme points of the brain (e.g. most anterior, most inferior, most left…) in all 3 planes. Then these anatomical brain images that are transformed into Talairach space are averaged to obtain a sole template anatomic brain image further to be used as an underlay image for group level analysis results. Not only structural brain images but also functional ones were needed to be transformed into Talairach space using **adwarp** command, which resamples a 'data parent' dataset to the grid defined by an 'anat parent' dataset, meaning that the statistical maps are transposed onto a talairach space with respect to the talairached anatomic image.

3.4.2.2. 2nd Level Group Analysis

Mixed Design ANOVAs such as we use for our behavioral analysis cannot be conducted in a single step as in a behavioral SPSS analysis. Therefore we split our statistical design into two in order to be able to consider all aspects that are crucial to compare our behavioral and fMRI results:

1) In order to pinpoint the activation patterns with respect to congruent-positive, congruent-negative, incongruent-positive and incongruent-negative cases without comparing the groups, a 2x2 repeated measures ANOVA is conducted using **Type4** 3dANOVA3 option, which only includes the within subject factors (congruency and valence). Therefore we have run this analysis two times, first within the depressed group, and then within the healthy group using congpos, congneg, incongpos and incongneg options from the 1st level analysis (Table 2). As a result, I obtained mean activation maps for four different conditions, namely Mean Congpos, Mean Incongpos, Mean Congneg, and Mean Incongneg.

From the same analysis I also obtained difference maps for congruency versus incongruency (incongruency subtracted from congruency), and for positive versus negative (negative subtracted by positive) for each group separately.

Table 2: 2nd Level Analysis for individual groups

		Factor (within subject)	**Level**	**Input**	**Output**
Groups (analyzed separately)	**Depression**	Congruency	Congruent	congpos congneg incongpos incongneg	Mean Congpos Mean Incongpos Mean Congneg Mean Incongneg
			Incongruent		
		Valence	Positive		
			Negative		
	Healthy	Congruency	Congruent	congpos congneg incongpos incongneg	Mean Congpos Mean Incongpos Mean Congneg Mean Incongneg
			Incongruent		
		Valence	Positive		
			Negative		

2) In order to capture the differences in brain activation patterns in between the groups, two different 2x2 mixed design ANOVAs are conducted first for congruent cases varying according to valence and second for incongruent cases varying according to valence. In order to create such a design we used **Type5** option of 3dANOVA3 code of AFNI, meaning that the analysis includes both between and within subject factors (See Appendix D3 for the codes). Therefore we have run this code two times, first to compare congruent-positive and congruent-negative cases between the groups, and second, to compare incongruent-positive and incongruent-negative cases between the groups (Table 3). As a result I obtained difference maps reflecting group differences with respect to four conditions, namely Depcongpos VS Contcongpos (group difference with respect to congruent-positive case), Depcongneg VS Contcongneg (group difference with respect to congruent-negative case), Depincongpos VS Contincongpos (group difference with respect to incongruent-positive case), and Depincongneg VS Contincongneg (group difference with respect to incongruent-negative case).

Table 3: 2nd Level Analysis between-group comparison

<table>
<tr><th></th><th>Factor (within subject)</th><th>Levels (analyzed separately)</th><th>Input</th><th>Output</th></tr>
<tr><td rowspan="6">Group (between subject)</td><td>Congruency</td><td>Congruent</td><td rowspan="3">congpos
congneg</td><td rowspan="3">Depcongpos VS Contcongpos
and
Depcongneg VS Contcongneg</td></tr>
<tr><td rowspan="2">Valence</td><td>Positive</td></tr>
<tr><td>Negative</td></tr>
<tr><td>Congruency</td><td>Incongruent</td><td rowspan="3">incongpos
incongneg</td><td rowspan="3">Depincongpos VS Contincongpos
and
Depincongneg VS Contincongneg</td></tr>
<tr><td rowspan="2">Valence</td><td>Positive</td></tr>
<tr><td>Negative</td></tr>
</table>

3) In order to find out about how the valence of face stimuli influence brain activations with respect to two different groups, a 2x2 ANOVA is conducted using **Type4** 3dANOVA3 option, which includes one within subject factor, valence (positive face (posface) vs. negative face (negface)); and one between subject factor, group (healthy and depressed) (Table 4). As a result, I obtained difference maps reflecting group differences with respect to face expressions' emotional load, namely

Depposface VS Contposface (group difference with respect to happy faces) and Depnegface VS Contnegface (group difference with respect to sad faces).

Table 4: 2nd Level Analysis between-group comparison with respect to face stimuli

<table>
<tr><th></th><th>Factor (within subject)</th><th>Levels</th><th>Input</th><th>Output</th></tr>
<tr><td rowspan="2">Group (between subject)</td><td rowspan="2">Emotional Expression of Faces</td><td>Happy</td><td rowspan="2">posface
negface</td><td rowspan="2">Depposface VS Contposface
and
Depnegface VS Contnegface</td></tr>
<tr><td>Sad</td></tr>
</table>

3.4.1.1.Post-Processing

The group analyses reveal mean functional statistical activation maps of the subjects. To be able to show that these activation maps actually form significant clusters, a family-wise error method to correct multiple comparisons is applied: **AlphaSim code of AFNI** that is based on Monte Carlo simulations. This code provides us to choose the minimum cluster size that corresponds to corrected p value, which eventually helps us to get rid of the false positive results. As a result, we obtained a cluster size of 14 that corresponds to a Bonferroni corrected $p<0.001$ significance for our group analysis results. Therefore if the clusters survive above the threshold value ($p< 0.001$) and their voxel size are larger than 14 voxels they can be considered as task-relevant significant activations (See Appendix D4).

CHAPTER 4

RESULTS

Before conducting the behavioral analyses the descriptive statistics of the data from 40 participants are explored and found not to be distributed normally. Therefore a logarithmic transformation (compute log = LG10(x)) is conducted. Moreover z-scores are also calculated for all conditions in order to reveal the univariate outliers. Since the sample size of this study is smaller than 80, cases with standard scores higher and/or equal to 2.5 are excluded. There were only 1 healthy participant and 1 patient who met this outlier criterion. Furthermore, 2 participants' debriefings revealed that one of them had trouble reading especially short words because of his astigmatism and the other reported that he felt highly anxious in the scanner and had trouble concentrating on the task. Moreover two more from each group are excluded assuming that their relatively lower education level affected their performance to conduct the task successfully. Therefore 8 participants (4 from each group) are excluded from both behavioral and fMRI analyses due to the reasons mentioned above.

All ANOVAs mentioned in this section are Bonferroni corrected.

Subjects: 16 Healthy (8 F, 8 M; age: 31.31±7.12, education: 15.25±3.24, BDI: 6.63±3.93) & 16 Depressed (9 F, 7 M; age: 31.13±8.95, education: 13±2.56; HAM-D: 22.88±3.3; BDI: 40.43±5.32)

4.1. Classical Stroop Analysis

A 3x2x2 mixed design ANOVA with repeated measures on Stroop (color naming, word reading, interference) as a within subject factor and "depression" (healthy and depressed) and gender (female and male) as between-subject factors, on reaction times revealed a significant difference for the **Stroop** effect $F(2, 48) = 348.266$, $\eta^2 = 0.936$, $p<0.001$. Pairwise analyses show that all three conditions differed significantly from each other, meaning that all participants were faster towards the word reading case (when the name of the color and its print color are the same), and they were all slowest towards the interference case (when the name of the color and its print color are different) regardless of the group factor.

Another 3x2x2 mixed design ANOVA with repeated measures on Stroop (color naming, word reading, interference) as a within subject factor and "depression" (healthy and depressed) and gender (female and male) as between-subject factors, on correct response rates revealed a significant difference for the **Stroop** effect $F(2, 48)$

= 21.965, η^2 = 0.478, p<0.001. Moreover a significant 3-way **interaction** between stroop effect, depression and gender $F(2, 48) = 6.548$, η^2 = 0.214, p<0.01, and significant interaction between **depression and gender** $F(1, 24) = 4.667$, η^2 = 0.163, p<0.05 are found. These all mean that all participants made the least error towards word reading case and the most error towards the interference case. However, for the interference case depressed individuals made more errors than healthy participants that differ according to the gender of the participants: Depressed male participants made more errors than healthy males; whereas depressed female participants made significantly less error compared to healthy females. Healthy female participants made more error than healthy males; but females made less error than males when they are depressed (Figure 18).

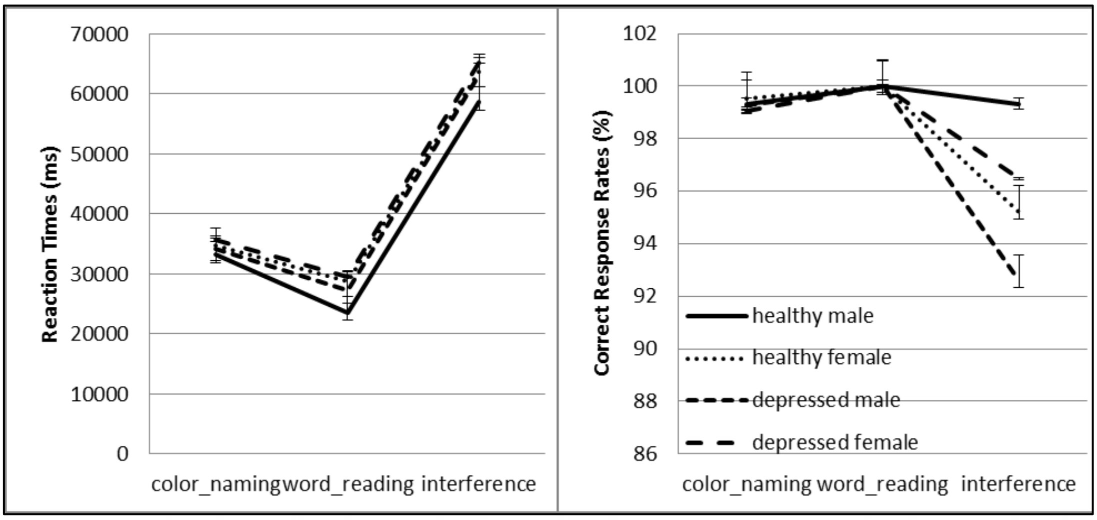


Figure 18: Significant difference between three conditions of Classical Stroop (color naming, word reading and interference) with respect to reaction times (left) and correct response rates (right).

Results from the Classical Stoop analysis reveal that **Hypothesis 2 is verified**, because patients and controls showed similar performance with respect to reaction times while conducting this task (Figure 18, left). However the correctness of their responses differed significantly towards the incongruent case depending on their group (depressed/healthy) and gender (female/male) (Figure 18, right). Although, as repeatedly shown in literature, depressed population was expected to make more incorrect judgments, the gender difference was not expected. Thus, it should be examined in more detail in a future study.

4.2. Behavioral Word-Face Stroop Analysis

4.2.1. Subject-Based Analysis

A 2x2x2x2 mixed design ANOVA with congruency categories (congruent, incongruent) and valence (positive, negative) as within-subject factors; depression (healthy, depressed) and gender (female, male) as between-subject factors on reaction times revealed significant differences in **congruency** $F(1, 28) = 16.392$, $\eta^2 = 0.369$, $p<0.001$, meaning that all of the participants reacted significantly slower to incongruent cases compared to congruent cases regardless of the group and the valence factors, and **valence** $F(1, 28) = 25.384$, $\eta^2 = 0.475$, $p<0.001$, meaning that all of the participants reacted significantly slower to negative words compared to positive words regardless of the other factors. So, our task succeeds in creating the interference effect as expected and revealed a positive-negative asymmetry effect towards emotional words. Moreover the **interaction between valence and depression** is found to be marginally significant $F(1, 28) = 4.148$, $\eta^2 = 0.129$, $p=0.051$, meaning that although both group reacted slower to negative words in general, patients reacted to negative words faster than the controls and controls reacted faster towards positive words compared to patients (Figure 19).

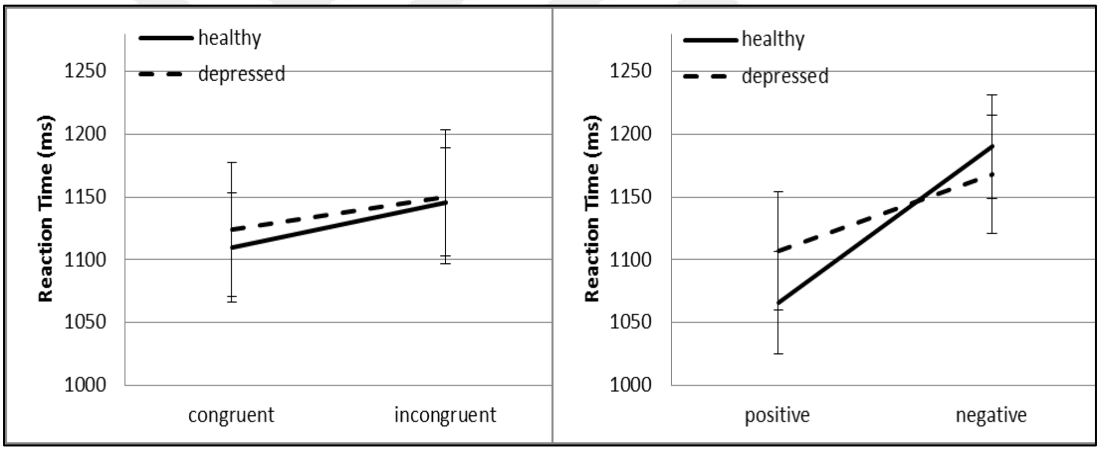


Figure 19: Significant effects of congruency (left) and valence (right) on the Reaction Times. The marginally significant interaction between valence and group can also be detected in the figure on the right.

Another 2x2x2x2 mixed design ANOVA with congruency categories (congruent, incongruent) and valence (positive, negative) as within-subject factors; depression (healthy, depressed) and gender (female, male) as between-subject factors on correct response rates revealed significant differences in **congruency** $F(1, 28) = 5.008$, $\eta^2 = 0.152$, $p<0.05$ –meaning that all of the participants made more errors evaluating the incongruent cases compared to congruent ones, regardless of the group and the valence factors— and **valence** $F(1, 28) = 5.435$, $\eta^2 = 0.163$, $p<0.05$, meaning that, regardless of the other factors, all of the participants made more errors evaluating the negative words compared to positive words (Figure 20). No group differences are found.

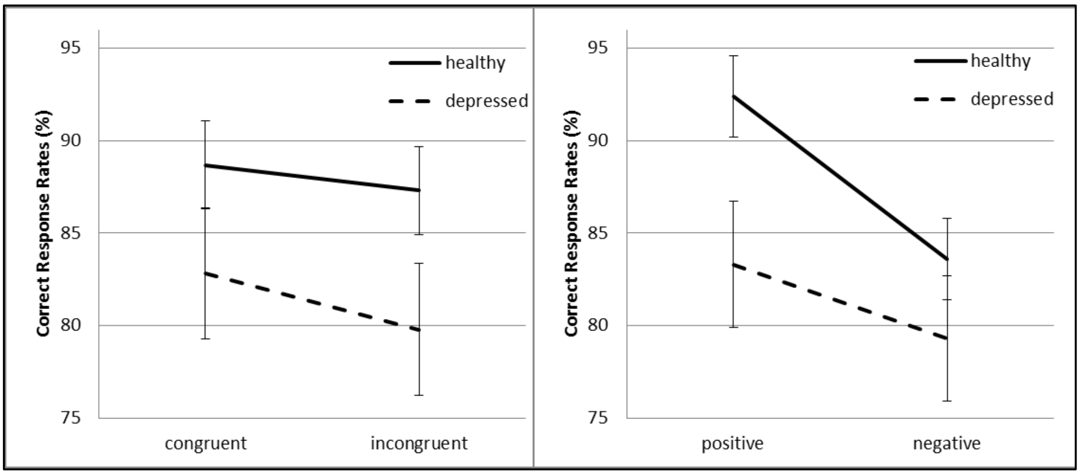


Figure 20: Significant effects of congruency (left) and valence (right) on the Correct Response Rates.

4.2.2. Item-Based Analysis

In order to strengthen the statistical significance, similar statistical designs mentioned above are also applied taking account of the words. Since all words appear both in congruent and incongruent cases, and since the word number (N=64) is twice the subject number (N=32), the statistical significance was expected to be higher for this item-wise analysis. This expectation is then verified by the results.

Since the ‘subjects’ of item-based analysis are the words, valence category becomes a between subject factor, whereas the group factor becomes a within subject factor. Therefore, a 2x2x2 mixed design ANOVA with the categories of group (healthy, depressed) and of congruency (congruent, incongruent) as within-subject factors and valence (positive, negative) as a between-subject factor on reaction times revealed significant differences in **valence** $F(1, 62) = 16.427$, $\eta^2 = 0.209$, p=0.001, meaning that the reaction times towards negative words were significantly slower compared to positive words; and in the interaction between **group and valence** $F(1, 62) = 11.708$, $\eta^2 = 0.159$, p=0.001, meaning that, although positive words are evaluated faster than negative words in general, depressed group reacted faster to negative words compared to controls (Figure 21).

Finding no significant main effect of congruence means that **Hypothesis 1 is declined**. Even if the difference between patients’ reaction times towards congruent and incongruent cases seems smaller than controls (Figure 21, left), unfortunately this result is not significant. Additionally there is no significant group difference, which actually means that patient group performed as good as controls in this task, just as in Classical Stroop Task, showing that they really do not have a specific emotional or cognitive deficit, which generally support my hypotheses.

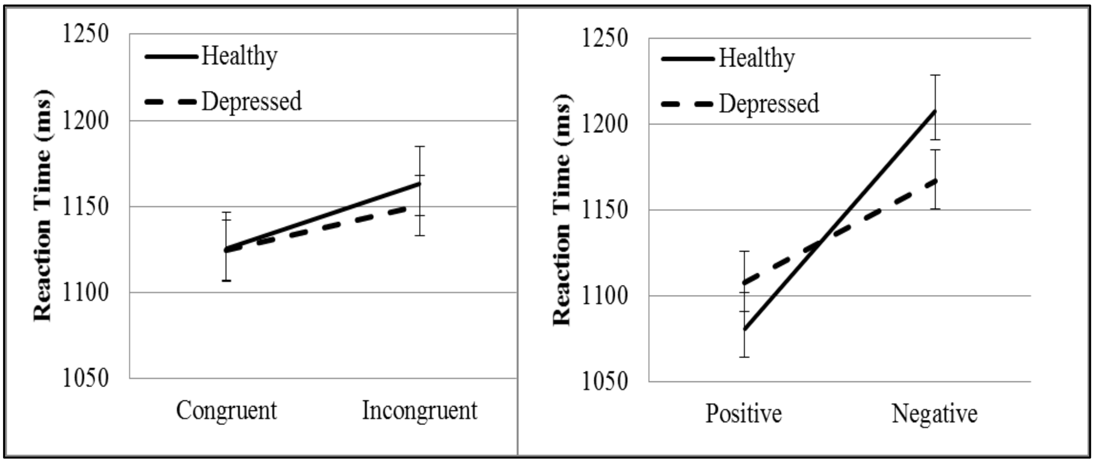


Figure 21: No significant effects of congruency and group (left); and the significant interaction between valence and group (right) on reaction times.

Another 2x2x2 mixed design ANOVA with the categories of group (healthy, depressed) and of congruency (congruent, incongruent) as within-subject factors and valence (positive, negative) as a between-subject factor on correct response rates revealed significant differences in **group** $F(1, 62) = 30.638$, $\eta^2 = 0.331$, $p=0.001$, meaning that the control group had significantly higher correct response rates; and **valence** $F(1, 62) = 6.061$, $\eta^2 = 0.089$, $p<0.05$, meaning that positive words were responded more correctly than negative ones. Moreover, a significant interaction is found between **group and valence** $F(1, 62) = 6.577$, $\eta^2 = 0.096$, $p<0.05$, meaning that the group difference towards positive words (i.e. controls being more correct than patients) shrinks towards negative words (Figure 22).

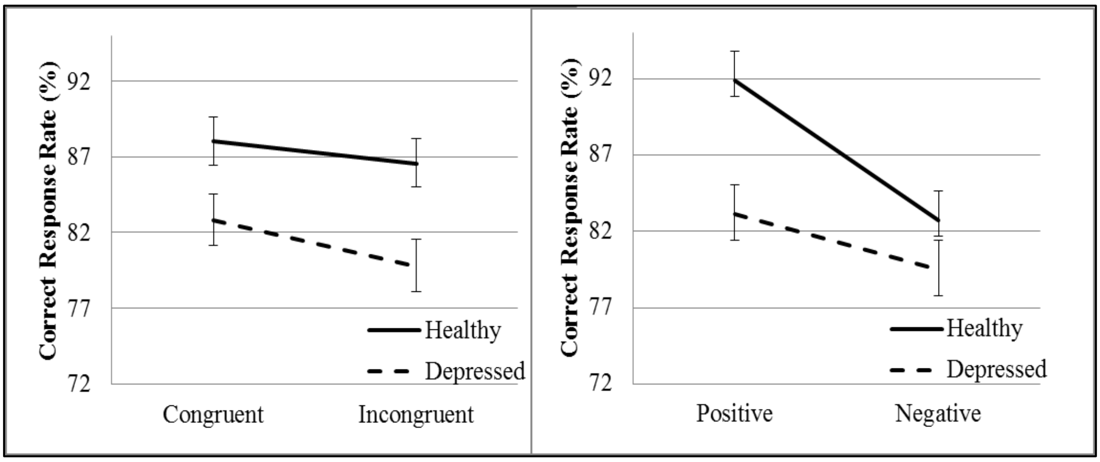


Figure 22: A significant group difference is found (left). There also is a significant interaction between valence and group on correct response rates (right).

Significant main effect of valence reveals that **Hypothesis 3 is verified**, meaning that both group successfully showed the negative-positive asymmetry effect, slowing down more while evaluating negative words in contrast to positive words. The interaction between group and valence clarifies that although both groups react faster to positive words, their reaction pattern differ depending on the words' valence: Patients react faster to negative words when compared to control group, and controls react faster to positive words when compared to patient group. Similar pattern is also observed when correct response rates are considered: Although both groups made more errors towards negative words, when compared to each other the difference between the groups towards negative words is smaller, meaning that patients responded almost as correctly as controls towards negative words, while the difference is significantly bigger between the groups towards positive words. All these point out to a negatively-skewed behavioral pattern in patients, which confirms that **Hypothesis 4 is verified** too.

4.3. Correlation Analysis

Only for the Word-Face Stroop Task, but not the classical Stroop Task, a congruency score (CS) is calculated by subtracting the mean RT of incongruent cases from mean RT of congruent cases for each patient:

$$CS = Mean(RTcongruent) - Mean(RTincongruent)$$

Since RT for congruent cases is supposed to be less than that of incongruent cases for the healthy population, the emotional interference effect, i.e. being slower to incongruent cases than congruent cases, is expected to be manifested as negative CS. HAM-D and BDI scores of the patients provide a diagnostic guideline for the level of depression. Therefore I investigated whether the congruency scores for the subjects were related to the level of depression as indicated by their HAM-D or BDI scores.

The correlation analyses revealed no significant correlation between patients' congruency scores and their HAM-D or BDI scores.

This result means that **Hypothesis 5 is declined**, probably because of the relatively small sample size, and levels of depression—as measured by HAM-D and BDI—with low standard deviation. The task should be conducted on a larger participant pool with more varying levels of depression, so that I can find a significant correlation again as in previous studies (Başgöze, 2008; Başgöze et al., 2014).

4.4. fMRI Analysis

As mentioned earlier in Methods section, first of all each individual's functional and anatomical images are preprocessed. Next, their individual GLM are studied for the concatenated four runs and then second level group analyses are performed.

From each individual I obtained activation maps for 4 coefficients: congpos, congneg, incongpos, incongneg and contrast maps for Congpos vs. Incongpos, Congneg vs. Incongneg, Congpos vs. Congneg and Incongpos vs. Incongneg (Figure 23, where 'Blue' means higher activations in the Anterior Cingulate Cortex for the incongruent-positive cases compared to congruent ones; whereas 'Red', means more activations in the caudate towards congruent-positive cases compared to incongruent ones.

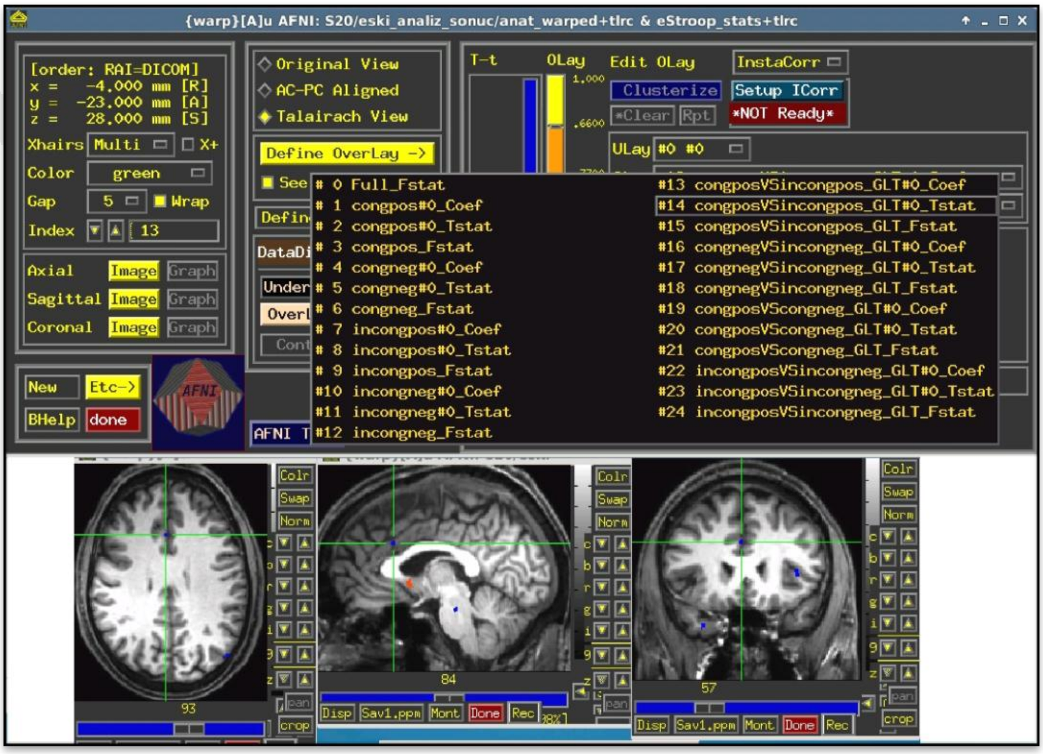


Figure 23: Results for congposVSincongpos for one individual and the list of its outputs seen in the black box.

According to the different kinds of 2nd Level Analyses mentioned in the Methods Section, I obtained 4 different results for different purposes:

1) 2x2 Repeated Measures ANOVA: To see the different activation patterns for our task's four factors: congruent-positive, congruent-negative, incongruent-positive and incongruent-negative (Table 2)

a. Mean activation maps for congruent-positive, congruent-negative, incongruent-positive and incongruent-negative conditions within the Depressed Group, using congpos, congneg, incongpos and incongneg T-Stat

files as inputs and obtaining mean congpos, mean incongpos, mean congneg and mean incongneg files as outputs.
b. Mean activation maps for congruent-positive, congruent-negative, incongruent-positive and incongruent-negative cases within the Healthy Group, using congpos, congneg, incongpos and incongneg T-Stat files as inputs and obtaining mean congpos, mean incongpos, mean congneg and mean incongneg files as outputs.
c. Difference map for congruency VS. incongruency, and for positive VS. negative within the depressed group.
d. Difference map for congruency VS. incongruency, and for positive VS. negative within the control group.

Notice that since there is no baseline condition in this fMRI task (such as a separate trial where participants are shown some visuals besides emotional faces and words, and are asked to push response buttons), we cannot subtract the activations that are caused by vision and hand motion from the mean activations that are caused by our task's independent variables. Thus the discussion is made accordingly and the fMRI results that compare the groups, which will be explained in the next section, automatically eliminate this disadvantageous situation via comparing the groups.

2) 2x2 Mixed Design ANOVA: To see the group differences with respect to valence in congruent and incongruent cases (Table 3)

a. Differences between Healthy and Depressed Groups with respect to Congruent-Positive and Congruent-Negative Cases, using 'congpos' and 'congneg' T-Statistic files as inputs; and obtaining depcongpos VS contcongpos and depcongneg VS contcongneg contrast files as outputs.
b. Differences between Healthy and Depressed Groups with respect to Incongruent-Positive and Incongruent-Negative Cases, using 'incongpos' and 'incongneg' T-Statistic files as inputs; and obtaining depincongpos VS contincongpos and depincongneg VS contincongneg contrast files as outputs.

3) 2x2 Mixed Design ANOVA for face stimuli: To see the group differences with respect to valence in faces (Table 4)

Differences between Healthy and Depressed Groups with respect to happy and sad faces, using 'posface' and 'negface' T-statistic files as inputs; and obtaining depposface VS congposface and depnegface VS contnegface contrast files as outputs.

For all of the contrasts that are going to be depicted here in the fMRI results section, p value is always chosen lower than 0.001, and the cluster size is always chosen as 14, as our AlphaSim calculation provided us to pinpoint family-wise corrected task-relevant significant activations. The significant activations shown overlaid on the average brain image—which I calculated via averaging the warped and talairached anatomical brain images of the 32 participants— might sometimes reveal hot (red/yellow) or cold (blue/pale blue) colors. When we are looking at contrast results, hot colors mean that the contrast's first member showed higher significance, whereas cold colors mean that the contrast's second member showed higher significance. For example when we compare depressed and healthy group for a specific case, since the contrast is created via subtracting the healthy population's map from the depressed population's map, yellowish activation on an area means depressed group showed more activations compared to control group on that area. On the other hand, when we look at the mean activation maps, yellowish colors over a brain region mean that the activation is positively correlated with the task waveform, whereas bluish colors correspond to a negative correlation between the BOLD response and the task waveform. Moreover significance values are higher for yellow than for orange activations; and significance values for pale blue are higher than the dark blue (Figure 24).

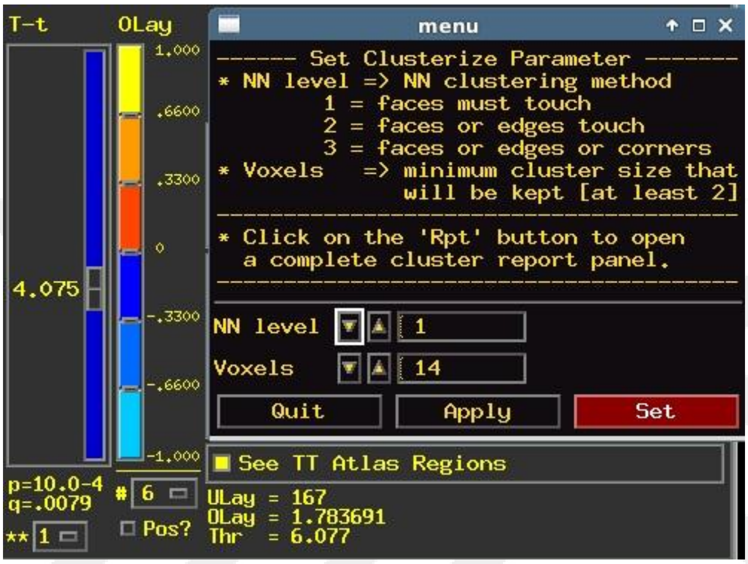


Figure 24: p values (bottom left), t-values (left slider) and the color codes for activation maps (right slider), cluster size (right).

In order to compare the behavioral results with fMRI results much better here is a comparison between depressed and healthy groups with respect to the reaction times and correct response rates (Table 5):

Table 5: Comparison of Patient and Control Groups with respect to mean Reaction Times and Correct Response Rates towards 4 main cases of WFS Task

DVs	**Group**	**Congruent Positive**	**Congruent Negative**	**Incongruent Positive**	**Incongruent Negative**
Reaction Times (ms)	**Depressed**	1095.66 ±194.89	1153.23 ±253.26	1117.68 ±187.64	1182.77 ±224.15
	Healthy	1053.79 ±169.15	1165.92 ±180.24	1077.76 ±163.75	1214.21 ±184.34
Correct Response Rates (%)	**Depressed**	84.57 ±14.00	81.06 ±19.18	82.03± 14.14	77.54± 19.84
	Healthy	92.78 ±9.46	84.57 ±11.21	91.99 ±8.46	82.62 ±13.97

4.4.1. Within Patient Group: Main effect of congruent-positive, incongruent-positive, congruent-negative and incongruent-negative in Patients

Congruent-Positive

The most prominent voxel clusters that show significant activations are indicated in the Table 6, meaning that patients' brain activations showed significant positive correlations (excitation or hyperactivation) with the congruent-positive cases of our e-Stroop task, where words are positive and faces are happy, except the ones indicated in blue, which refers to negative correlation (inhibition or deactivation).

Table 6: Significant clusters of Patient group towards Congruent-positive cases

No of Voxels	MNI Coordinate	Name of the Region	Processes for which the region activates
86664	14, -89, 5 -16, -96, 6	Bilateral Cuneus, BA17 (Figure 25a)	Primary Visual Cortex
33934	-55, -15, 39	Left Postcentral, BA1	Primary Sensory Cortex
4532	-24, 1, 6 22, -2, 12	Bilateral Putamen	Category learning, feed-back processing in rule-based tasks working with pre-frontal
3232	47, 4, 39	Right Precentral, BA6	Dorsal Premotor Cortex: Cognitive-sensory control of behavior (Abe & Hanakawa, 2009)
2170	-3, -5, 49	Left Middle Cingulate Gyrus, BA24, dACC (Figure 25b)	Cognitive processing, attention, associated with valence
1853	27, -50, 37 -27, -62, 42	Bilateral Precuneus, BA7	Self-Consciousness, Conscious information processing (Vogt & Laureys, 2005)
932	50, 11, 3 -57, 9 ,9	Bilateral Pars Opercularis, BA44	Part of Broca's Area, phonological and syntactic processing, response suppression. Also, part of Ventral Attentional Network (VAN) (Corbetta, 2008)
747	50, -34, 9	Right Superior Temporal, BA22	Affective Face Processing (Pitcher, Garrido, Walsh, and Duchaine, 2008)
148	-13, -60, -44 12, -65, -50	Bilateral Cerebellum	Regulatory role in the processing of emotional material of both positive and negative valence, though with behavioral

			consequences only for pleasant stimuli (Turner et al., 2007)
139	38, 1, 9 -35, -4, 15	Bilateral Insula	Empathy, emotional self-awareness
168	-37, -14, -20	Left Parahippocampal Gyrus	Identifying Visual and Social Context (Rankin et al., 2009)
38	-16, 31, 22	Left Anterior Cingulate Cortex, BA32, rACC (Figure 25c)	Emotion regulation, conflict detection
29	19, -23, -4 -14, -28, 0	Bilateral Thalamus	Relay Station

(a)
(b)
(c)

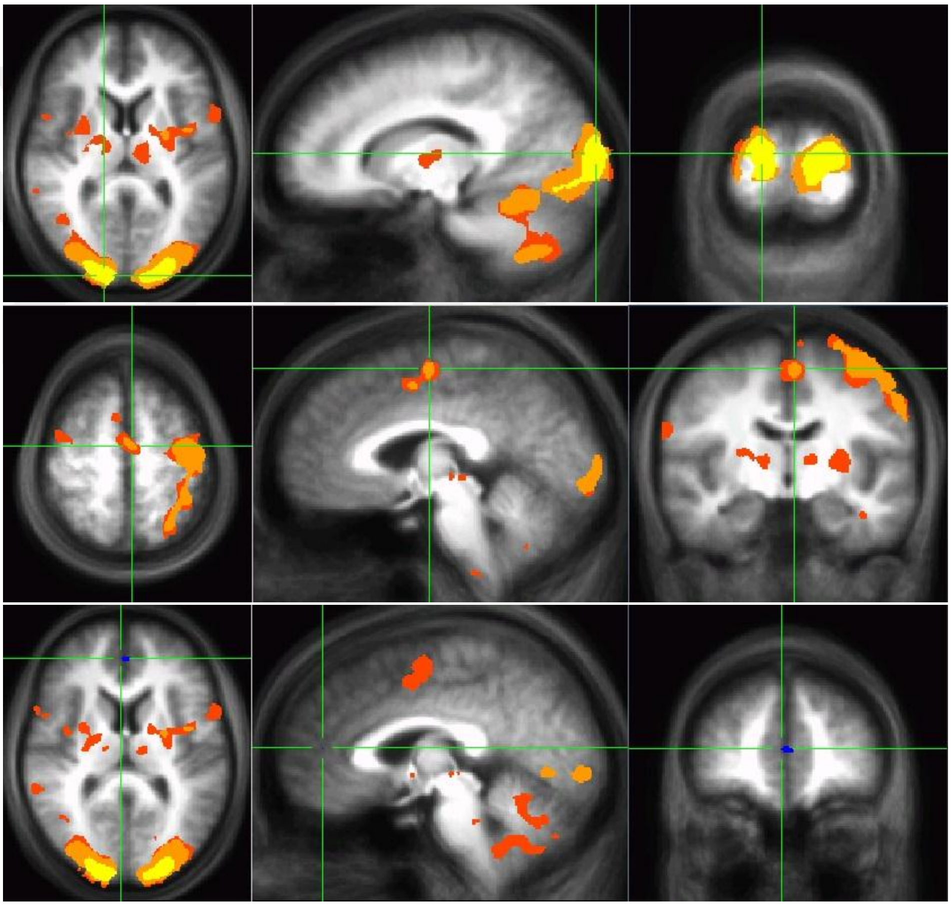


Figure 25: Significant main effect maps of patients towards congruent positive cases.

Figure 25 depicts significant (a) Bilateral Cuneus, Thalamus and Putamen activations, (b) Left Hemisphere activity covering dACC, left Postentral gyrus, left Inferior Parietal Lobe and bilateral Precuneus, and (c) Deactivation in left rACC, hyperactivity in left dACC in patients towards congruent positive cases.

Congruent-Negative

The most prominent voxel clusters that show significant activations are indicated in the Table 7, meaning that patients' brain activations showed significant positive correlations (excitation or hyperactivation) with the congruent-negative cases of our e-Stroop task, where words are negative and faces are sad, except the ones indicated in blue, which refers to negative correlation (inhibition or deactivation).

Table 7: Significant clusters of Patient group towards Congruent-negative cases

No of Voxels	MNI Coordinate	Name of the Region	Processes for which the region activates
77640	24, -67, -14 -25, -73, -15	Bilateral Fusiform Gyrus, BA37 (Figure 26a)	Face Recognition & Visual expertise (Gauthier et al., 1999)
33001	-55, -16, 39 54, -24, 47	Bilateral Postcentral, BA1	Primary Sensory Cortex
17943	47, 5, 42 -43, -2, 51	Bilateral Precentral, BA6	Dorsal Premotor Cortex: Cognitive-sensory control of behavior (Abe & Hanakawa, 2009)
10520	0, -3, 49	Left Anterior Cingulate Gyrus, BA24, dACC (Figure 26b)	Cognitive processing, attention, associated with valence
6658	17, -54, -46 -29, -59, -52	Bilateral Cerebellum	Regulatory role in the processing of emotional material of both positive and negative valence, though with behavioral consequences only for pleasant stimuli (Turner et al., 2007)
5250	29, -48, 40 -28, -58, 46	Bilateral Precuneus, BA7	Self-Consciousness, Conscious information processing (Vogt & Laureys, 2005)
2316	54, -33, 11 -60, -39, 15	Bilateral Superior Temporal Gyrus, BA22	Affective Face Processing (Pitcher et al., 2008)
2311	-24, 2, 5 24, -4, 11	Bilateral Putamen	Category learning, feed-back processing in rule-based tasks working with pre-frontal
470	-51, 20, -6 47, 14, 0	Bilateral Pars Orbitalis, BA47, Orbitofrontal Cortex	Behavioral and motor inhibition, (Vollm et al., 2006 and Del-Ben et al., 2005); adverse emotional inhibition (Berthoz, 2002), conflict involving decision making (Rogers et al., 1999)
439	-40, 2, 6	Left Insula	Empathy, emotional self-awareness
212	29, 3, -35 -28, -3, -36	Bilateral Parahippocampal Gyrus	Identifying Visual and Social Context (Rankin et al., 2009)

188	35, 49, 25	Right Middle Frontal Gyrus, BA10	Part of bottom-up attention mechanism, VAN (Corbetta et al., 2008), conflict and reward involving decision making (Rogers et al., 1999), cognitive integration, joint attention (Williams et al., 2005) → Central Executive of Baddeley's Working Memory Model
139	19, -23, -4 -16, -27, 0	Bilateral Thalamus	Relay station
114	-13, 45, 5	Left Anterior Cingulate Cortex, BA32, rACC (Figure 26c)	Emotion regulation, conflict detection
81	-5, 40, -16	Left Gyrus Rectus, BA11	Face-Name Association (Herholz et al., 2001), Decision Making involving reward (Rogers et al., 1999)

(a)

(b)

(c)

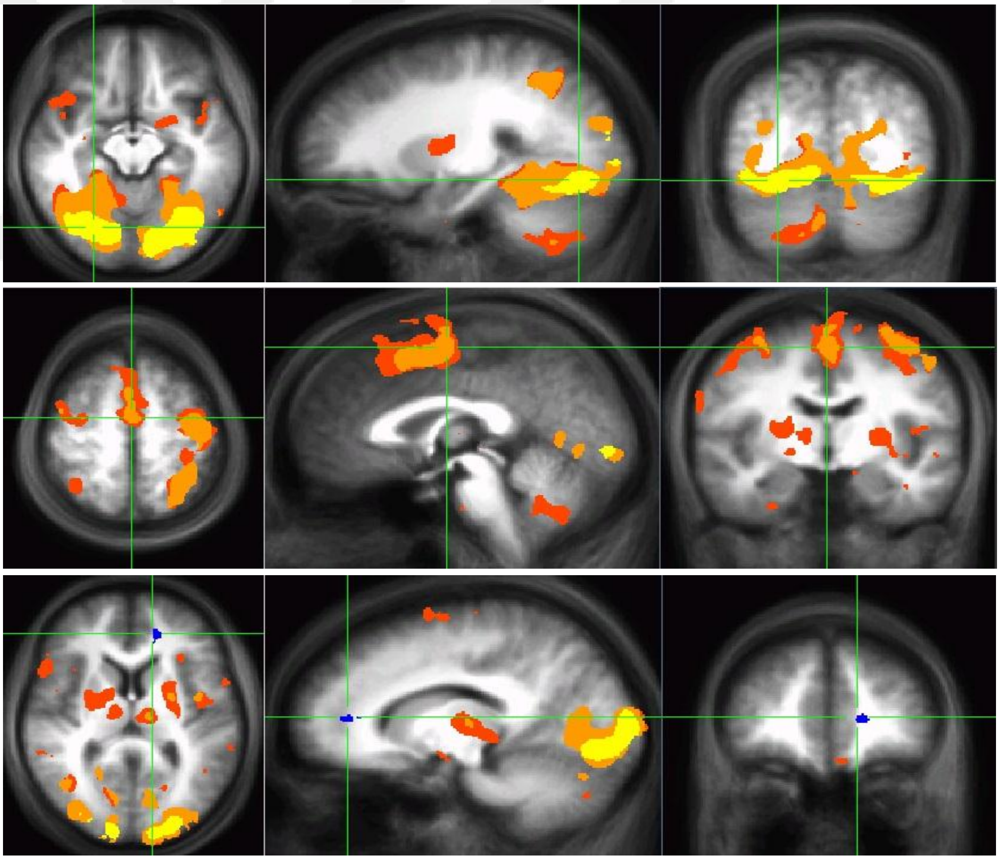


Figure 26: Significant main effect maps of patients towards congruent negative cases.

Figure 26 depicts significant (a) bilateral Fusiform Gyrus, right Cerebellum, bilateral insula and left parahippocampal, (b) dACC and Middle Frontal Gyrus activations, and (c) rACC deactivation, accompanied with thalamus and putamen hyperactivities in patients towards congruent negative cases.

Incongruent-Positive

The most prominent voxel clusters that show significant activations are indicated in the Table 8, meaning that patients' brain activations showed significant positive correlations (excitation or hyperactivation) with the incongruent-positive cases of our e-Stroop task, where words are positive and faces are sad, except the ones indicated in blue, which refers to negative correlation (inhibition or deactivation).

Table 8: Significant clusters of Patient group towards Incongruent-positive cases

No of Voxels	MNI Coordinate	Name of the Region	Processes for which the region activates
167851	14, -88, 5 -14, -96, 6	Bilateral Calcarine Gyrus, BA17 (Figure 27a)	Primary Visual Cortex
8408	29, -49, 37 -30, -58, 43	Bilateral Precuneus, BA7	Self-Consciousness, Conscious information processing (Vogt & Laureys, 2005)
7184	46, 5, 43 -44, -2, 52	Bilateral Precentral, BA6	Dorsal Premotor Cortex: Cognitive-sensory control of behavior (Abe & Hanakawa, 2009)
4668	3, 20, 42	Right FEF (Frontal Eye Field), BA8 (Figure 27b)	Part of top-down attention mechanism, DAN (Corbetta, 2008), Executive Behavior Control, Memory retrieval, resolving uncertainty (Volz et al., 2004)
3971	57, 19, 10 -57, 12, 17	Bilateral Pars Opercularis, BA44	Part of Broca's Area, phonological and syntactic processing, response suppression. Also, part of Ventral Attentional Network (VAN) (Corbetta, 2008)
2135	60, -7, 20 -60, -15, 26	Bilateral Postcentral, BA1	Primary Sensory Cortex
1807	59, -33, 13	Right Superior Temporal Gyrus, BA22	Affective Face Processing (Pitcher et al., 2008)
931	-19, 29, 18	Left Anterior Cingulate Cortex, BA32, rACC	Emotion regulation, conflict detection
500	38, 28, -4	Right Pars	Behavioral and motor inhibition,

		Orbitalis, BA47, Orbitofrontal Cortex	(Vollm et al., 2006 and Del-Ben et al., 2005); adverse emotional inhibition (Berthoz, 2002), conflict involving decision making (Rogers et al., 1999)
476	-31, -18, -23 32, -12, -14	Bilateral Hippocampus	Memory Formation
217	31, -4, -9 -30, -9, -5	Bilateral Putamen	Category learning, feed-back processing in rule-based tasks working with pre-frontal
167	35, 45, 32	Right Dorsolateral Prefrontal Cortex, BA9 (Figure 27c)	Suppressing sadness, working memory, recognizing the emotions of others, planning, attention to positive emotions
93	-24, -43, -45 14, -60, -51	Bilateral Cerebellum	Regulatory role in the processing of emotional material of both positive and negative valence, though with behavioral consequences only for pleasant stimuli (Turner et al., 2007)

(a)
(b)
(c)

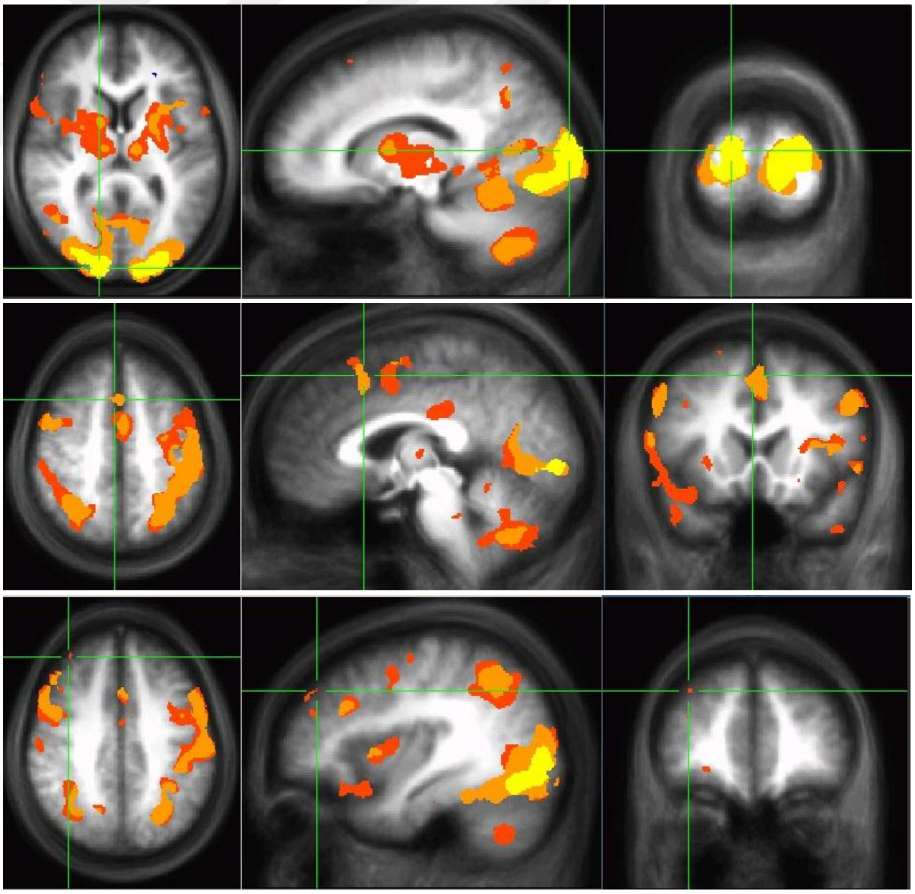


Figure 27: Significant main effect maps of patients towards incongruent positive cases.

Figure 27 depicts significant (a) bilateral Calcarine Gyrus, bilateral Putamen, thalamus and bilateral cerebellum activations, (b) Right Frontal Eye Field, bilateral dACC and precuneus activations, and (c) Right DLPFC activation in patients towards incongruent positive cases.

Incongruent-Negative

The most prominent voxel clusters that show significant activations are indicated in the Table 9, meaning that patients' brain activations showed significant positive correlations (excitation or hyperactivation) with the incongruent-negative cases of our e-Stroop task, where words are negative and faces are happy, except the ones indicated in blue, which refers to negative correlation (inhibition or deactivation).

Table 9: Significant clusters of Patient group towards Incongruent-negative cases

No of Voxels	MNI Coordinate	Name of the Region	Processes for which the region activates
335665	14, -89, 5 -15, -97, 6	Bilateral Calcarine Gyrus, BA17	Primary Visual Cortex
9620	48, 21, -10 -53, 18, -5	Bilateral Pars Orbitalis	BA47, Orbitofrontal Cortex, Behavioral and motor inhibition, (Vollm et al., 2006 and Del-Ben et al., 2005); adverse emotional inhibition (Berthoz, 2002), conflict involving decision making (Rogers et al., 1999)
5502	28, -48, 40 -28, -56, 46	Bilateral Precuneus, BA7	Self-Consciousness, Conscious information processing (Vogt & Laureys, 2005)
1463	60, -6, 19 -61, -12, 26	Bilateral Postcentral Gyrus, BA4	Primary Motor Cortex
931	-19, 33, 10	Left Anterior Cingulate Cortex, BA32, rACC	Emotion regulation, conflict detection
589	-2, -7, 49	Left Anterior Cingulate Gyrus, BA24, dACC (Figure 28a)	Cognitive processing, attention, associated with valence
572	54, 16, 32 -48, 15, 32	Bilateral Pars Opercularis, BA44	Part of Broca's Area, phonological and syntactic processing, response suppression, Also, part of Ventral Attentional Network (VAN) (Corbetta, 2008)
402	18, 7, -6 -17, 6, -6	Bilateral Putamen	Category learning, feed-back processing in rule-based tasks working with pre-frontal

336	2, 39, -11 -5, 38, -11	Bilateral Gyrus Rectus, BA11 (Figure 28b)	Face-Name Association (Herholz et al., 2001), Decision Making involving reward (Rogers et al., 1999)
325	61, -40, 14 -59, -40, 22	Bilateral Superior Temporal Gyrus, BA22	Affective Face Processing (Pitcher et al., 2008)
195	35, 52, 31	Right Dorsolateral Prefrontal Cortex, BA9 (Figure 28c)	Suppressing sadness, working memory, recognizing the emotions of others, planning, attention to positive emotions
191	-38, -8, -28 40, -13, -28	Bilateral Fusiform, BA37	Face Recognition & Visual expertise (Gauthier et al., 1999)
109	-59, -37, 23 54, -37, 23	Bilateral Inferior Parietal Lobe , BA40	Supramarginal Gyrus, Part of a Mirror Neuron System, adapting to sudden environmental changes (action reprogramming) (Hartwigsen et al., 2012)
107	33, 52, -3 -26, 51, -4	Bilateral Middle Frontal Gyrus, BA10	Part of bottom-up attention mechanism, VAN (Corbetta et al., 2008), conflict and reward involving decision making (Rogers et al., 1999), cognitive integration, joint attention (Williams et al., 2005) → Central Executive of Baddeley's Working Memory Model
106	31, -3, -36	Right Parahippocampal Gyrus	Identifying Visual and Social Context (Rankin et al., 2009)
104	20, -25, 2 -22, -25, 2	Bilateral Thalamus	Relay Station
67	8, -72, -26 -8, -74, -26	Bilateral Cerebellum	Regulatory role in the processing of emotional material of both positive and negative valence, though with behavioral consequences only for pleasant stimuli (Turner et al., 2007)
34	-37, 17, 9 36, 15, 8	Bilateral Insula	Empathy, emotional self-awareness

(a)

(b)

(c)

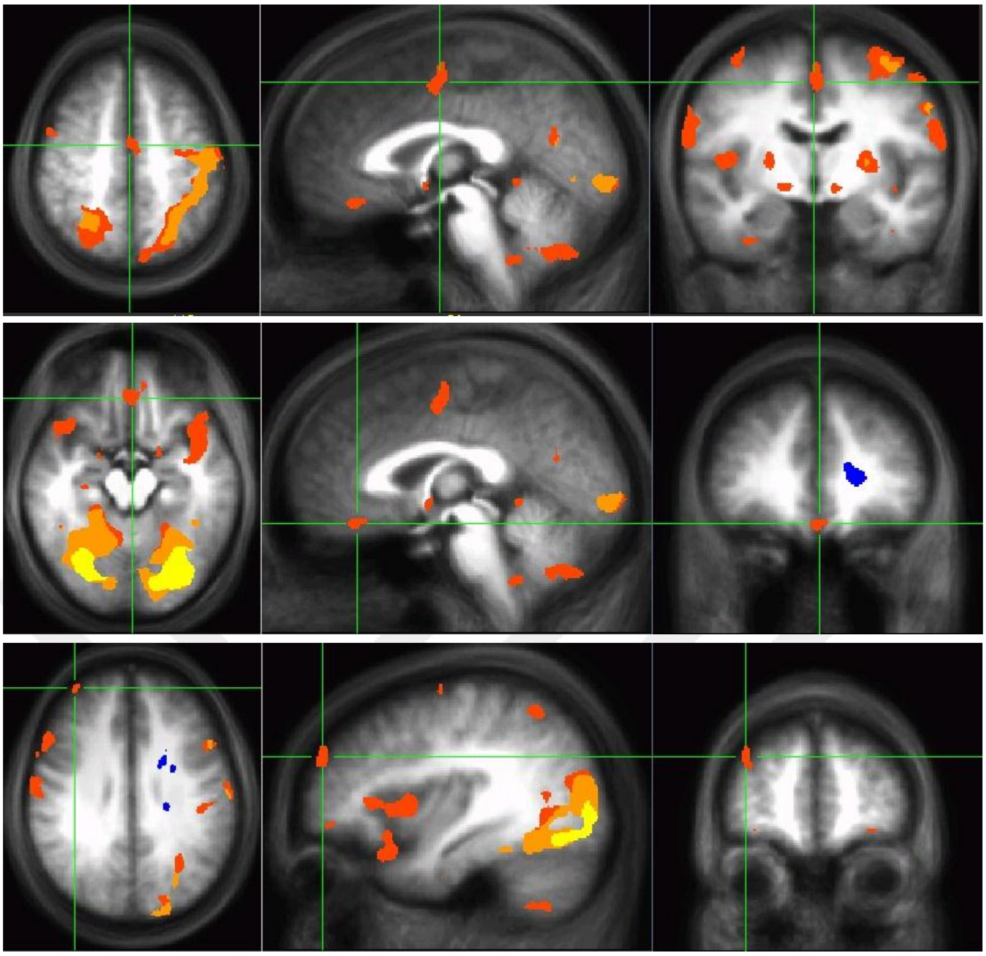


Figure 28: Significant main effect maps of patients towards incongruent negative cases.

Figure 28 depicts significant (a) left dACC and left precuneus activations, (b) left Gyrus Rectus, bilateral temporal pole and bilateral cuneus activations and left rACC deactivations, and (c) right DLPFC, bilateral Insula and bilateral fusiform activations in patients towards incongruent-negative cases.

The fact that patients showed significant deactivation in rACC towards almost all cases, whereas they show hyperactivity in dACC support theories claiming differential activation within cingulate gyrus & theories claiming emotional rACC is deactive whereas cognitive dACC is hyperactive in patients (Whalen et al., 1999; Bush et al., 2000; Mayberg et al., 2003; Davis et al., 2005). Therefore **Hypothesis 6 is verified**. Wagner et al. (2008) and Schlösser et al. (2008) claimed that patients fail at deactivating rACC, which is not the case in our findings. However one should notice that the tasks on their studies are not emotional Stroops. Our results are more compatible with Mitterschiffthaler et al.'s (2008) findings, who used an emotional Stroop paradigm. Thus, emotional content might be drastically changing how ACC react to conflicts.

4.4.2. Within Control Group: Main effect of congruent-positive, incongruent-positive, congruent-negative and incongruent-negative in Patients

Congruent-Positive

The most prominent voxel clusters that show significant activations are indicated in the Table 10, meaning that controls' brain activations showed significant positive correlations (excitation or hyperactivation) with the congruent-positive cases of our e-Stroop task, where words are positive and faces are happy, except the ones indicated in blue, which refers to negative correlation (inhibition or deactivation).

Table 10: Significant clusters of Healthy group towards Congruent-positive cases

No of Voxels	MNI Coordinate	Name of the Region	Processes for which the region activates
172957	-15, -97, 2 18, -97, 2	Bilateral Middle Occipital Gyrus, BA18 (this cluster also covers BA19 & Fusiform, BA37)	Visual Association Area: Image interpretation
4658	-29, -23, 71	Left Postcentral Gyrus, BA4	Primary Motor Cortex
2326	56, 8, 25	Right Pars Opercularis, BA44 (Figure 29a)	Part of Broca's Area, phonological and syntactic processing, response suppression, word and face encoding (McDermott et al., 2003), Also, part of Ventral Attentional Network (VAN) (Corbetta, 2008)
2126	-4, -12, 54 1, -3, 54	Bilateral Precentral, BA6	Dorsal Premotor Cortex: Cognitive-sensory control of behavior (Abe & Hanakawa, 2009)
1553	63, -25, 25	Right Supramarginal Gyrus, BA40	Part of a Mirror Neuron System, adapting to sudden environmental changes (action reprogramming) (Hartwigsen et al., 2012)
591	22, -27, 3 -16, -22, 8	Bilateral Thalamus	Relay Station
466	57, -4, -4	Right Superior Temporal Gyrus, BA22	Affective Face Processing (Pitcher et al., 2008)
429	-33, -8, -3	Left Claustrum	Consciousness on-off
413	-6, -38, 74	Left Parietal Cortex, BA5	Somatosensory processing and association
308	3, -41, -17 -5, -42, -17	Bilateral Cerebellum	Regulatory role in the processing of emotional material of both positive and negative valence, though with behavioral

			consequences only for pleasant stimuli (Turner et al., 2007)
239	22, -3, -9	Right Globus Pallidus	Encoding social rewards (lesions to GP is shown to cause anhedonia) (Miller et al., 2006)
226	-11, -1, 12 13, 2, 10	Bilateral Caudate	Goal-directed action, approach-attachment behavior, romantic love
205	-51, -17, 47	Right Postcentral Gyrus, BA1	Primary Somatosensory Cortex
166	14, 42, 16	Right Middle Frontal Gyrus, BA10 (Figure 29b)	Part of bottom-up attention mechanism, VAN (Corbetta et al., 2008), conflict and reward involving decision making (Rogers et al., 1999), cognitive integration, joint attention (Williams et al., 2005) → Central Executive of Baddeley's Working Memory Model
158	-1, 7, 34	Left Anterior Cingulate Cortex, BA24, dACC	Cognitive processing, attention, associated with valence
132	-30, -15, -21	Left Hippocampus	Memory Formation
84	46, 10, -17	Right Temporal Pole	BA38, Visual processing of emotional images (Lane et al., 1999), Structural judgment of familiar objects (Kellenbach et al., 2005), irony processing (Nakamura et al., 2001)
72	-17,-48, -6	Left Inferior Occipital Gyrus	BA19, Visuo-spatial information processing, Face-Name Association, Visual Mental Imagery
63	-27, -10, 6	Left Putamen	Category learning, feed-back processing in rule-based tasks working with pre-frontal
34	11, 47, 48	Right Prefrontal Cortex (Figure 29c)	BA9, Suppressing sadness, working memory, recognizing the emotions of others, planning, attention to positive emotions
30	-44, -8, 2	Left Insula	Empathy, emotional self-awareness

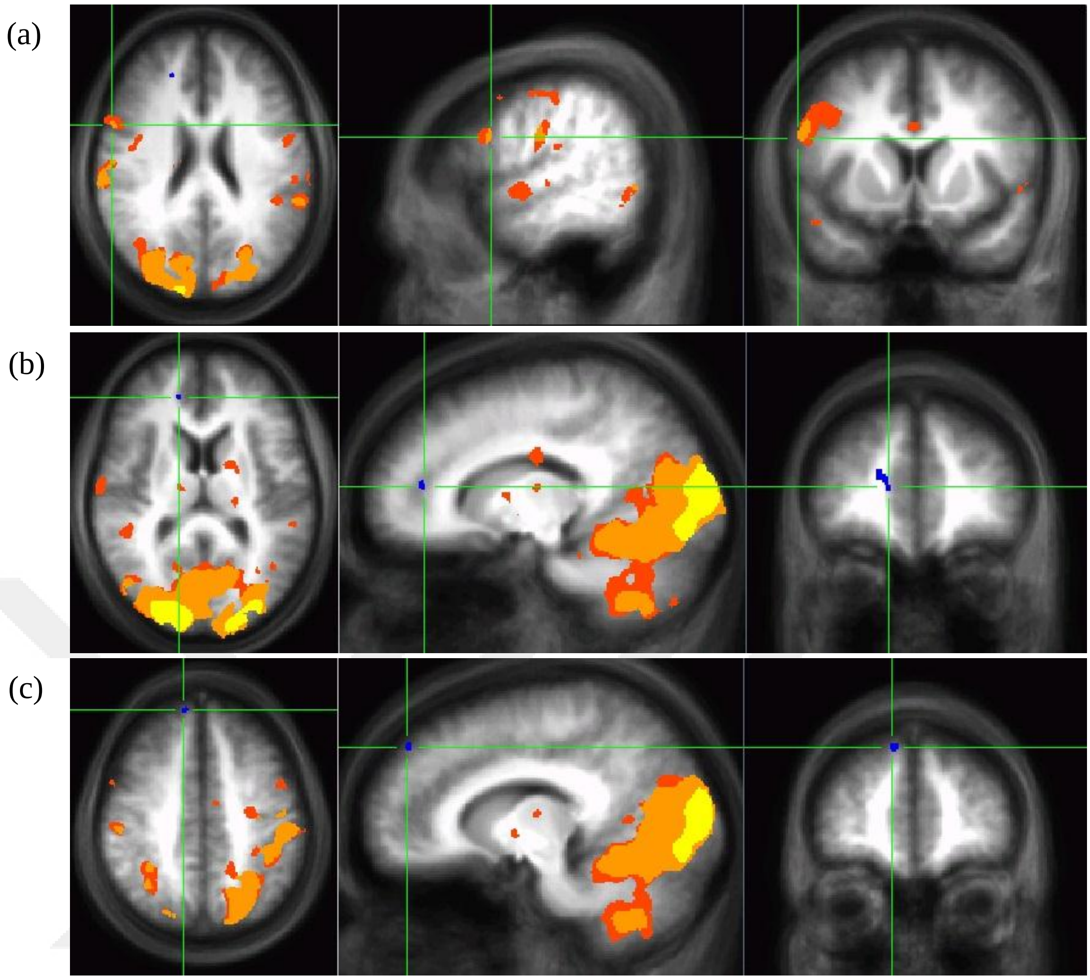


Figure 29: Significant main effect maps of controls towards congruent positive cases.

Figure 29 depicts significant (a) right Pars Opercularis, bilateral middle occipital gyrus and right superior temporal gyrus activations, (b) right middle frontal (BA10) deactivation, along with dACC, occipital lobe, Globus Pallidus and Cerebellum activations, and (c) prefrontal cortex (BA9) deactivation in controls towards congruent-positive cases.

Congruent-Negative

The most prominent voxel clusters that show significant activations are indicated in the Table 11, meaning that controls' brain activations showed significant positive correlations (excitation or hyperactivation) with the congruent-negative cases of our e-Stroop task, where words are negative and faces are sad, except the ones indicated in blue, which refers to negative correlation (inhibition or deactivation).

Table 11: Significant clusters of Healthy group towards Congruent-negative cases

No of Voxels	MNI Coordinate	Name of the Region	Processes for which the region activates
43557	14, -93, 8 -16, -93, 8	Bilateral Calcarine Gyrus, BA17	Primary Visual Cortex
4313	24, -56, -22 -19, -62, -23	Bilateral Cerebellum	Regulatory role in the processing of emotional material of both positive and negative valence, though with behavioral consequences only for pleasant stimuli (Turner et al., 2007)
3699	-31, -57, 43	Left Inferior Parietal Lobe, Angular Gyrus, BA39	Attentional reorientation in 3D space (Chen et al., 2012)
3101	-41, -33, 39	Left Supramarginal Gyrus, BA40	Part of a Mirror Neuron System, adapting to sudden environmental changes (action reprogramming) (Hartwigsen et al., 2012)
3006	31, -46, -19 -33, -52, -17	Bilateral Fusiform, BA37 (Figure 30a)	Face Recognition & Visual expertise (Gauthier et al., 1999)
2778	30, -46, 48 -40, -47, 48	Bilateral Precuneus, BA7	Self-Consciousness, Conscious information processing (Vogt & Laureys, 2005)
2265	58, -18, 34	Right Postcentral	Primary Somatosensory Cortex
682	1, -5, 57 -3, -5, 57	Bilateral Precentral, BA6	Dorsal Premotor Cortex: Cognitive-sensory control of behavior (Abe & Hanakawa, 2009)
492	56, 10, 23	Right Pars Opercularis, BA44	Part of Broca's Area, phonological and syntactic processing, response suppression, word and face encoding (McDermott et al., 2003), Also, part of Ventral Attentional Network (VAN) (Corbetta, 2008)
365	-27, 6, -38 28, 6, -38	Bilateral Temporal Pole, BA38 (Figure 30b)	Visual processing of emotional images (Lane et al., 1999), Structural judgment of familiar objects (Kellenbach et al., 2005), irony

			processing (Nakamura et al., 2001)
341	21, -25, 1	Right Thalamus	Relay Station
254	-35, -79, -13	Right Inferior Occipital Gyrus, BA19	Visuo-spatial information processing, Face-Name Association, Visual Mental Imagery
197	-55, 1, 39	Left Precentral Gyrus, BA6	Dorsal Premotor Cortex: Cognitive-sensory control of behavior (Abe & Hanakawa, 2009)
167	-44, -6, 3 41, -6, 3	Bilateral Insula	Empathy, emotional self-awareness
71	-27, -15, -22	Left Hippocampus	Memory Formation
71	13, 43, 17	Right Middle Frontal Gyrus, BA9&BA10 (Figure 30c)	Suppressing sadness & part of bottom-up attention mechanism, VAN (Corbetta et al., 2008)
42	48, -27, -0	Right Superior Temporal, BA22	Affective Face Processing (Pitcher et al., 2008)
20	-9, 10, -5	Left Caudate	Goal-directed action, approach-attachment behavior, romantic love

(a)

(b)

(c)

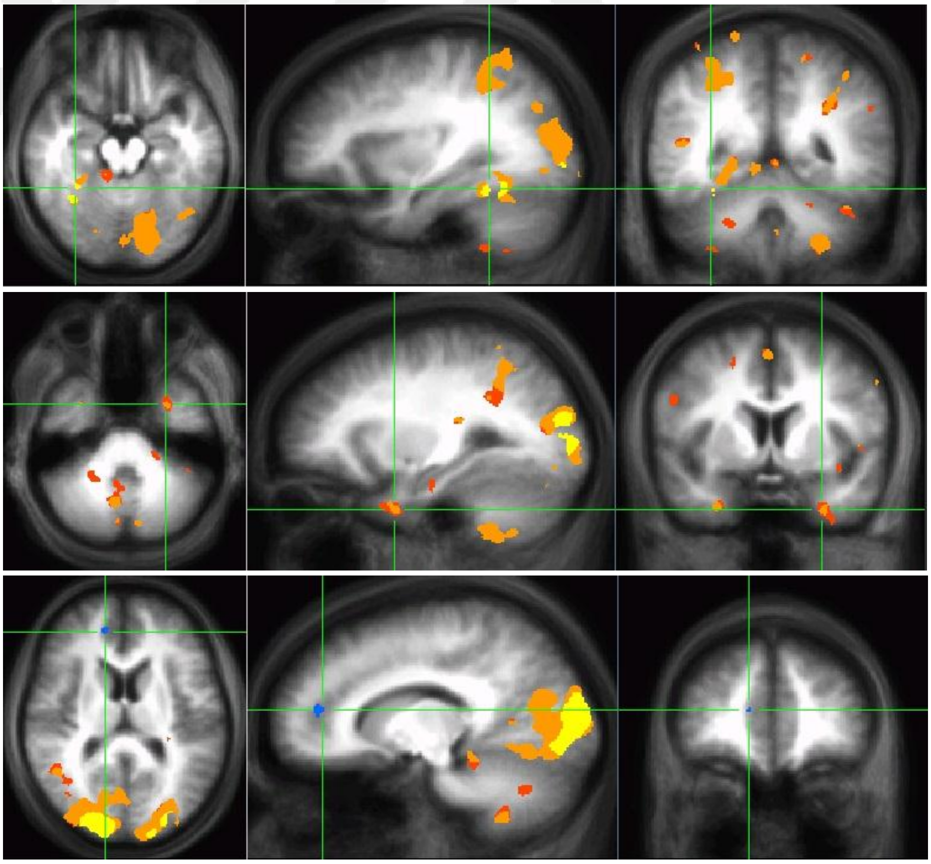


Figure 30: Significant main effect maps of controls towards congruent negative cases.

Figure 30 depicts significant (a) right Fusiform, bilateral Supramarginal gyrus and bilateral Cerebellum activations, (b) bilateral Superior Temporal Pole, left Hippocampus and bilateral precentral gyrus activations, and (c) right Middle Frontal Gyrus deactivation in controls towards congruent-negative cases.

Incongruent-Positive

The most prominent voxel clusters that show significant activations are indicated in the Table 12, meaning that controls' brain activations showed significant positive correlations (excitation or hyperactivation) with the incongruent-positive cases of our e-Stroop task, where words are positive and faces are sad, except the ones indicated in blue, which refers to negative correlation (inhibition or deactivation).

Table 12: Significant clusters of Healthy group towards Incongruent-positive cases

No of Voxels	MNI Coordinate	Name of the Region	Processes for which the region activates
74903	-15, -98, 5 17, -98, 5	Bilateral Superior Occipital Gyrus, BA18	Visual Association Area: Image interpretation (this cluster also covers BA19 & Fusiform)
5771	-53, -25, 45	Left Supramarginal Gyrus, BA40 (Figure 31a)	Part of a Mirror Neuron System, adapting to sudden environmental changes (action reprogramming) (Hartwigsen et al., 2012)
3213	21, -52, -57 -27, -56, 57	Bilateral Cerebellum	Regulatory role in the processing of emotional material of both positive and negative valence, though with behavioral consequences only for pleasant stimuli (Turner et al., 2007)
1559	-23, -67, 38	Left Precuneus, BA7	Self-Consciousness, Conscious information processing (Vogt & Laureys, 2005)
635	20, -24, 1	Right Thalamus	Relay Station
524	-1, -4, 52	Left Anterior Cingulate Gyrus, BA24, dACC (Figure 31b)	Cognitive processing, attention, associated with valence
446	31, -58, 46 -30, -59, 46	Bilateral Inferior Parietal Lobe, Angular Gyrus, BA39	Attentional reorientation in 3D space (Chen et al., 2012)
438	-44, -6, 12	Left Insula	Empathy, emotional self-awareness
336	44, -27, 31 -44, -28, 34	Postcentral Gyrus, BA1	Primary Somatosensory Cortex
253	-18, -65, 9 15, -66, 8	Bilateral Posterior Cingulate Gyrus, BA23	Awareness
117	-15, 12, 52	Left Precentral	Dorsal Premotor Cortex: Cognitive-

		Gyrus, BA6	sensory control of behavior (Abe & Hanakawa, 2009)
85	-64, -37, -2	Left Middle Temporal Gyrus, BA21	auditory processing & language
85	47, -41, 9	Right Superior Temporal Gyrus, BA22 (Figure 31c)	Affective Face Processing (Pitcher et al., 2008)
62	13, 43, 47	Right FEF, BA8	Part of top-down attention mechanism, DAN (Corbetta, 2008), Executive Behavior Control, Memory retrieval, resolving uncertainty (Volz et al., 2004)
19	-2, 46, -9	Left Gyrus Rectus, BA10	Face-Name Association (Herholz et al., 2001), Decision Making involving reward (Rogers et al., 1999)
15	-42, 22, -27	Left Temporal Pole, BA38	Visual processing of emotional images (Lane et al., 1999), Structural judgment of familiar objects (Kellenbach et al., 2005), irony processing (Nakamura et al., 2001)

(a)
(b)
(c)

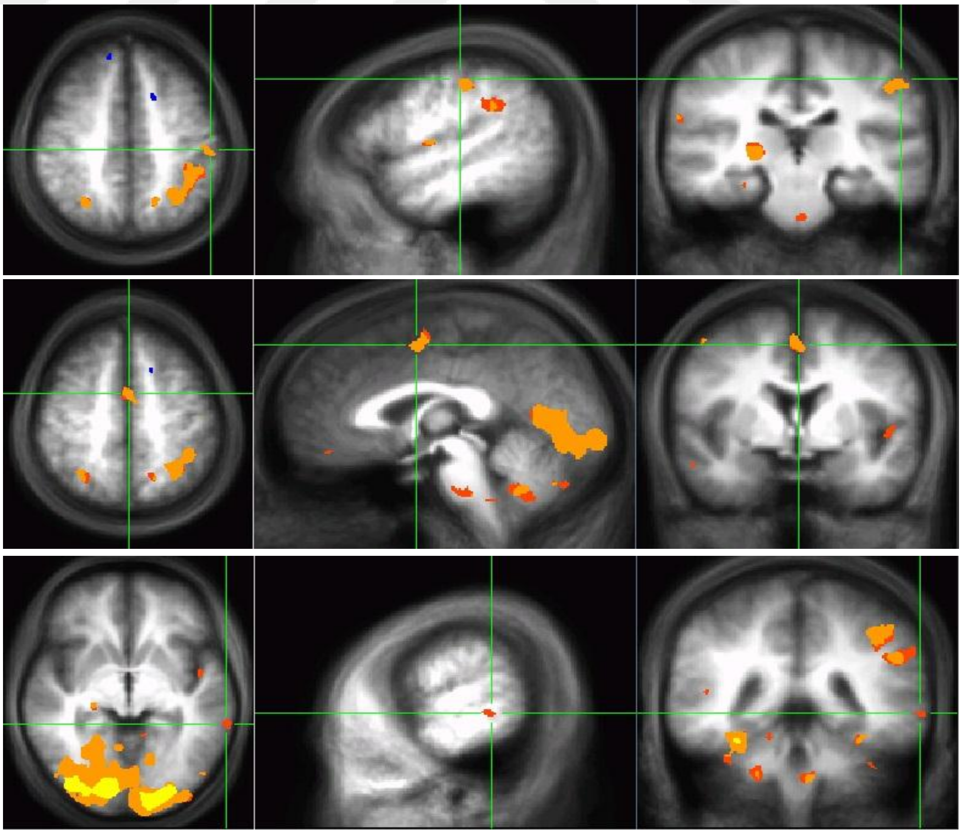


Figure 31: Significant main effect maps of controls towards incongruent positive cases.

Figure 31 depicts significant (a) left Supramarginal gyrus and Inferior Parietal activations, along with left precentral and right FEF deactivations, (b) left dACC, bilateral cerebellum and bilateral lingual gyrus activations, and (c) left superior temporal, left insula and right fusiform activations in controls towards incongruent-positive cases.

Incongruent-Negative

The most prominent voxel clusters that show significant activations are indicated in the Table 13, meaning that controls' brain activations showed significant positive correlations (excitation or hyperactivation) with the incongruent-negative cases of our e-Stroop task, where words are negative and faces are happy, except the ones indicated in blue, which refers to negative correlation (inhibition or deactivation).

Table 13: Significant clusters of Healthy group towards Incongruent-negative cases (Blue: deactivation)

No of Voxels	MNI Coordinate	Name of the Region	Processes for which the region activates
96317	-22, -91, 4 19, -91, 4	Bilateral Middle Occipital Gyrus, BA18	Visual Association Area: Image interpretation
3443	57, -20, 24	Right Supramarginal Gyrus, BA40	Part of a Mirror Neuron System, adapting to sudden environmental changes (action reprogramming) (Hartwigsen et al., 2012)
2041	18, -55, -57 -23, -56, -57	Bilateral Cerebellum	Regulatory role in the processing of emotional material of both positive and negative valence, though with behavioral consequences only for pleasant stimuli (Turner et al., 2007)
1026	-3, -9, 52	Left Anterior Cingulate Gyrus, BA24, dACC	Cognitive processing, attention, associated with valence
889	29, -45, 48 -30, -50, 47	Bilateral Precuneus, BA7 (Figure 32a)	Self-Consciousness, Conscious information processing (Vogt & Laureys, 2005)
873	18, 46, 34	Right Middle Frontal Cortex, BA9 (Figure 32b)	Suppressing sadness, working memory, recognizing the emotions of others, planning, attention to positive emotions
736	54, -24, 43 -52, -24, 43	Bilateral Postcentral, BA1	Primary Somatosensory Cortex
580	-39, -16, 11 44, -7, 12	Bilateral Insula	Empathy, emotional self-awareness
450	-8, -26, 69	Left Postcentral Gyrus, BA4	Primary Motor Cortex

399	31, 5, -35	Right Temporal Pole, BA38	Visual processing of emotional images (Lane et al., 1999), Structural judgment of familiar objects (Kellenbach et al., 2005), irony processing (Nakamura et al., 2001)
322	44, -6, 56	Right Precentral, BA6	Dorsal Premotor Cortex: Cognitive-sensory control of behavior (Abe & Hanakawa, 2009)
289	20, -25, 1	Right Thalamus	Relay Station
273	5, 29, 20 -13, 33, 20	Bilateral Anterior Cingulate Cortex, BA32, rACC (Figure 32c)	Conflict Detection and Monitoring
245	-41, 9, -17	Left Enthorinal Cortex, BA34	Memory Formation & Learning
60	-45, -54, -11 43, -50, -10	Bilateral Fusiform, BA37	Face Recognition and Visual expertise (Gauthier et al., 1999)

(a)
(b)
(c)

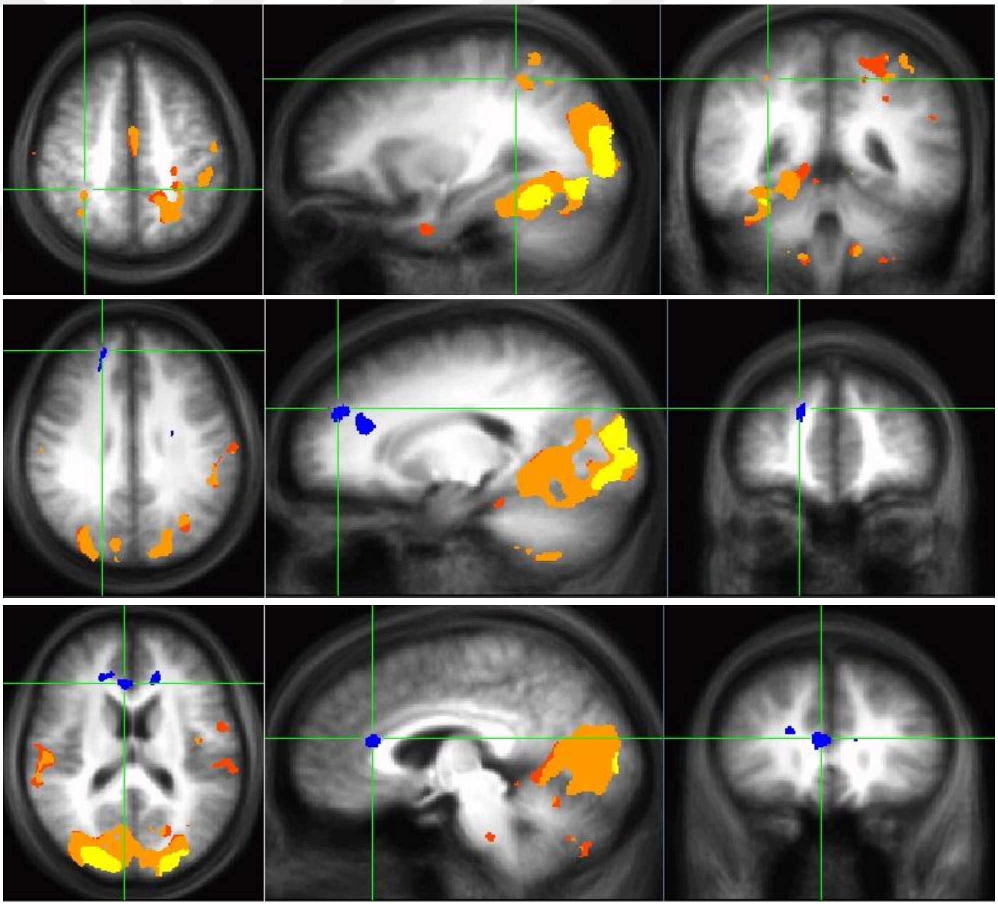


Figure 32: Significant main effect maps of controls towards incongruent negative cases.

Figure 32 depicts significant (a) bilateral precuneus, bilateral fusiform and left Middle Cingulate Gyrus activations, (b) Right Middle Frontal Gyrus and (c) right rACC deactivations in controls towards incongruent-negative cases.

These results demonstrate that controls' fusiform is hyperactive towards both of the congruent cases, whereas patients' fusiform is hyperactive while evaluating negative words, suggesting that patients are vigilant to process negative stimuli, which facilitates their performance towards these cases. This facilitation reflects itself behaviorally too, as reacting faster towards negative words in contrast to the control group, though they react faster towards positive words in contrast to negative ones. Thus, **H7 is verified**, at least with respect to word evaluation.

Whenever the patient group faces with a positive stimulus, either as a face or a word, their ventral attentional system gets hyperactive (especially perceived as frontal gyri, operculum and insula hyperactivities together). This might mean that positive stimuli trigger their VAN, because positivity constitutes an explicit goal for them. Moreover, their DAN (especially perceived as FEF and precuneus—being a crucial part of superior parietal lobe— hyperactivities) is especially triggered when they face a negative stimulus. On the other hand, controls' VAN is triggered for almost all cases, thus healthy group shows no bias towards negativity. Additionally control group does not show any VAN hyperactivity towards any case, and they even show FEF deactivation towards incongruent positive case, probably because they were trying to reorient their attention from the distractor negative face towards their positive target, a facilitator condition that they are used to process. These results mean that **Hypothesis 9 is verified**.

4.4.3. Within group congruency and valence differences

Congruent – Incongruent Differences within Patients

The regions indicated in bold are hyperactive in **incongruent** cases, plain black ones are hyperactive in congruent cases (Table 14 & 15).

Table 14: Significant clusters for incongruency subtracted from congruency for patients

No of Voxels	MNI Coordinate	Name of the Region	Processes for which the region activates
636	**11, -83, 7**	**Right Calcarine Gyrus (bilateral)**	**BA17, Primary Visual Cortex**
227	**28, 52, -3**	**Right Middle Frontal Gyrus**	**BA10, part of bottom-up attention mechanism, VAN (Corbetta et al., 2008), conflict and reward involving decision making (Rogers et al., 1999), cognitive integration, joint attention (Williams et al., 2005) → Central Executive of Baddeley's Working Memory Model**
199	-12, -19, 75	Left Precentral	BA6, Dorsal Premotor Cortex: Cognitive-sensory control of behavior (Abe & Hanakawa, 2009)
132	-0, 11, 7	Left Caudate	Goal-directed action, approach-attachment behavior, romantic love

Congruent – Incongruent Differences within Controls

Table 15: Significant clusters for incongruency subtracted from congruency for controls

No of Voxels	MNI Coordinate	Name of the Region	Processes for which the region activates
354	-21, -6, 37	Left Middle Cingulate Gyrus, BA32, dACC	Cognitive processing, attention, associated with valence
184	-24, -17, 56	Left Precentral, BA6	Dorsal Premotor Cortex: Cognitive-sensory control of behavior (Abe & Hanakawa, 2009)
90	22, -3, -6	Right Putamen	Category learning, feed-back processing in rule-based tasks working with pre-frontal
66	-28, 13, 44	Left Parahippocampal Gyrus	Identifying Visual and Social Context (Rankin et al., 2009)

Positive - Negative (words) Differences within Patients

The regions indicated in bold are hyperactive in **negative** words, plain black ones are hyperactive in positive words (Table 16 &17).

Table 16: Significant clusters for negative subtracted from positive words for patients

No of Voxels	MNI Coordinate	Name of the Region	Processes for which the region activates
379	**-29, -28, 66**	**Left Postcentral Gyrus**	**BA4, Primary Motor Cortex**
324	**-9, -72, 4 7, -71, 4**	**Bilateral lingual gyrus**	**BA18, Visual Association Area**
216	-13, 55, 11	Left Middle Frontal Gyrus	BA10, part of bottom-up attention mechanism, VAN (Corbetta et al., 2008), conflict and reward involving decision making (Rogers et al., 1999), cognitive integration, joint attention (Williams et al., 2005)
133	**-17, -52, -55**	**Left Cerebellum**	**Regulatory of both pos & neg, with behavioral consequences only for positive (Turner et al., 2007)**

Positive - Negative (words) Differences within Controls

Table 17: Significant clusters for negative subtracted from positive words for controls

No of Voxels	MNI Coordinate	Name of the Region	Processes for which the region activates
1554	**19, -46, 68**	**Right Precuneus, BA7**	**Self-Consciousness, Conscious information processing (Vogt & Laureys, 2005)**
115	19, -94, -19	Right lingual gyrus, BA18	Visual Association Area
95	32, -82, -24 -25, -69, -49	Bilateral Cerebellum	Regulatory of both pos & neg, with behavioral consequences only for positive (Turner et al., 2007)
88	-39, -69, -21	Right Inferior Occipital Gyrus, BA19	Visuo-spatial information processing, Face-Name Association, Visual Mental Imagery
71	**-15, -31, 73**	**Left Postcentral Gyrus, BA4**	**Primary Motor Cortex**

66	-14, 24, 38	Left FEF, BA8	Part of top-down attention mechanism, DAN (Corbetta, 2008), Executive Behavior Control, Memory retrieval, resolving uncertainty (Volz et al., 2004)
53	-8, -12, 12	Left Thalamus	Relay Station

These findings reveal that towards incongruent cases patients exhibited right calcarine and right MFG hyperactivities in contrast to congruent cases. Right MFG is crucial in reorienting attention from exogenous to endogenous, working like an orchestra chef between different attentional systems (Japee et al., 2015). Therefore patients can detect the conflict, but try to reorient their attention back towards their ruminative state, supporting Analytical Rumination Theory (Andrews & Thomson, 2009). Patients also exhibited lingual gyrus & cerebellum hyperactivity towards negative words, meaning that the brain regions mostly responsible for recognition and regulation of emotional words (Turner et al., 2007) are highly active for patients towards negative words; whereas controls exhibited hyperactivity in these same areas (cerebellum and lingual gyrus) towards positive cases only. Thus **Hypothesis 8 is verified**.

Furthermore, patients showed left MFG hyperactivity towards positive words. This region is part of VAN, which means that positive words triggered patients' exogenous attentional mechanism. Being different from their negative baseline, these positive words worked like distracters for the patients. Thus again, **H9 is verified**, this time via within group difference for the main effect of valence.

4.4.4. Within group happy and sad face differences

The regions indicated in bold are hyperactive towards **sad** faces; plain black ones are hyperactive towards happy faces (Table 18 &19).

Happy-Sad Face Differences within patients

Table 18: Significant clusters for sad subtracted from happy faces for patients

No of Voxels	MNI Coordinate	Name of the Region	Processes for which the region activates
1912	**39, 15, 50**	**Right FEF, BA8 (Figure 33a)**	**Part of top-down attention mechanism, DAN (Corbetta, 2008), Executive Behavior Control, Memory retrieval, resolving uncertainty (Volz et al., 2004)**
1479	**41, -53, 41**	**Right BA39, Angular Gyrus**	**Attentional reorientation in 3D space (Chen et al., 2012)**
372 **27**	**25, 4, 63** **-47, 6, 49**	**Bilateral Superior Frontal Cortex, BA6**	**Dorsal Premotor Cortex: Cognitive-sensory control of behavior (Abe & Hanakawa, 2009)**
106	**57, -44, -6**	**Right Fusiform, BA37 (Figure 33b)**	**Face Recognition and Visual expertise (Gauthier et al., 1999)**
93	**36, 37, 47**	**Right DLPFC, BA9**	**Suppressing sadness, working memory, processing emotions and self-reflection in decision making (Deppe et al., 2005), planning, error processing/detection (Chevrier et al., 2007)**
77	**12, -4, 18**	**Right Caudate**	**Goal-directed action, approach-attachment behavior, romantic love**
71	**31, 59, 0**	**Right Middle Frontal Gyrus, BA10**	**Part of bottom-up attention mechanism, VAN (Corbetta et al., 2008), conflict and reward involving decision making (Rogers et al., 1999), cognitive integration, joint attention (Williams et al., 2005)**
63	**55, 22, 19**	**Right Pars-Opercularis, BA44**	**Part of Broca's Area, phonological and syntactic processing, response suppression, word and face encoding (McDermott et al., 2003) Also part of**

			VAN (Corbetta, 2008)
28	**53, -2, -19**	**Right Middle Temporal Gyrus, BA21**	**Auditory processing & language**

(a)

(b)

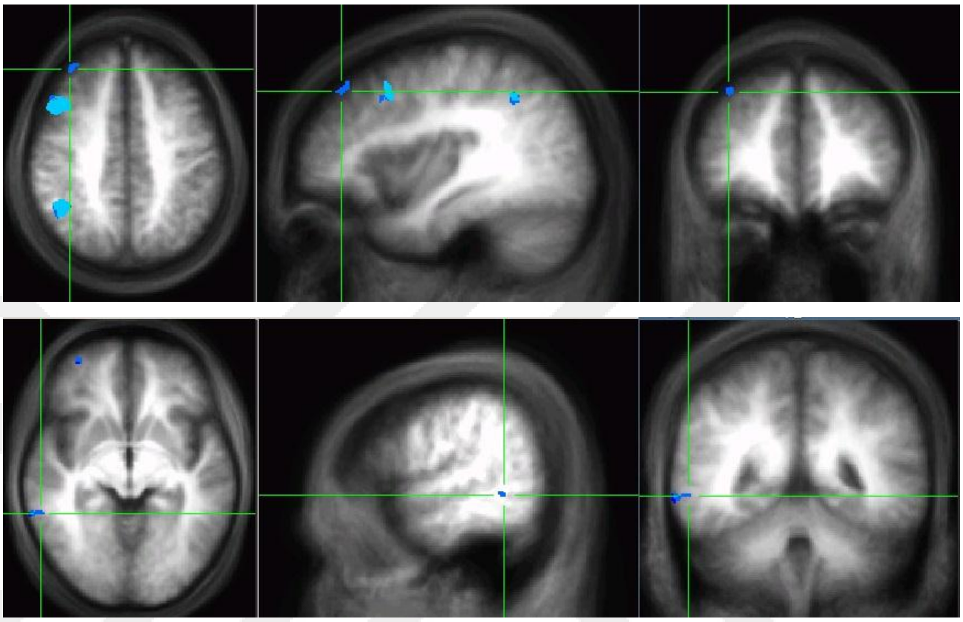


Figure 33 Significant activation differences between sad and happy faces within the depressed group

Depressed group exhibited higher cognitive control activations in regions such as right FEF, right superior frontal and right DLPFC, towards sad faces in contrast to happy faces (Figure 33a). Furthermore right Fusiform is also more active towards sad faces compared to happy faces (Figure 33b), as expected because patients are used to process negative stimuli. These results **verify Hypothesis 7** once more.

Happy-Sad Face Differences within controls

Table 19 Significant clusters for sad subtracted from happy faces for controls.

No of Voxels	MNI Coordinate	Name of the Region	Processes for which the region activates
136	60, -22, 9	Right BA41 (Figure 34a)	Primary Auditory Cortex
130	-8, -28, 54	Left BA5	Sensory Association Cortex
115 **39**	**-26, -40, 10** **19, -37, 17**	**Bilateral Caudate (Figure 34b)**	**Goal-directed action, approach-attachment behavior, romantic love**
75	-28, -45, -24	Left Cerebellum	Regulatory of both pos & neg, with behavioral consequences only for positive (Turner et al., 2007)
48	-59, -1, 3	Left Middle Frontal Gyrus, BA6	Cognitive-sensory control of behavior (Abe & Hanakawa, 2009)

(a)

(b)

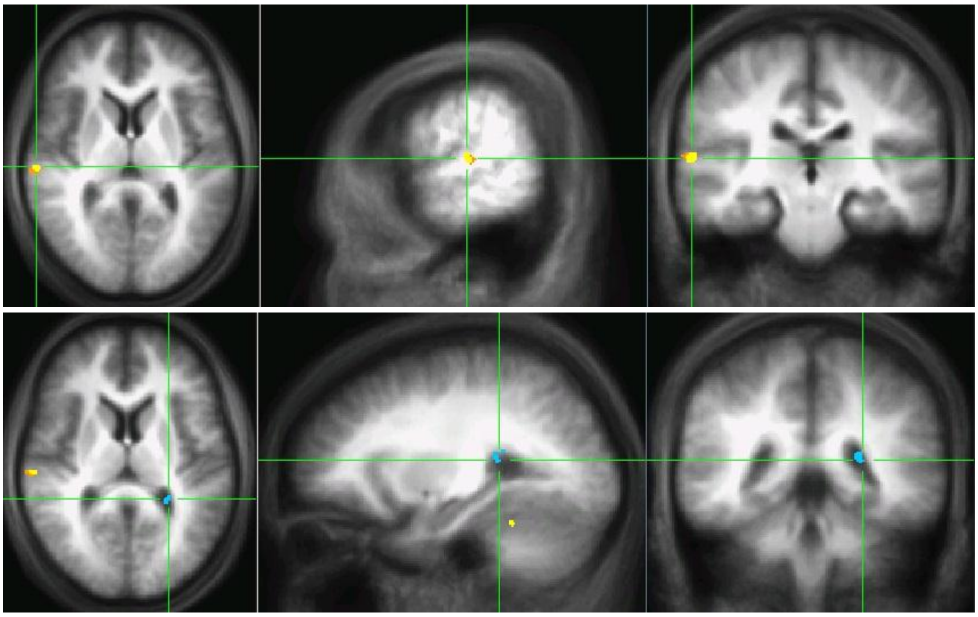


Figure 34 Significant activation differences between sad and happy faces within the control group

Healthy group exhibited higher right primary auditory cortex, left sensory association left cerebellum and left middle frontal gyrus activations towards happy faces in contrast to sad faces (Figure 34a), whereas they showed higher bilateral caudate activations towards sad faces in contrast to happy faces (Figure 34b).

The fact that patients mostly exhibit right hemisphere activity towards sad faces, whereas controls show mostly left hemisphere activity towards happy faces supports the theories of hemispheric lateralization of emotion (Harmon-Jones et al., 2010).

4.4.5. Between group differences with respect to congruent-positive, incongruent-positive, congruent-negative and incongruent-negative words

Depressed VS Control for Congruent-Positive

The voxel clusters that show significant activations are indicated in the Table 20, in which all activations indicated with **bold** are the regions where controls showed higher activity towards congruent-positive cases compared to controls, while in plain black, patients showed higher activations compared to controls.
Table 20: Significant clusters for DepCongPos VS ContCongPos

No of Voxels	MNI Coordinate	Name of the Region	Processes for which the region activates
108	**-16, 27, 33**	**Left FEF, BA8 (Figure 33)**	**Part of top-down attention mechanism, DAN (Corbetta, 2008), Executive Behavior Control, Memory retrieval, resolving uncertainty (Volz et al., 2004)**
95	54, 23, 33	Right Dorsolateral Prefrontal Cortex, BA9	Suppressing sadness, working memory, recognizing the emotions of others, planning, attention to positive emotions
73	-27, -83, -33	Left Cerebellum	Regulatory of both pos & neg, with behavioral consequences only for positive (Turner et al., 2007)
66	8, 21, 62	Right Superior Frontal Cortex, BA6	Dorsal Premotor Cortex: Cognitive-sensory control of behavior (Abe & Hanakawa, 2009)

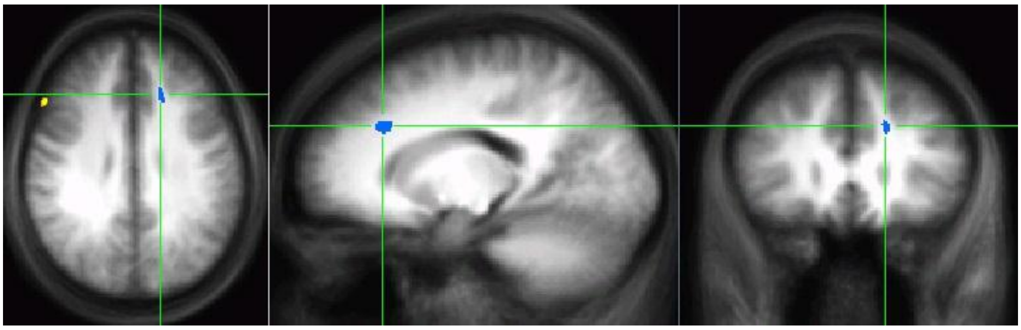


Figure 35: Significant group difference towards congruent positive case.

Control group showed higher left FEF activity towards congruent-positive cases in contrast to patients; whereas patients showed higher right DLPFC activation compared to control group (Figure 35). Controls used regions responsible for control, whereas patients used regions mostly responsible for emotion suppression and regulation.

Depressed VS Control for Congruent-Negative

The voxel clusters that show significant activations are indicated in the Table 21, where all activations are significantly higher for depressed group compared to healthy group towards congruent-negative cases.

Table 21: Significant clusters for DepCongNeg VS ContCongNeg

No of Voxels	**MNI Coordinate**	**Name of the Region**	**Processes for which the region activates**
876	6, 16, 59	Right Superior Frontal Cortex, BA6 (Figure 36a)	Dorsal Premotor Cortex: Cognitive-sensory control of behavior (Abe & Hanakawa, 2009)
337	52, 23, 34	Right Dorsolateral Prefrontal Cortex, BA9 (Figure 36b)	Suppressing sadness, working memory, recognizing the emotions of others, planning, attention to positive emotions
323	-58, -17, 24	Left Postcentral, BA1	Primary Sensory Cortex
188	41, -65, 2	Right Inferior Occipital Gyrus, BA19	Visuo-spatial information processing, Face-Name Association, Visual Mental Imagery
173	17, -66, -50	Right Cerebellum	Regulatory of both pos & neg, with behavioral consequences only for positive (Turner et al., 2007)
44	-23, -1, 8	Left Putamen (Figure 36c)	Encoding social rewards (lesions to GP is shown to cause anhedonia) (Miller et al., 2006)
36	-54, 10, 20	Left Pars Opercularis, BA44	Part of Broca's Area, phonological and syntactic processing, response suppression, word and face encoding (McDermott et al., 2003) Also part of VAN (Corbetta, 2008)
34	-48, -3, -35	Left Inferior Temporal Gyrus, BA20	Semantic processing, creativity
33	-7, -15, 9	Left Thalamus	Relay Station
22	39, 20, 1	Right Insula	Empathy, emotional self-awareness
18	57, -34, -8	Right Middle Temporal Gyrus	BA21, auditory processing

(a)

(b)

(c)

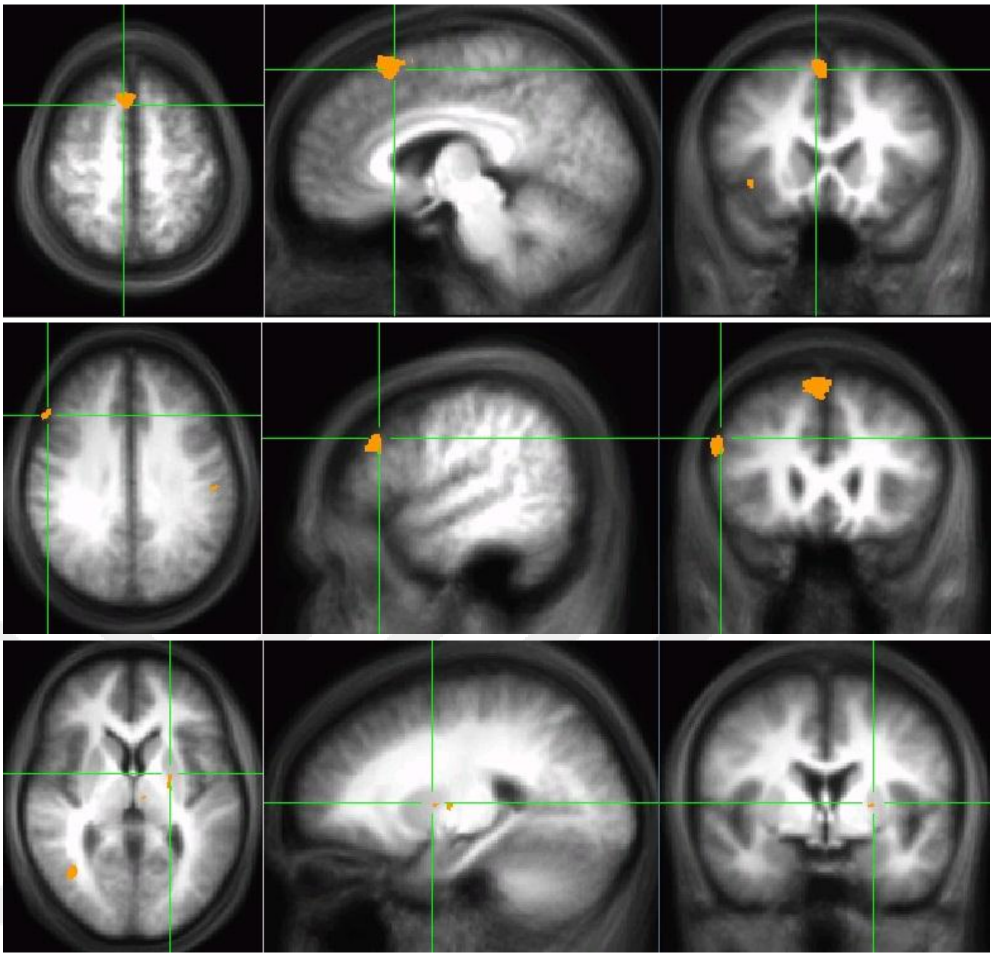


Figure 36: Significant group difference towards congruent negative case.

Depressed group showed right superior frontal cortex and right insula activations compared to control group towards congruent-negative cases (Figure 36a). They also showed high level cognitive control area activations, such as right DLPFC and right FEF, towards negative cases in contrast to controls (Figure 36b). Furthermore in a subcortical level too, patients exhibited higher left putamen, letf thalamus and right middle temporal activations compared to controls towards these cases (Figure 36c).

Towards these purely negative cases patients mostly exhibited right hemispheric activity in higher cortical areas, probably because of overtaxing and paying more attention towards these cases. Thus, emotional lateralization is again prominent. They also showed subcortical area activations known as responsible for a negatively biased emotion system (Diener et al., 2012). No region showed higher activity in controls in contrast to patients for this case.

Hypothesis 8 is verified according to these results.

Depressed VS Control for Incongruent-Positive

The voxel clusters that show significant activations are indicated in the Table 22, in which all activations indicated with **bold** are the regions where controls showed higher activity towards incongruent-positive cases compared to controls, while in plain black, patients showed higher activations compared to controls.

Table 22: Significant clusters for DepIncongPos VS ContIncongPos

No of Voxels	MNI Coordinate	Name of the Region	Processes for which the region activates
801	35, 9, 5	Right Insula & Claustrum (Figure 37a)	Empathy, emotional self-awareness
448	-52, 13, 38 54, 15, 38	Bilateral FEF, BA8	Part of top-down attention mechanism, DAN (Corbetta, 2008), Executive Behavior Control, Memory retrieval, resolving uncertainty (Volz et al., 2004)
334	54, 19, 34	Left Pars Opercularis, BA44	Part of Broca's Area, phonological and syntactic processing, response suppression, word and face encoding (McDermott et al., 2003) Also part of VAN (Corbetta, 2008)
241	-13, -83, -14	Left Lingual Gyrus, BA18	Visual Association Area
224	-58, -18, 26	Left Postcentral, BA1	Primary Sensory Cortex
202	6, 18, 58 -12, 18, 58	Bilateral Superior Frontal Cortex, BA6	Dorsal Premotor Cortex: Cognitive-sensory control of behavior (Abe & Hanakawa, 2009)
122	-18, 6, -10 19, 10, 1	Bilateral Putamen	Category learning, feed-back processing in rule-based tasks working with pre-frontal
52	-9, -23, 6 3, -20, -1	Bilateral Thalamus	Relay Station
35	18, -54, -17	Right Cerebellum	Regulatory of both pos & neg, with behavioral consequences only for positive (Turner et al., 2007)
20	-20, 54, 34	Left DLPFC, BA9 (Figure 37b)	Suppressing sadness, working memory, recognizing the emotions of others, planning, attention to positive emotions
15	**-45, -1, 2**	**Left Insula**	**Empathy, emotional self-awareness**

(a)

(b)

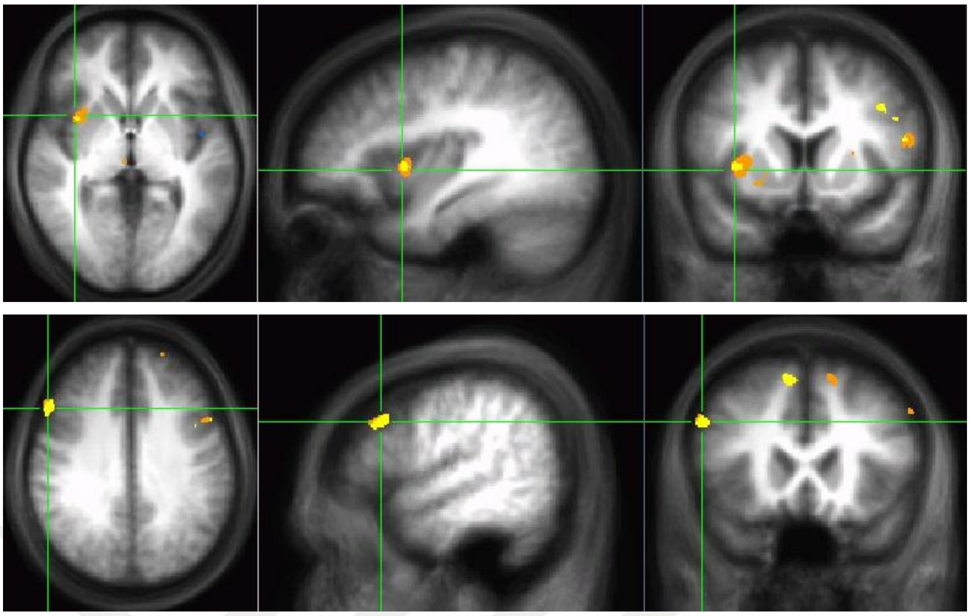


Figure 37: Significant group difference towards incongruent positive case.

Depressed group showed higher right insula & Claustrum, bilateral putamen, thalamus and left Pars opercularis activations compared to control group towards incongruent-positive cases; whereas controls showed higher left Insula activation (Figure 37a). Depressed group also showed higher left DLPFC and bilateral FEF activations in contrast to control group towards incongruent positive cases (Figure 37b). These results point to a more active cognitive control mechanism in patients, most probably caused by trying to disengage their attention that is stuck on the negative face towards the positive target. Again these results support Hypothesis 8.

Depressed VS Control for Incongruent-Negative

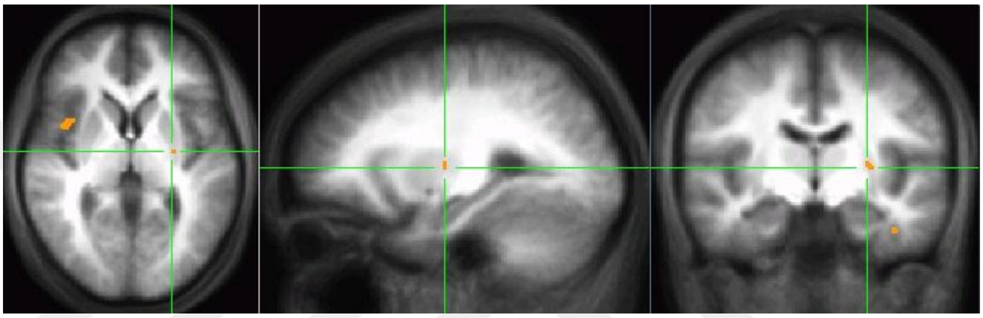
The voxel clusters that show significant activations are indicated in the Table 23, where all activations are significantly higher for depressed group compared to healthy group towards incongruent-negative cases.

Table 23: Significant clusters for DepIncongNeg VS ContIncongNeg

No of Voxels	MNI Coordinate	Name of the Region	Processes for which the region activates
402	54, 19, 34 -52, 17, 39	Bilateral FEF, BA8	Part of top-down attention mechanism, DAN (Corbetta, 2008), Executive Behavior Control, Memory retrieval, resolving uncertainty (Volz et al., 2004)
212	40, 9, 6	Right Insula	Empathy, emotional self-awareness
119	17, 12, -0 -27, -11, 7	Bilateral Putamen (Figure 38a)	Category learning, feed-back processing in rule-based tasks working with pre-frontal
43	51, 20, -4	Right Inferior Frontal Gyrus, BA47	Orbitofrontal Cortex, Behavioral and motor inhibition, (Vollm et al., 2006 and Del-Ben et al., 2005); adverse emotional inhibition (Berthoz, 2002), conflict involving decision making (Rogers et al., 1999)
41	34, 51, -3	Right Middle Frontal Gyrus, BA10 (Figure 38b)	Part of bottom-up attention mechanism, VAN (Corbetta et al., 2008), conflict and reward involving decision making (Rogers et al., 1999), cognitive integration, joint attention (Williams et al., 2005)
22	-38, -9, -28	Left Fusiform Gyrus, BA37	Face Recognition and Visual expertise (Gauthier et al., 1999)

21	64, -16, -18	Right Middle Temporal Gyrus, BA21	Auditory processing & language
17	53, 18, -1	Right Pars Opercularis, BA44	Part of Broca's Area, phonological and syntactic processing, response suppression, word and face encoding (McDermott et al., 2003) Also part of VAN (Corbetta, 2008)
15	-5, -3, 1	Left Thalamus	Relay Station

(a)



(b)

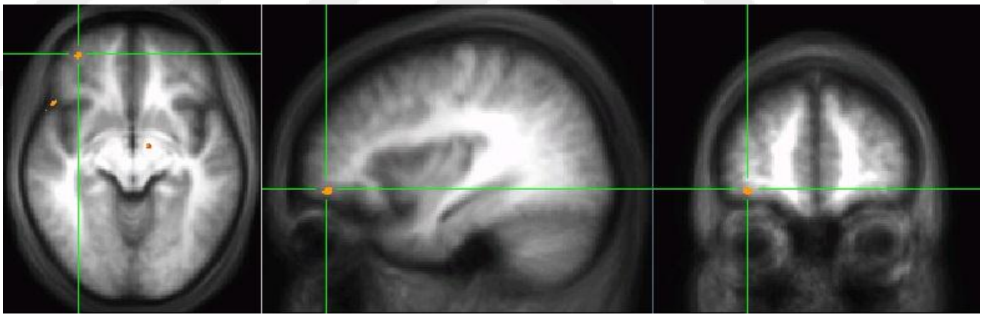


Figure 38: Significant group difference towards incongruent negative case.

Depressed group showed higher right insula, bilateral putamen and left Fusiform activations in contrast to control group towards incongruent-negative cases (Figure 38a). They also showed higher right Middle Frontal Gyrus, rigth Inferior frontal gyrus and left Thalamus activations compared to control group towards these cases (Figure 38b).

Right MGF works in reorienting attention from exogenous to endogenous stimuli, thus from positive face to negative target. Not much cognitive control and suppression is observed (no significant right DLPFC & superior frontal activation differences towards this case) probbaly because the positive face does not attract much attention as a negative face for patients. Therefore, this highly working negatively biased cognitive control mechanism might be responsible for the fact that patients behave faster towards these cases compared to controls, again verifying Hypothesis 8.

4.4.5. Between group differences with respect to happy and sad faces

<u>Depressed VS Control towards happy faces</u>

The voxel clusters that show significant activations are indicated in the Table 24, where all activations are significantly higher for depressed group compared to healthy group for happy faces.

Table 24: Significant clusters for happy faces

No of Voxels	MNI Coordinate	Name of the Region	Processes for which the region activates
316	-51, 21, 31	Left Dorsolateral Prefrontal Cortex, BA9 (Figure 39a)	Suppressing sadness, working memory, processing emotions and self-reflection in decision making (Deppe et al., 2005), planning, error processing/detection (Chevrier et al., 2007)
203	-20, -75, -15	Left Lingual Gyrus, BA18 (Figure 39b)	Visual Association Area
181	11, 28, 53	Right FEF, BA8 (Figure 39c)	Part of top-down attention mechanism, DAN (Corbetta, 2008), Executive Behavior Control, Memory retrieval, resolving uncertainty (Volz et al., 2004)
90	54, 23, 0	Right Pars Triangularis, BA45	Semantic processing
82	38, 13, 0	Right Insula	Empathy, emotional self-awareness
23	37, 26, -23	Right Pars Orbitalis, BA47	Orbitofrontal Cortex, Behavioral and motor inhibition, (Vollm et al., 2006 and Del-Ben et al., 2005); adverse emotional inhibition (Berthoz, 2002), conflict involving decision making (Rogers et al., 1999)
18	-37, -8, -25	Left Parahippocampal Gyrus	Identifying Visual and Social Context (Rankin et al., 2009)

(a)

(b)

(c)

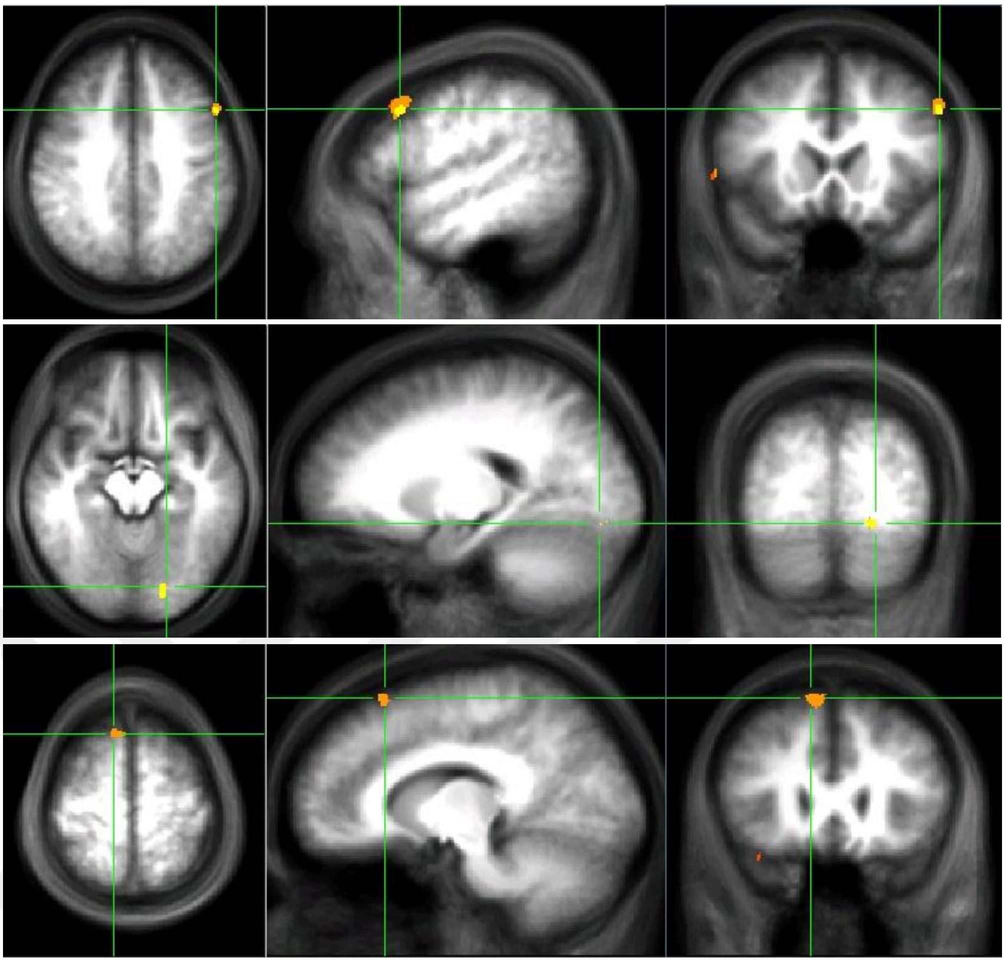


Figure 39: Significant group difference towards happy faces.

Compared to the control group, depressed group showed higher left DLPFC (Figure 39a), left lingual gyrus (Figure 39b), right FEF and right Pars Orbitalis activations (Figure 39c).

Depressed VS Control towards sad faces

The voxel clusters that show significant activations are indicated in the Table 25, where all activations are significantly higher for depressed group compared to healthy group towards sad faces.

Table 25: Significant clusters for sad faces

No of Voxels	MNI Coordinate	Name of the Region	Processes for which the region activates
2774	6, 22, 46	Right FEF, BA8 (Figure 40a)	Part of top-down attention mechanism, DAN (Corbetta, 2008), Executive Behavior Control, Memory retrieval, resolving uncertainty (Volz et al., 2004)
535	-6, -11, 4 5, -11, 4	Bilateral Thalamus	Relay Station
525	-23, -72, -14	Left Lingual Gyrus, BA18	Visual Association Area
421	35, 13, -1 33, 13, -1	Bilateral Insula	Empathy, emotional self-awareness
271	-45, 13, 23	Left Pars Opercularis, BA44	Part of Broca's Area, phonological and syntactic processing, response suppression, word and face encoding (McDermott et al., 2003) Also part of VAN (Corbetta, 2008)
259	-57, -11, 19	Left Postcentral Gyrus, BA4	Primary Motor Cortex
231	54, 23, -1	Right Pars Triangularis, BA45	Semantic processing
144	53, 25, 25	Right DLPFC, BA9 (Figure 40b)	Suppressing sadness, working memory, processing emotions and self-reflection in decision making (Deppe et al., 2005), planning, error processing/detection (Chevrier et al., 2007)
122	-23, 8, 5 21, 8, 5	Bilateral putamen	Category learning, feed-back processing in rule-based tasks working with pre-frontal
72	-4, 8, 62 3, 8, 62	Bilateral Superior Frontal Cortex, BA6	Dorsal Premotor Cortex: Cognitive-sensory control of behavior (Abe & Hanakawa, 2009)
49	-30, -59, -16	Left Fusiform,	Visual expertise (Gauthier et al., 1999)

		BA37 (Figure 40c)	
25	38, 29, -22	Right Pars Orbitalis, BA47	Orbitofrontal Cortex, Behavioral and motor inhibition, (Vollm et al., 2006 and Del-Ben et al., 2005); adverse emotional inhibition (Berthoz, 2002), conflict involving decision making (Rogers et al., 1999)
23	-43, -6, -32	Left Inferior Temporal Gyrus, BA20	Semantic processing, creativity

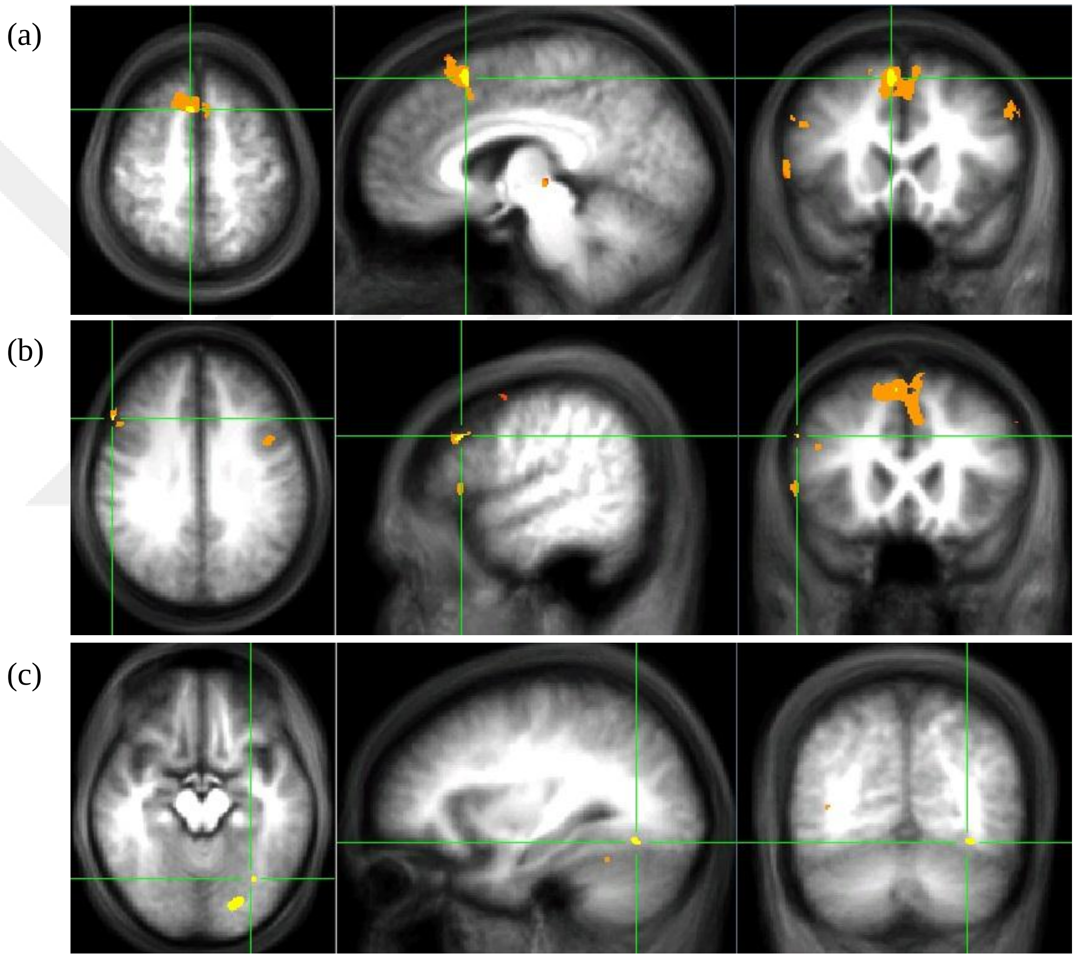


Figure 40: Significant group difference towards sad faces.

Depressed group showed higher right FEF activations towards sad faces, even covering some parts of BA32, dorso-rostral ACC, which all are activated stronger than same region activations towards happy faces (Figure 40a). Depressed group also showed higher right DLPFC activation than control group towards sad faces, yet lower than the activations towards happy faces (Figure 40b). Additionally patients exhibited higher Fusiform activations compared to controls towards sad faces, besides showing more activations in lingual gyrus compared the activations towards positive faces (Figure 40c).

All these findings again support Hypotheses 7 and 8, pointing out to a negatively skewed attention mechanism in depressed individuals.

CHAPTER 5

DISCUSSION

The main aim of this dissertation was to propose a new way of understanding of depression that is based on a negatively biased attentional relocation. The results of this study backed up our hypotheses, which additionally support theories depending on networking of the human cognition, and thus the human brain.

5.1. Behavioral Analysis

The behavioral analysis for the Classical Stroop Task replicated the earlier studies with respect to the results obtained from reaction time analyses (Markela-Lerenc et al., 2006; Gohier et al., 2009), revealing that all participants were faster towards the case where they were expected to read the color names. In addition, all of them were significantly slower towards the interference case, where they were expected to exclaim the colors of the words that did not match with the written color name. There is no group difference with respect to reaction times, which is not compatible with the literature. The reason might be the medication status of the patients, because the studies finding group differences in classical Stroop performance recruited patients who are already on medication (Markela-Lerenc et al., 2006; Gohier et al., 2009). Our participant group was unmedicated, so this might have led them to perform as well as controls. On the other hand, with respect to correct response rates, although all participants made the least error towards word reading case and the most error towards the interference case, the significant interaction between stroop effect, depression and gender indicate that there is a performance difference towards the interference case. It means that depressed women performed better than healthy ones, whereas depressed men performed worse than healthy men. Thus, in a purely cognitive context, depression might not be causing an attentional deficit, especially for women, and apparently could even ameliorate attentional mechanisms depending on the context. Previous studies that conducted classical Stroop with patients that are mentioned in this dissertation (Markela-Lerenc et al., 2006; Gohier et al., 2009; Kikuchi et al., 2012) were not as controlled as this study (i.e. my patient group consists of medication- & therapy-free highly depressed individuals). Therefore, medication status changes the results immensely, probably because the antidepressants modulate not only the emotional percept, but also the attentional mechanism, which are closely linked as I previously mentioned in the literature review.

Subject-based behavioral analysis of the Word-Face Stroop Task (WFS) revealed that all participants exhibited the interference effect, i.e. they reacted significantly slower towards incongruent cases than congruent cases; and positive-negative asymmetry effect, i.e. they were all faster towards positive cases, which are both compatible with previous literature (Stenberg et al., 1998; Haas et al., 2006; Etkin et al., 2006; Başgöze, 2008 & 2015; Egner, 2008; Zhu et al., 2010; Hu et al., 2012; Strand et al., 2013; Chechko et al., 2013). Moreover, the marginally significant interaction found between valence and depression points to the fact that patients reacted to negative words faster than healthy group, whereas healthy participants reacted faster towards positive words compared to depressed individuals. As for the correct response rates, all participants made more errors evaluating the incongruent cases and negative cases compared to congruent and positive ones, regardless of the group to which they belong. No significant group or gender difference was found with respect to correct response rates in WFS task. Apparently, when emotions are involved, group and gender differences disappear, probably because differently skewed attentional mechanisms (positively skewed in controls, negatively skewed in patients no matter the gender is) might be canceling each other out.

The item-based analysis, where the number of items in experimental conditions is higher than the number of subjects, is also conducted to strengthen the statistical power of the analyses. With this item-wise analysis, positive-negative asymmetry effect got even stronger again with a positive bias; and the interaction between group and valence has turned to be $p=0.001$-significant, again pointing to the fact that although patients and controls' reaction times did not differ towards positive words, patients were faster towards negative words compared to controls. As for the correct response rates, the group difference was significant: Healthy group had higher correct response rates in contrast to the patients. Again a group-valence interaction is found, revealing that healthy individuals responded to positive cases more correctly than patients; but two groups did not differ as much while responding to negative cases. Hence, patients were responding faster towards negative cases compared to controls; but they do not make more mistakes because they are faster, supporting the ideas that depressed patients have an attention bias towards negative case (Joorman and Gotlib, 2007: Epp, et al., 2012) and that they even display better performances towards negative stimuli (Erickson et al., 2005; Karparova et al., 2007, Fritzsche et al., 2010). Therefore, one might claim that they become negativity 'experts', meaning that they are used to process negative cases, which in turn facilitates the processing of this type of stimuli. Since they are over-attentive to the negative stimuli as proposed by the aforementioned studies, they might seem as if they have problems in processing positive stimuli, just as we can see from our behavioral results (patients react to positive words not so worse than healthy group; but they make more mistakes than controls); however, this case might also be caused by their intense attention towards negative words rather than a problem processing the positive words.

The significant main effect of congruency disappeared in the item-based analysis, possibly because incongruent cases appear to have a tendency to be evaluated faster by depressed individuals in contrast to healthy individuals (Figure 20), which was expected based on our previous studies (Başgöze, 2008; Başgöze et al., 2015). The differential response of depressed individuals towards incongruent situations seems to depend on the nature of interference: If the interference occurs at the cognitive level, as in the Classical Stroop Task, the patients react with a similar speed compared to healthy controls; by contrast if the interference occurs at the emotional level, the patients start to show a tendency to react differently than controls, based on their negativity preference, which makes the congruency effect disappear, especially when the statistical power is strengthened with an analysis such as item-based. Still, this does not explain why there is no interaction. Therefore this investigation is akin to be repeated with a larger subject pool.

Correlation analysis revealed no significant correlation between the HAM-D scores and the congruency scores of the patients. The size and the variance of the patient group might have limited the chances to capture such a correlation. Since only 16 patients could be included in the analyses, and that their levels of depression do not vary considerably (Mean HAM-D score: 22.88±3.3), the probability of finding a significant correlation drastically diminishes. In the future, the task must be conducted to more patients with various levels of depression (in a scale varying from mild to major depression).

To sum up, three of our hypotheses about behavioral analyses are supported: Hypotheses 2, 3 and 4. Hypothesis 2 claims that patients react with a similar speed to healthy group in a purely cognitive interference task, demonstrating that patients have no specific cognitive deficit. Hypothesis 3 and 4 assert that although patients show the positive-negative asymmetry effect, when compared to controls, they react faster towards negative stimuli and perform just as well. These findings support the idea that patients have no specific emotional or cognitive deficits, rather they have a differently allocated attention, favoring the negative cases.

5.2. fMRI Analysis

fMRI analyses showed that two groups differed significantly in reacting to congruency and valence factors with respect to brain functioning; but first I will interpret the differences in mean activation maps of depressed and healthy groups with respect to congruent-positive, congruent-negative, incongruent-positive and incongruent-negative cases.

5.2.1. Mean Activation Maps for congruent-positive, congruent-negative, incongruent-positive and incongruent-negative cases

Mean activation maps cannot directly lead to a conclusion about the differences between the groups or the cases, because they are not results of any subtractive analysis; rather they manifest the general pattern of how the brain reacts to our WFS task. This way we can make sure our WFS task generates activities in areas relevant to the behavioral, cognitive and emotional expectancies of this task, relevant to the literature.

The areas that show task-relevant significant activations towards almost all of the cases are: (1) Bilateral Middle Occipital Gyrus (BA18) and bilateral Primary Visual Cortex (BA17), (2) bilateral Precentral Gyrus (BA6), (3) bilateral Postcentral Gyrus (BA1), (4) bilateral Cerebellum, (5) bilateral Thalamus, (6) bilateral Inferior Frontal Gyrus (Pars Opercularis (BA44), Pars Orbitalis (BA47)), (7) bilateral Precuneus (BA7, part of superior parietal lobule), (8) bilateral Insula, and (9) bilateral Cingulate gyrus. These areas were expected to show significant activities in the face of our WFS task, since they are continuously shown to process (1) general visual processing, visual association (participants perceive and interpret words superimposed on faces), (2) cognitive-sensory control of behavior (they make a decision appropriate to their aims and experiences, and then push a button accordingly), (3) somatosensory stimuli (they respond in line with their decision making via touching the buttons), (4) emotional material on a valence axis (they evaluate emotionally loaded words as positive and negative), (5) as a relay station between the cerebral cortex and the limbic structures (transmitting the alarming emotional information coming from limbic system to the neocortex and vice versa to provide control and regulation), (6) word and face encoding, phonological and syntactic properties of the words and then suppress the response when needed (participants evaluate words appearing on faces), (7) conscious information and self-consciousness (participants are awake in order to conduct the task and most importantly they are aware of what is going on) (McDermott et al., 2003; Vogt & Laureys, 2005; Turner et al., 2007; Abe & Hanakawa, 2009), (8) emotional biases and self-awareness, and (9) conflict detection and valence-based attention (they try to resolve emotional conflicts).

I will now comment on some of the regions in detail, which are worth mentioning; but I will delve into the actual discussion later when inquiring about the fMRI group ANOVA results.

Cingulate Gyrus shows task relevant significant activations in all cases both for patients and controls. However, different subsections of this region get activated or deactivated depending on the condition and on the group. For example, towards all cases, except the incongruent positive case, patients showed hyperactivity in left dorsal ACC (BA24), which is also known as the cognitive part of ACC; whereas they showed deactivation in left rostral ACC (BA32), which is also known as the emotional part of ACC. Towards incongruent positive case, they kept showing rACC deactivation, yet did not demonstrate any dACC hyperactivity. Controls, however, showed dACC hyperactivity towards all cases except the congruent negative case; and they showed rACC deactivation only towards incongruent negative case.

Decrease in the emotional rACC activity is mostly linked with increase in the cognitive dACC activity (Davis et al., 2005). Therefore, deactivation of rACC and hyperactivity of dACC that is perceived simultaneously in patients might be an indication of a hypervigilance in patients' attentional system, which shuts down the rACC more than necessary. Therefore, these findings are compatible with the studies claiming a presence of differential activation patterns within cingulate gyrus in patients, as mentioned in Chapter 2 (Whalen et al., 1999; Bush et al., 2000), and with the findings that there is a difference in the roles of rostral, dorsal and pregenual ACC (Mayberg et al., 2003; Schlösser et al., 2008). However, it is not safe to assert that ACC "fails" to show hyperactivity or show deactivation as most of the studies mentioned in the Chapter 2 do. It is crucial to emphasize that different sub-compartments of ACC have different roles in patients and in controls. These results also supported the claim that dACC is not only crucial in resolving cognitive conflicts, but also in resolving emotional conflicts as well, as stated by Shackman et al. (2011). The findings about the failure of deactivating rACC in patients was also not the case with this study as Wagner et al., 2008 and Schlösser et al., 2008 claimed. The difference between those studies and this one is that they did not conduct an emotional Stroop to their patient group. Therefore, emotional content might be drastically changing how ACC react to conflicts. Our results seem to be more compatible with Mitterschiffthaler et al.'s (2008), since that study also used an emotional Stroop paradigm. These findings verified Hypothesis 6, which aimed to replicate previous studies on the relation between ACC and MDD, showing the differential activations within ACC subsections depending on the content of the conflicts to be resolved.

Furthermore, while evaluating negative words (towards congruent negative and incongruent negative cases), patients' brains got overactive in an area called **Gyrus Rectus,** where face-name associations and reward-involving decision making is processed (Rogers, 1999; Herholz, 2001). This area is closely connected with Orbitofrontal Gyrus and pregenual ACC, where Mayberg et al. conduct deep brain stimulation to refractory depression patients via electronically lessening the hyperactivity of this area (2003).

Right Middle Frontal Gyrus (BA10) is shown to be hyperactive in patients towards congruent negative and incongruent negative cases, when patients try to evaluate negative words. However, same region gets deactive in controls towards congruent positive and congruent negative cases, which are all congruent cases. This difference might be reflecting the fact that as long as the target of the patients is negative, the faces do not comprise a distraction for the patients, therefore making patients faster towards the evaluation of the negative words as found in behavioral analyses. Middle Frontal Gyrus will be discussed further in the next sections.

Dorsolateral Prefrontal Cortex (DLPFC) shows task-relevant activation for our patient group only towards incongruent cases; whereas control group only shows deactivation of right DLPFC towards congruent-positive case. The hyperactivity of right DLPFC in patients is always accompanied by deactivation of rACC. In the literature, the fact that a brain region gets hyperactive whereas another region gets deactive is usually interpreted as reflecting a selective attentional processing which causes one part to be suppressed whereas other one works hard on the selection of attentional direction (Drevets et al., 1995). Therefore, the hyperactivity of right DLPFC and deactivation of left rACC in patients might be an indication of an attentional process selectively working on incongruent cases more than a healthy individual. This hypoactivity in rACC is mostly related to mood congruent bias and impaired cognitive control in the literature (Diener et al., 2012). However, when patients are totally medication-free as in this study, to compensate for this bias, other cognitive control mechanisms help this biased system via showing itself as hyperactivities in right DLPFC. Therefore there appear to be no group differences towards incongruent cases in the behavioral analyses. Not only right DLPFC but also **right Inferior Frontal Lobes** (Pars Opercularis (BA44), working on response suppression, and Pars Orbitalis (BA47), working on behavioral, motor and emotional inhibition) (Rogers et al., 1999; Berthoz, 2002; Del-Ben et al., 2005; Vollm et al., 2006) help resolving the conflicts via showing hyperactivities in the patient group.

DLPFC is going to be discussed in more detail, in the next section where group differences are presented.

Putamen is found to be active for all the cases in the patient group bilaterally; however, for the healthy group, left putamen seems to be active only for the congruent-positive case. In contrast, **Caudate** did not show any task-relevant activation in the patient group, and demonstrated task-relevant activity only in the healthy group towards congruent cases. Putamen and Caudate have recently been shown to regulate different kinds of action control mechanisms. A meta-analysis study mentioned in the background pinpoints the importance of putamen and caudate in depression (Diener et al., 2012). However, there is no study that could clarify exactly in what way the differences in activations of Putamen and Caudate might be crucial for patients. Putamen is mostly found to be responsible for habituated actions toward stimuli, which are not rewarding anymore; whereas caudate is mostly responsible for goal-directed actions toward stimuli, which still might be rewarding (de Wit et al., 2012). Some studies have shown Putamen having less gray matter volumes in patients (Husain et al., 1991) and some have shown it has increased free radical producing enzyme activity in depressed individuals (Michel et al., 2010). Our results line up with researches that found Caudate volume and blood flow decrease in depressed individuals (Baxter et al., 1985; Drevets et al., 1992; Krishnan et al., 1992; Baumann et al., 1999 in Drevets, 2000).

Parahippocampal gyrus is a structure well-known from its role in formation of explicit memory for many years (Scoville & Milner, 1957). Both of the groups showed task-relevant parahippocampal region or hippocampus activations towards all cases. In contrast, the control group failed to show hippocampus activation towards incongruent positive case only.

Fusiform Gyrus is an area of the brain which is mostly known to be the face recognition area. However, recent studies showed that this region is actually an ‘expertise’ area, and it was thought to be a face recognition area for many years only because human beings are human face experts (Gauthier et al., 1999; Bilalić, Grottenthaler, Nägele, and Lindig, 2014). Only while evaluating negative words (towards congruent negative and incongruent negative cases) patients showed fusiform activity; whereas healthy group showed fusiform activity for all of the cases. This case is also compatible with the behavioral finding that patients were faster in evaluating the negative words (not compared to positive words, but compared to control group), and were as correct as the controls; because they are oriented in processing negative stimuli, which facilitates further processing and evaluation of this kind of emotional stimulus. This claim is also supported by both within and between face analyses: Patients showed more activity in Fusiform in contrast to controls towards sad faces, and they displayed more activity in Fusiform towards sad faces in contrast to happy faces. No such Fusiform hyperactivity is found in patients towards happy faces, and no such differences are found in the control group. These findings verify Hypothesis 7, asserting that higher Fusiform activations might be associated with an "expertise" in negativity, i.e. an automatization towards negative cases caused by habituation of processing negative stimuli, which in turn facilitates the evaluation of them.

5.2.2. Congruency and Valence Differences within Groups

The differences stated in this sub-section are only between congruent and incongruent cases; as well as between positive and negative word evaluations within the patient and healthy groups, separately. Therefore, these do not show any significant group differences; but only show differences between the two main factors of WFS task within a group.

Patients show Right Calcarine and Right Middle Frontal Gyrus hyperactivation towards incongruent cases compared to congruent cases. Right Middle Frontal Gyrus, although it was first thought to be a part of Ventral Attentional Network (VAN), has recently been demonstrated to have a crucial role in reorient the attention from exogenous (bottom-up) to endogenous (top-down) (Japee et al., 2015). This means that, when faced with an incongruent case, patients, though they detect the conflict, immediately reorient their attention from the conflict towards their own endogenous ruminative state. This result supports the Analytical Rumination theory, which asserts that patients always try to focus on their own problems, thus does not get much influenced from stimuli that are irrelevant to their own negatively biased ruminative state. In contrast, controls did not show any attentional mechanism hyperactivities towards incongruent cases.

While evaluating positive words, patients showed higher Left Middle Frontal Gyrus activation (left MFG is not the same as right MFG, it is just a part of VAN) (Japee et al., 2015), meaning that positive words worked more like distracters for patients, making their Ventral Attentional Network hyperactive, as if the positive words were not the targets, and triggered their exogenous attention system. For the controls, on the contrary, positive word evaluation triggered the dorsal attentional network (DAN), which made their endogenous attention system more hyperactively. This differential patterning of the attentional systems of the patients and the controls would enlighten the behavioral differences two groups showed, reflected as group-valence interactions. The areas that are found to be hyperactive towards evaluating negative words support my hypothesis that patients start to react to negative cases more automatically than positive cases, which is not the case for controls. Both cerebellum and lingual gyrus are mostly found active during regulation and recognition of emotional words (Turner et al., 2007). Therefore, the lingual gyrus and the cerebellum got hyperactive towards negative words in patients, whereas these same regions got hyperactive towards positive words in controls; as if those are the type of words they are used to process quickly and easily. These findings verify Hypothesis 8, asserting higher control, regulation and attention towards negative cases; and Hypothesis 9, asserting the existence of a close link between attention networks and depression.

5.2.3. Between and Within Group Differences towards face expressions

The analysis comparing two groups' brain activations towards happy and sad face expressions revealed that patients' brain regions involved in cognitive control (Kaiser et al., 2015; Japee et al., 2015) (such as right DLPFC, Pars Opercularis (BA44), Primary Motor Cortex (BA4), Superior frontal gyrus (BA6)) were significantly hyperactive towards sad faces in contrast to controls, reflecting over-attending and ruminating when faced with these cases. Furthermore, these regions are also recently claimed to be parts of the cognitive connection network (CCN), which is comprised by closely and significantly connected specific areas particularly in depressed individuals' brains (Shen et al., 2015). Although Shen et al. interpreted this highly connected network as a disrupted mechanism in depressed population (2015), these areas might have been connected more tightly than controls because patients' allocation of attention, and interpretation of emotions are constructed differently, displaying a bias towards negativity. Additionally right FEF is also more active in patients towards sad faces in contrast to controls, supporting my hypothesis

By contrast, towards happy faces, left DLPFC, Pars Triangularis, Pars Orbitalis and left parahippocampal hyperactivities were found in patients in contrast to controls. These findings are compatible with the findings regarding DLPFC lateralization by Grimm et al. (2008), asserting that left DLPFC is mostly activated for emotion perception, whereas right DLPFC is mostly responsible for attending to emotional stimuli. Furthermore these findings also support the frontal lateralization of emotion processing, right being more active towards negativity, and left being more active towards positivity (Harmon-Jones et al., 2010).

Within group face analyses exhibited support for emotional lateralization, overtaxing in negativity, and importance of fusiform gyrus in facilitation of negative stimuli processing, thus verifying Hypotheses 7 and 8. Within the patient group, sad faces highly activated following regions in contrast to happy faces: Right FEF, right angular gyrus, right DLPFC, right Fusiform, right superior frontal gyrus, right caudate, right middle MFG, right operculum, and right middle temporal gyrus. No area showed hyperactivity towards happy faces in contrast to sad faces within the patient group. Additionally all areas that show hyperactivity towards sad faces are on the right hemisphere. Especially, FEF, angular gyrus, and MFG point out to an attention reorientation towards sadness, whereas DLPFC and superior frontal hyperactivities point out to overtaxing to over-control sadness. Plus, right caudate hyperactivity might be pointing out to a goal-directed behavior, implicitly directed to negativity.

Within the control group, on the other hand, mostly left hemispheric (such as left BA6, left BA5 and left cerebellum) hyperactivity is found towards happy faces.

5.2.4. Group Differences towards 4 main factors of WFS

Interpreting the results of the fMRI analyses in this task merely by commenting on the activation differences towards words or towards faces is not adequate, because the participants always encounter with words and faces together, and try to evaluate the words whilst distracted by faces. Therefore, the way the faces comprise a distraction and the way the words are evaluated vary drastically for the patient group and the healthy group. For instance, sometimes patients do not get distracted by positive faces as much as healthy participants do (e.g. in incongruent negative case) or they get distracted (or attend to) more than controls by negative faces (e.g. in incongruent positive case). This is why examining the activation differences of these two groups towards four main factors (congruent positive, congruent negative, incongruent positive and incongruent negative) of WFS is necessary. In order to make it easier to pursue (and compare) participants' behavioral results towards these four cases, the reaction times and correct response rates are indicated in column charts below (Figure 41).

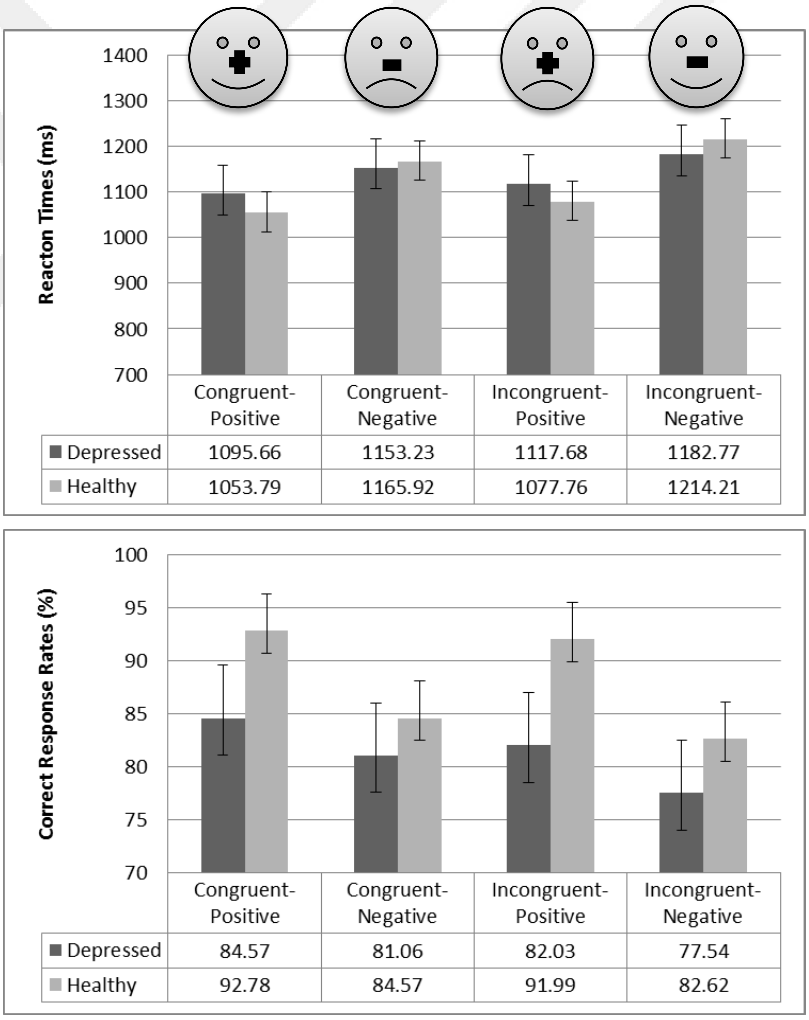


Figure 41: Behavioral results with respect to reaction times (top) and correct response rates (bottom)

Group differences mainly point out that, in contrast to controls, patients show significantly more activation bilaterally in the Frontal Eye Field (FEF) and in the right DLPFC for almost all conditions. These are both crucial members of regulatory/control system of the brain, working especially on planning, decision making, cognitive integration, working memory, processing emotion, and attention (Fincham et al., 2002; Zhang et al., 2003; Deppe et al., 2005; Williams et al., 2005; Nakai et al., 2005). Furthermore, especially FEF is an important part of the Dorsal Attentional Network that provides attention to be oriented top-down. Thus, patients seem to be prone to overthink about and thus over-control the situation, especially if the case they face is negative, from which they are troubled to disengage their attention.

Towards **congruent-positive** cases, where the words and the faces are both positive, patients showed higher right DLPFC, left cerebellum and right Superior Frontal Gyrus (SFG) activations in contrast to controls; whereas controls showed hyperactivities in left FEF (BA8). Frontal Eye Field (FEF) is an important part of the Dorsal Attention Network (DAN), providing particularly a top-down control over visual cortex (Corbetta et al., 2008; Japee et al., 2015). Apparently, these purely positive cases lead to top-down attention processing in controls more than patients. Instead right DLPFC and SFG activations were higher in patients to process successfully these positively valenced cases. These areas are known to recognize and suppress emotional stimuli. As one may notice, the significant activation differences between the groups are much lower towards congruent positive cases, in contrast to other cases. These findings are also compatible with our behavioral results indicating that patients are faster and more correct towards these cases in contrast to other cases. The group difference seems bigger in the charts above because controls are much faster and more correct towards these cases, which is supported with heightened FEF activations that enlarged their attention towards positive cases. In contrast to other cases, this case is much easier to process for both of the groups, nullifying probable effects brought by anhedonia in the patients. These results support what Clasen et al. (2013) claimed for patients as having an attentional bias towards negative stimuli; rather than impairment in positive information processing. As for the healthy population, it is their baseline case, so they process with ease, using their top-down attention system.

Towards **congruent-negative** cases, where the words and the faces are both negative, patients showed higher activations in Right Superior Frontal Cortex (BA6), right DLPFC (BA9), left postcentral (BA1), right Inferior Occipital Gyrus (BA19), right Cerebellum, left Putamen, left Pars Opercularis (BA44), left Inferior Temporal Gyrus (BA20), left Thalamus, right Insula, and right Middle Temporal Gyrus (BA21), in contrast to healthy population. In general, patients reacted faster towards these cases in contrast to controls, and they made relatively less error.

Right dorsolateral prefrontal cortex is mostly associated with planning (Fincham et al., 2002) and attention towards emotional stimuli (Grimm et al., 2008). As mentioned in Chapter 2, DLPFC is one of the most important brain regions that have been considered to be ‘impaired’ in depression. Although without a connectivity analysis it is difficult to propose a mechanism which explains its relations with other regions of the brain, we might clearly state that, in our study, in contrast to controls, right DLPFC is found to be more active in patients towards all cases except the incongruent negative case, where the face is happy whereas the word to be evaluated is negative. This might reflect the fact that the positive face did not actually create a conflicting case to work on for the patients. DLPFC was mostly proposed to resolve the conflicts (Pardo et al., 1990; Egner & Hirsch, 2005) and to fail to show necessary hyperactivities in patients to inhibit amygdala (Drevets, 2000; Mayberg, 1999&2003), which is the opposite of what we have observed. Recall that our task is designed in order to exclude arousal processing, which would therefore change the neural circuitry, since it does not cause any significant amygdala activation differences between the groups. Most recent studies about neural circuitry in depression support our findings (Schlosser et al., 2008; Grimm et al. 2008; Diener et al., 2012 (mentioned as BA9 rather than DLPFC); Shen et al., 2015). A particular study states that when affective stimuli are used, patients fail to show the necessary deactivations in Anterior Cingulate Cortex (ACC), DLPFC and right superior frontal cortex (Frodl et al., 2007). This seems to be the case in our study too, except ACC. ACC hyperactivities are probably perceived when emotional content has high arousal values, which is eliminated in this task. Frodl et al. (2007) states that, either depressed individuals over-activate certain areas in their brains in contrast to controls, or they attend more to negative stimuli. Another study that is compatible with our findings demonstrated a differential pattern of activity within DLPFC in patients, compared to healthy population: Patients showed higher right DLPFC activity, associated mostly with attention (Grimm et al., 2008). Therefore, the hyperactivities we are observing in high level regulation areas (such as right DLPFC, Superior and Inferior Frontal Gyri) is probably a sign that patients pay more attention mostly to the sad stimuli. When the negative case is their target, they can respond quickly to such cases with low rate of error.

The fact that we mostly find right DLPFC activation differences is also compatible with studies claiming a lateralization of DLPFC involving emotion stimuli (Terzian & Cecotto, 1959; Alema et al., 1961, Perria et al., 1961 in Harmon-Jones et al., 2010). Furthermore, the higher left Pars Opercularis activation is also worth mentioning, since this BA44 area is not only known as being a part of Broca’s area, but it is also an important part of ventral attention network (VAN) that carries bottom-up attentional processing. This area is thought to get active towards targets that are important but not very distinctive (Indovina and Macaluso, 2007, in Japee et al., 2015).

In patients, left putamen and left thalamus are hyperactive towards not only congruent negative but also towards incongruent negative cases, i.e. towards all cases where patients needed to evaluate negative words. Putamen and thalamus activations are crucial in order to strengthen the claim that patients have a negatively skewed emotional bias, because thalamus and striatum (part of basal ganglia covering caudate, putamen and nucleus accumbens) are shown to be the center of depressed patients’ emotional bias at the subcortical level (Diener et al., 2012).

No region showed significantly higher activity in controls towards this case in contrast to patients.

Towards the **incongruent-positive** cases, where words are positive but faces are negative, patients showed higher activations in right Insula & Claustrum, left FEF (BA8), left Pars Opercularis (BA44), left Lingual Gyrus, left postcentral (BA1), right Superior Frontal Cortex (BA6), bilateral Putamen, bilateral Thalamus, right Cerebellum, and right DLPFC (BA9) in contrast to healthy population; whereas controls showed higher left Insula activations in contrast to patients.

The regions showing hyperactivity in patients are almost the same as the congruent-negative case, except higher left FEF (BA8) activations towards this incongruent case. Since they still see a negative face we still observe right DLPFC, putamen, thalamus, postcentral, lingual gyrus, and cerebellum activations; however, this time the negative face was supposed to work as a distracter, yet for patients positive words seem to be what distracts them, reflecting itself as higher FEF activations. These areas are hyperactive probably because patients need to disengage their automatically involved attention from the negative face and move it towards the positive word which they need to evaluate. Therefore, in order to be able to do this disengagement, they overtax their left FEF (BA8) which is an important part of the Dorsal Attention Network (DAN) that is thought to work in top-down control of attention, especially to attend to differences in a scene, and to prepare the subject to respond accordingly (Corbetta et al, 2008; Japee et al. 2015). Therefore, with the help of the overtaxed FEF, patients can successfully attend to the positive word, which is actually different from their baseline negativity, although the sad face expression attracts their attention easily and deeply. However, they perform worse when compared to healthy individuals, who showed higher left Insula activations. The lateralization of Insula towards this case between patients and controls might again constitute a support for lateralization of emotion. Showing higher left Insula activation might be an indication of controls having more left hemispheric activation and thus attention towards positive words; whereas right Insula activation shown in patients along with the claustrum might be an indication of patients' tendency to be influenced by the sad face more than controls, and that they tried hard to disengage their attention from sad face towards positive word, making the CCN more active towards this case, reflecting as higher FEF, right DLPFC, postcentral gyrus, and Pars Opercularis activations (Shen et al., 2015). Face analyses of this study also support this view, because when patients encounter with a sad face expression, top-down attentional network gets activated, thus make patients 'stuck' on the negative face.

Towards the **incongruent-negative** cases, where the words are negative and the faces are happy, patients demonstrate hyperactivities in bilateral FEF (BA8), right Insula, bilateral Putamen, right Orbitofrontal Cortex (BA47), right Middle Frontal Gyrus (BA10), left Fusiform, right Middle Temporal Gyrus (BA21), right Pars Opercularis (BA44) and left Thalamus.

The main regional differences between the two incongruent cases for the patients are right Middle Frontal Gyrus (MFG), left Fusiform and right Orbitofrontal Gyrus activations. MFG is demonstrated to play an important role in reorienting attention from bottom-up to top-down control of attention (Japee et al., 2015). Right MFG probably gets hyperactive to reorient patients' attention from irrelevant positive face to the actual negative case that they should evaluate. Since this time the distracter is not a case that attracts their attention deeply and easily, not much of the cognitive control network gets activated (such as postcentral gyrus working along with DLPFC) (Shen et al., 2015). Their right MFG might be helping in reorienting the attention from positive face towards the negative word, the target. Happy face does not attract their attention as much as a sad face, so it is not as distractive, thus as exhausting, as a sad face for the patients (Bourke et al., 2010; Elliot et al., 2010). This case is also supported with our face analyses, since regions that are crucial in cognitive control mechanism and cognitive connection network are active towards sad faces, not towards happy faces in patients. For the healthy group, happy faces could work as a distracter successfully; therefore behaviorally they were slower towards incongruent-negative cases compared to patients.

These results verify once more Hypotheses 8 and 9.

5.2.5. General Evaluation with respect to previous findings in the literature

It is particularly delicate to compare and contrast fMRI studies that use an emotional Stroop paradigm with the WFS used in this study, because either the design of the tasks vary a great deal, or they are not always conducted on depressed individuals, or depressed populations' levels of depression or medication status are different. For example, Etkin et al.'s study (2006) revealed that rACC inhibits amygdala activation when there is an emotional conflict, however, they used a word-face Stroop where emotion words were evaluated, such as anger, fear, happy, without eliminating the arousal dimension. Moreover, their study was not conducted in depressed individuals. In this study, we found no significant amygdala activity, not even towards sad faces, which is not compatible with previous studies finding significant amygdala activations towards sad faces (Drevets, 2000). However the studies that find amygdala hyperactivity in patients towards sad faces used solely face stimuli. Even if the face analyses in this study are conducted via selecting the time series when sad or happy faces appear, one should keep in mind that those happy or sad faces never appeared to participants without a word on them. The words and faces never appear alone, but they always appear together, congruently or incongruently.

In Haas et al.'s study (2006), the one that was the most similar to ours, no rACC hyperactivity is found towards incongruent cases. In our study, we also did not find any rACC hyperactivation in control group towards incongruent cases. However their task was not conducted on patients. Egner and Hirsh's study (2005) was significantly different in both design- and participant-wise (the task was designed on a face evaluation basis that specifically triggered fusiform activation and there was no patient group).

The fMRI studies that are more similar to this one than the others are Mitterschiffthaler et al.'s study (2008), especially with respect to the subject group (unmedicated depressed individuals), and Chechko et al.'s study (2013) especially regarding the task (an emotional Word-Face Stroop Task, but using emotion names as distracters, and faces as targets). Although they used house and face pairs as stimuli, since it was an emotional interference task and since the participants were all unmedicated depressed individuals, Fales et al.'s study (2007) can also be one of the studies that we can compare our results with in a more relevant way. These are also the ones that made an emphasis on emotional conflict resolution (for instance there is no conflict resolution in Grimm et al.'s (2008) and Eliott et al.'s (2002) studies).

Hence comparing our study to these fMRI studies, although the compartmentalization of ACC was evident especially from our main activation analyses results, ACC showed no significantly different activation between our patient and control groups. When we check the findings of the above studies, only Mitterschiffthaler et al. found a group difference in ACC activations when there is a conflicting case (2008). The reason is probably because only this study used a non-face/non-picture version of an emotional Stroop, but just used an emotional color Stroop. This might mean that ACC can still work properly when the emotional conflict is not caused by a visually more information-loaded stimulus (such as a picture or face). Moreover we have designed an emotional stroop using two specific emotional systems (evaluating emotionally loaded stimuli distracted by other emotionally loaded stimuli): In emotional color stroop the target has no emotional content, so that kind of emotional stroop does not create a purely emotional conflict. Further testing is needed in order to verify these claims.

Chechko et al. (2013) demonstrated that depressed individuals' limbic system gets hyperactive (especially amygdala) whereas the cortical regions get deactive (especially DLPFC) towards emotional cases. This result is the opposite of what we have found probably because a mixture of medicated and unmedicated patients was evaluating face expressions, which include highly arousing stimuli. As explained in the literature review, since arousal and valence are differently processed in the brain, it is crucial to select emotional stimuli used in the task in a distinctive way with respect to these dimensions; and to clarify the neural network that shows differences in depressed patients accordingly.

Almost the same result (an impaired DLPFC that cannot inhibit amygdala) is found in Fales et al.'s study (2007), which also used arousing face stimuli (e.g. fearful face). On the other hand, a recent study that used an emotional color-word Stroop[12] comparing their results with a classical Stroop task revealed that cognitive control systems in the brain is connected more to internal-attention systems in depressed individuals (Kaiser et al., 2015). What is important about this recent study is that they conducted an affective task and a non-affective, purely cognitive task. Therefore, they could understand if overtaxing of control mechanism has anything to do with affective stimuli or not. What they found is when highly depressed individuals face with negative stimuli they attend more to their internal thoughts and

[12] Since this task does not involve any emotionally loaded face or picture, just as in Mitterschiffthaler et al.'s study, they mostly found dACC activation differences between the patient and control groups, and thus considered this region as another part of the cognitive control system.

have hard time to disengage their attention from these negative material, which interferes with their actual goal (Kaiser et al., 2015). This finding is perfectly compatible with our findings that cognitive control regions, thus top-down attentional mechanism, in patients' brains get overactive when there is a negative case. Therefore, the problem is not about lateral frontal cortices that cannot inhibit a limbic area; but it is about an overworking of the internal attentional mechanism (endogenous, top-down) in a negatively biased way.

Keeping in mind the differences in the behavioral results of Classical and Emotional Word-Face Stroop Tasks, in the future, the classical Stroop task should also be conducted in the scanner to be able to compare the brain activation differences. This purely attentional bias task would also be used as a control case with another task using emotional evaluation without interference. Therefore, the results would help us clarify if the difference between the patients and the controls is really based on an emotionally skewed attentional mechanism.

5.3. Limitations

Due to time restrictions of the patients in the outpatient clinic, IQ assessment was not done. Instead, years of education was used.

The emotional stimuli were not evaluated across the valence and arousal dimensions by the participants. Instead, the norm values obtained from healthy populations in the TUDADEN (Gokcay and Smith, 2012) and Productive Aging Lab Face Database (Minear and Park, 2004) were used. Moreover, TÜDADEN was normalized according to a healthy population, not a depressed population. To compensate for this bias the words used in our experiment might have been evaluated by our patient group before or after the experiment, however both cases might have been problematic for the purposes of the experiment: If they evaluated the words before they perform, they would have learned the words, so we would not want this in order to prevent priming, moreover if they evaluated after the task, the patients would not be able to evaluate the words in a neutral environment, since they have already experienced these emotional words and plus with emotional faces which would affect their evaluation of those specific words.

Since it was very difficult to find unmedicated highly depressed patients, plus to convince them to participate in this study—which approximately takes 2 hours in total—, I could not scan more than 20 patients. After the elimination of data, sample size shrank to 16, for each group, which is suitable for an fMRI analysis, yet not adequate for behavioral analyses.

Furthermore, the admission procedure did not include record-keeping on the menstrual cycle of the participants, hence we were unable to add this information as a covariate. For the healthy controls, only short interviews were conducted by me, not by a clinician, inquiring their sanitary background and mood within the past months.

CHAPTER 6

CONCLUSION

This study aims at enlightening the mechanism behind the deficits depressed individuals show in tasks involving emotional conflict resolution. Inquiring and eliciting the processing of emotional and cognitive networks in a depressed brain enhances our understanding of the neuropsychological foundations of this disorder. This would help cognitive scientists and neuropsychologists work together for developing new cognitive neural network models compatible with real neural networks (such as attentional, emotional or default networks that are discovered so far with the help of neuroimaging).

Regarding both our behavioral and fMRI results, the different mechanisms depressed individuals use while dealing with a complex task in which emotional words and faces exchange roles continuously, appear to cause patients to lose the emotional interference effect behaviorally: Incongruent cases are not always conflicting for them, and congruent cases are not always easy to deal with because of their negative preference. In **congruent positive cases** they try to suppress positivity, perhaps because this purely positive case is actually incongruent with their automatic preference, which is negative. Consequently, compared to controls, they slow down more towards these cases and more importantly they make more mistakes than controls. **Congruent negative cases** appear to be the case they are more attentive to perhaps because they subscribe to the negativity. This is probably why they respond towards these cases more quickly in contrast to controls. During the **incongruent positive condition**, patients' attention is enhanced towards the sad face. This situation slows them down and makes them perform badly compared to controls, yet they can still resolve the conflict (though the conflict is caused by the word not the face), and perform fast enough. In **incongruent negative cases** their attention is engaged in evaluating the negative word, and also high level areas are highly engaged in suppressing the happy face, therefore we observe activation of attention reorientation areas. With the help of their profound attention towards the negative word which is not distracted enough by the positive face patients were faster in responding to these cases compared to controls. Both our behavioral and brain activity profiles support the theories claiming that patients have enhanced processing towards negative information, and that they have an attentional bias towards negative emotional stimuli (Clasen et al., 2013).

It seems that the deficits that patients were claimed to have for many years, demonstrated in various studies using both cognitive and emotional tasks, might actually be referred as a different allocation of attention towards patients' preferred case, which is negative. This claim is supported by the Analytical Rumination theory, according to which, when given a laboratory task, depressed people ruminate about other things, and consume limited cognitive resources that diminishes their ability to perform well on the assignment. However, when the laboratory task on which performance is to be evaluated is related closely to the depressogenetic problem, such as sustained analysis or problem solving on a complex task, the patients are found to perform even better than healthy individuals (Andrews and Thompson, 2009). So, ruminating and over-attending to cases with negativity might actually provide people new ways of thinking as long as attention can be reallocated in a proper way. Hence, Joshua Wolf Shenk migh have had a point when he claimed that Abraham Lincoln was such a great president because of his melancholy, in his book called "Lincoln's Melancholy: How Depression Challenged a President and Fueled His Greatness" (Shenk, 2006).

Apparently attentional and cognitive control areas of the brain such as DLPFC, FEF, SFG, and MFG display hyperactivities in patients, because patients use a differently biased attentional mechanism. Thus, a differently structured regulatory system working in accordance with their negative bias, which has been automatized in their cognitive system, accelerates the processing of negative stimuli for patients compared to controls.

The fMRI-compatible valence-specific Turkish Word-Face Stroop that is used in this study is a genuine emotional Stroop task that can be used in functional neuroimaging research, because it is designed to satisfy all the crucial issues mentioned along this dissertation to elicit the mechanism for emotional conflict resolution more clearly: 1) Not the words, but the faces are distracters, 2) Words are specifically selected varying on valence axis only, keeping arousal neutral, 3) Words are concrete nouns, balanced with respect to word length and frequency, 4) Emotionally loaded words are evaluated instead of emotion names (e.g. 'anger', 'happy'), 5) There are no neutral case, because neutral cases fail at working as a baseline, and even induce difficulty for participants. This study is not only rigorous with respect to its task design. I was also exceptionally careful recruiting a very specific group of patients who are all unmedicated, mostly in their first episode of MDD, and who are not having any kind of psychotherapy.

When the emotional content used along with conflict which does not involve arousal, the limbic system, which was found hyperactive in patients in most of the studies mentioned in the review section, does not get hyperactive after all. Therefore, the design of our task which eliminated the arousal level also eliminated the grave problems usually found in cortico-limbic circuitry in depressed individuals (e.g. hyperactive amygdala that cannot be inhibited by DLPFC). So, what we obtained in this study is a valence-specific functional mechanism in the brain, which accounts for the pleasantness rather than motivation. Pezawas et al. (2005) also supports our finding that we do not see significant ACC differences between the groups, because our valence-specific task does not lead to any significant amygdala activation.

The theories that claim a failed ACC that causes failures in DLPFC that cannot send proper feedbacks to ACC, which eventually convert into a vicious cycle that causes anhedonia in patients is not supported by this study, because ACC and DLPFC (and especially right DLPFC) are hyperactive in patients rather than deactivated. This result leads to more attention-based claims about the cognitive/emotional processing in depressed individuals (more high-level activation differences), rather than a low-level problem. For example, studies that try to claim such cortico-limbic deficiencies (e.g. Drevets, 2000; Kennedy et al., 2001; Mayberg et al., 2003) based their theories to the idea that depression patients constantly fail in cognitive tasks that especially demand attention. However, recent studies (such as Attentional Rumination Theory) showed that patients might actually perform even better in tasks that are relevant to their persistent mood (i.e. negative). This study also supports the recent findings asserting that depressed individuals have a negatively biased attentional system that use more of internal sources (i.e. endogenous attention, top-down processing), which causes them to ruminate, i.e. overthinking about their negatively loaded problems. This study's findings verify that patients can successfully process positive stimuli, reflected as intact positive-negative asymmetry effect. However, as reflected in the interaction between group and valence, and in neuroimaging results, they have hard time disengaging their attention from a negative bias to move it towards the positive stimuli. Thus, they have no problems in processing emotional stimuli; they rather have a different attentional direction, mostly in a negatively skewed way.

Apart from the fact that this study reveals compatible results with the most recent findings on focusing attentional-emotional mechanisms in depression, our findings also support early but solid findings such as the lateralization of the frontal cortices, i.e. right lateral prefrontal cortex, which is associated with negative emotions (Grimm et al., 2008; Terzian & Cecotto, 1959; Alema et al., 1961, Perria et al., 1961 in Harmon-Jones et al., 2010).

Furthermore, this is the first study that connects the differential processing of dorsal and ventral attentional networks (Corbetta et al., 2008, Japee et al., 2015) to depressed individuals' differently shaped attentional system, hence directly creating a connection between the major depressive disorder and the attentional networks in the brain.

In conclusion, in line with our hypotheses, our behavioral findings revealed that patients performed no different than controls in a cognitive conflict resolution task (Classical Stroop Task), which indicates that patients have no specific cognitive/attentional deficit when there are no emotions involved. Moreover, both group slowed down more towards negative cases rather than positive cases, which indicates that patients have no specific emotional deficit. Rather patients might have a different way of processing emotionally loaded stimuli because of their negatively skewed attentional mechanism. This reflected itself as an interaction between valence and group: Patients were faster towards negative cases compared to controls.

Again compatible with our hypotheses, our brain imaging findings revealed that patients and controls showed different activation patterns that are relevant to our behavioral findings. The findings that regions related with high level attention, control and regulation mechanisms, reflecting as right DLPFC, right superior Frontal, Frontal eye Field and right Middle Frontal Gyrus hyperactivities were contrary to the earlier literature, but were compatible with recent literature mostly using connectivity analyses considering emotional, attentional and default mode networks. All these findings point out that this fMRI compatible valence-specific WFS Task succeeded in catching up with the recent findings. Moreover, the way this dissertation handled the data and the interpretation of the data on a network basis opens up new areas of research in order to understand depression from a cognitive scientific point of view. In the future, differently connected network models might be programmed in order to understand better how attention and emotion work in a parallel and distributed way, and how and why this system might be reshaped in different kinds of mental illnesses.

While evaluating negative words, mostly parts of DAN were found to be hyperactive in patients, perhaps because their bias towards negativity becomes an implicit goal for them. For positive words, on the other hand, VAN hyperactivities are found indicating a distraction to their negativity bias, thus becoming an explicit goal for them. Furthermore, hyperactivities detected in patients' right MFG, particularly towards incongruent negative cases, points out to an attentional orchestra chef that highly prefers to focus on negativity, when there seems to be a distracting mood-incongruent stimulus (happy face). Mostly seeing both VAN and DAN activations together towards negative stimuli (both words and faces), regardless of the congruency, might be the sign for an unconscious control mechanism, i.e. VAN working for unconsciously oriented attention towards negativity, and DAN working to control over this negativity. Patients subscribe to a vicious cycle: They easily attend to negative cases, and start trying to control this situation and even focus more on the negativity (rumination), actually to be able to solve it inducing a huge trap they cannot get out.

Therefore we can conclude that MDD patients do not seem to have any cognitive-specific or emotion-specific deficit, so they can perform as well as controls. However their allocation of attention is negatively biased, therefore what distracts them or what they are more attended to is differently structured in contrast to healthy individuals.

Further studies should cover Region of Interest (ROI) analyses using connection-based approaches in order to find out about causal relationships between the regions mentioned in this dissertation. As mentioned before both emotion-related and purely cognitive interference/attention tasks should be functionally conducted and compared. Moreover, in order to be able to generalize the findings and to be able to find significant correlations and statistically strengthen the behavioral results, a larger cohort with varying depression levels must be studied.

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APPENDICES

APPENDIX A: Consent Forms

BİLGİLENDİRİLMİŞ GÖNÜLLÜ OLUR FORMU (HASTA GRUBU İÇİN)

Araştırmanın Adı: Normal popülasyon ve Majör Depresyon Hastalarında Duygusal Çelişki Çözümleme Sırasında Prefrontal Korteksteki Yapıların MR ve fMRI ile İncelenmesi

Bu çalışma Orta Doğu teknik Üniversitesi Enformatik Enstitüsü Bilişsel Bilimler Anabilim Dalında doktora öğrencisi Zeynep Başgöze ve tez danışmanı Yrd. Doç. Dr. Didem Gökçay'ın denetiminde gerçekleşmektedir. Araştırmanın amacı depresyon hastalarında görülen bazı davranış bozukluklarının temelinde yatan beyin işleyiş bozukluklarını ortaya çıkarabilmektir. Bu araştırma kapsamında Sağlık Bakanlığı onayı ile hizmet veren UMRAM (Ulusal Manyetik Rezonans Araştırma Merkezi)'da Duygusal Stroop adı verilen duygusal çelişki çözümleme testini gerçekleştireceksiniz. Testin öncelikle bilgisayar karşısında bir pratik aşaması olacak ve bu aşama en fazla 5 dakika sürecektir. Pratikleri başarıyla tamamladığınız takdirde MR çekimi yapılacak ve bu sırada bir ayna yardımıyla görebileceğiniz ve pratiğini yaptığınız Duygusal Stroop testini MR altında uygulamanız istenecektir. MR çekimi 1 saat kadar sürecektir.
MR çekimi uygun önlemler alındığı sürece zararsız bir işlemdir. Fakat kapalı yer korkusu olanların bu işlemi yapmaması gerekir. Vücudunda herhangi bir metal protez, kalp pili uygulaması ve bunun benzeri ameliyatlarla takılan nesne bulunduran hastaların MR çekimine katılmaması gerekmektedir. Diş dolgularının zararı bulunmamaktadır.
MR çekimi sırasında üşüyebilirsiniz, gerekirse üstünüz örtülebilir. İşlem başlayınca, takırtı mertebesinde sesler duyacaksınız. Personel bu sesi azaltmak için size kulak tıkacı ya da kulaklık verebilir. MR biriminde personelin sizinle konuşabileceği bir iç iletişim sistemi vardır. Birkaç personel yakınınızda olacak ve iç iletişim sistemi ile onlara kolayca ulaşabileceksiniz.
Araştırmaya katılmayı reddetme veya araştırmaya başladıktan sonra devam etmeme hakkına sahipsiniz. Bu koşullar gerçekleşirse size verilen el butonu ile çıkartılma sinyalini devreye sokabilirsiniz.
Bu araştırma katılımcılara tıbbi bir yarar sağlamamaktadır. Fakat tedavinizin kalan bölümünde bir aksama olmayacaktır.
Katılımcının kendi rızasına bakılmaksızın araştırmacı tarafından da araştırma harici bırakılabilirsiniz.
Araştırmaya gönüllü olarak katılmaktasınız ve bu araştırmaya toplam 30 kişi katılacaktır. Araştırma süresince uygulanacak testler ücretsiz sağlanacaktır ve sosyal güvencenizi sağlayan kurum mali yük altına girmeyecektir.
Katılımcı veya yakını herhangi bir zarar veya sıkıntı durumunda araştırmacıyla ilişki kurabilir:

Zeynep Başgöze
Yrd. Doç. Dr. Didem Gökçay

Phone numbers of the researchers that originally appear here are omitted for privacy reasons

ONAM FORMU
" Normal popülasyon ve Majör Depresyon Hastalarında Duygusal Çelişki Çözümleme Sırasında Prefrontal Korteksteki Yapıların MR ve fMRI ile İncelenmesi" başlıklı çalışma bana sözlü olarak da açıklandı. Çalışma ile ilgili tüm sorularıma tatmin edici cevaplar aldım. Çalışmaya kendi rızamla gönüllü olarak katılmayı kabul ediyorum.

Hastanın Adı soyadı	Tarih	İmza
Araştırıcı Adı Soyadı	Tarih	İmza

BİLGİLENDİRİLMİŞ GÖNÜLLÜ OLUR FORMU (KONTROL GRUBU İÇİN)

Araştırmanın Adı: Normal popülasyon ve Majör Depresyon Hastalarında Duygusal Çelişki Çözümleme Sırasında Prefrontal Korteksteki Yapıların MR ve fMRI ile İncelenmesi

Bu çalışma Orta Doğu teknik Üniversitesi Enformatik Enstitüsü Bilişsel Bilimler Anabilim Dalında doktora öğrencisi Zeynep Başgöze ve tez danışmanı Yrd. Doç. Dr. Didem Gökçay'ın denetiminde gerçekleşmektedir. Araştırmanın amacı depresyon hastalarında görülen bazı davranış bozukluklarının temelinde yatan beyin işleyiş bozukluklarını ortaya çıkarabilmektir. Bu amaçla araştırmaya alınan hastalarla verileri karşılaştırmak amacıyla bir kontrol grubunda da çalışma gerçekleştirilmektedir. Bu araştırma kapsamında Sağlık Bakanlığı onayı ile hizmet veren UMRAM (Ulusal Manyetik Rezonans Araştırma Merkezi)'da Duygusal Stroop adı verilen duygusal çelişki çözümleme testini gerçekleştireceksiniz. Testin öncelikle bilgisayar karşısında bir pratik aşaması olacak ve bu aşama en fazla 5 dakika sürecektir. Pratikleri başarıyla tamamladığınız takdirde MR çekimi yapılacak ve bu sırada bir ayna yardımıyla görebileceğiniz ve pratiğini yaptığınız Duygusal Stroop testini MR altında uygulamanız istenecektir. MR çekimi 1 saat kadar sürecektir.
MR çekimi uygun önlemler alındığı sürece zararsız bir işlemdir. Fakat kapalı yer korkusu olanların bu işlemi yapmaması gerekir. Vücudunda herhangi bir metal protez, kalp pili uygulaması ve bunun benzeri ameliyatlarla takılan nesne bulunduran hastaların MR çekimine katılmaması gerekmektedir. Diş dolgularının zararı bulunmamaktadır.
MR çekimi sırasında üşüyebilirsiniz, gerekirse üstünüz örtülebilir. İşlem başlayınca, takırtı mertebesinde sesler duyacaksınız. Personel bu sesi azaltmak için size kulak tıkacı ya da kulaklık verebilir. MR biriminde personelin sizinle konuşabileceği bir iç iletişim sistemi vardır. Birkaç personel yakınınızda olacak ve iç iletişim sistemi ile onlara kolayca ulaşabileceksiniz.
Araştırmaya katılmayı reddetme veya araştırmaya başladıktan sonra devam etmeme hakkına sahipsiniz. Bu koşullar gerçekleşirse size verilen el butonu ile çıkartılma sinyalini devreye sokabilirsiniz.
Bu araştırma katılımcılara tıbbi bir yarar sağlamamaktadır.
Katılımcının kendi rızasına bakılmaksızın araştırmacı tarafından da araştırma harici bırakılabilirsiniz.
Araştırmaya gönüllü olarak katılmaktasınız ve bu araştırmaya toplam 30 kişi katılacaktır. Araştırma süresince uygulanacak testler ücretsiz sağlanacaktır ve sosyal güvencenizi sağlayan kurum mali yük altına girmeyecektir.
Katılımcı veya yakını herhangi bir zarar veya sıkıntı durumunda araştırmacıyla ilişki kurabilir:

Zeynep Başgöze
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Katılımcının Adı soyadı	Tarih	İmza
Araştırıcı Adı Soyadı	Tarih	İmza

APPENDIX B: Word List

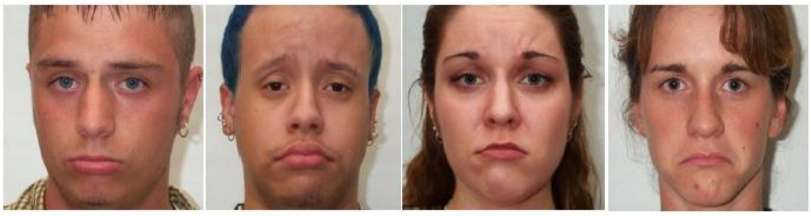
The word list is pseudo-randomized in order not to change the waveforms for every subject in the fMRI analyses. So every participant saw the words in the same order.

Congruency	Word	Face	Congruency	Word	Face
Run1			Run2		
cong	mayın	sad_m_1.bmp	cong	karakol	sad_m_2.bmp
incong	kuzu	sad_m_2.bmp	cong	çimen	happy_f_1.bmp
cong	hasar	sad_m_1.bmp	incong	ağrı	happy_f_2.bmp
incong	dede	sad_f_1.bmp	cong	kirlilik	sad_f_2.bmp
cong	komşu	happy_m_1.bmp	incong	kumsal	sad_m_1.bmp
incong	dayak	happy_f_1.bmp	cong	sakatlık	sad_m_1.bmp
cong	kitap	happy_m_2.bmp	incong	pire	happy_f_1.bmp
incong	oyuncak	sad_m_2.bmp	incong	muz	sad_m_1.bmp
incong	kambur	happy_f_1.bmp	cong	pasta	happy_m_2.bmp
cong	oyuncak	happy_m_2.bmp	cong	ağrı	sad_f_2.bmp
incong	sahil	sad_m_1.bmp	incong	çimen	sad_f_1.bmp
cong	yatak	happy_f_1.bmp	cong	nezle	sad_m_2.bmp
incong	ishal	happy_f_2.bmp	incong	sakatlık	happy_m_1.bmp
incong	komşu	sad_m_1.bmp	incong	tatlı	sad_m_1.bmp
cong	sigara	sad_m_2.bmp	cong	vergi	sad_f_1.bmp
incong	hasar	happy_m_1.bmp	incong	doğa	sad_f_1.bmp
incong	erozyon	happy_m_1.bmp	incong	karakol	happy_m_2.bmp
cong	gökyüzü	happy_f_2.bmp	incong	nezle	happy_m_2.bmp
cong	kuzu	happy_m_2.bmp	cong	tiyatro	happy_f_2.bmp
incong	sigara	happy_m_2.bmp	incong	esir	happy_m_2.bmp
cong	dayak	sad_f_1.bmp	cong	yıldız	happy_f_1.bmp
incong	kitap	sad_m_2.bmp	incong	yıldız	sad_f_1.bmp
cong	ishal	sad_f_2.bmp	cong	doğa	happy_f_1.bmp
incong	yatak	sad_f_1.bmp	incong	kirlilik	happy_f_2.bmp
incong	gökyüzü	sad_f_2.bmp	cong	kumsal	happy_m_1.bmp
cong	kambur	sad_f_1.bmp	cong	pire	sad_f_1.bmp
cong	erozyon	sad_m_1.bmp	incong	tiyatro	sad_f_2.bmp
incong	mayın	happy_m_1.bmp	incong	vergi	happy_f_1.bmp
cong	dede	happy_f_1.bmp	cong	muz	happy_m_1.bmp
incong	ülser	happy_f_2.bmp	cong	esir	sad_m_2.bmp
cong	sahil	happy_m_1.bmp	cong	tatlı	happy_m_1.bmp
cong	ülser	sad_f_2.bmp	incong	pasta	sad_m_2.bmp

Congruency	Word	Face	Congruency	Word	Face
Run3			Run4		
cong	ziyafet	happy_m_2.bmp	cong	konser	happy_m_2.bmp
incong	ilaç	happy_m_2.bmp	incong	yazar	sad_f_1.bmp
cong	idrar	sad_m_1.bmp	cong	masraf	sad_f_2.bmp
incong	ziyafet	sad_m_2.bmp	cong	şarap	happy_f_1.bmp
cong	bulut	happy_f_1.bmp	cong	tütün	sad_f_2.bmp
incong	cenaze	happy_m_2.bmp	incong	kucak	sad_m_1.bmp
cong	ayna	happy_f_2.bmp	incong	gözyaşı	happy_f_1.bmp
cong	kırık	sad_m_2.bmp	incong	altın	sad_m_1.bmp
incong	posta	sad_f_2.bmp	cong	mezar	sad_f_1.bmp
cong	cenaze	sad_m_2.bmp	cong	salata	happy_m_1.bmp
incong	hastane	happy_m_1.bmp	incong	yara	happy_m_1.bmp
incong	kokteyl	sad_m_2.bmp	cong	okyanus	happy_f_1.bmp
incong	dilenci	happy_f_1.bmp	incong	çamur	happy_m_1.bmp
cong	çöplük	sad_f_1.bmp	incong	leke	happy_f_2.bmp
incong	papatya	sad_m_1.bmp	cong	altın	happy_m_1.bmp
incong	gübre	happy_f_2.bmp	incong	mikrop	happy_m_2.bmp
cong	ilim	happy_m_2.bmp	cong	bebek	happy_f_1.bmp
incong	koşu	sad_m_1.bmp	incong	şarap	sad_f_1.bmp
incong	ayna	sad_f_2.bmp	cong	leke	sad_f_2.bmp
cong	dilenci	sad_f_1.bmp	cong	kucak	happy_m_1.bmp
cong	papatya	happy_m_1.bmp	cong	çamur	sad_m_1.bmp
incong	ilim	sad_m_2.bmp	incong	mezar	happy_f_1.bmp
cong	hastane	sad_m_1.bmp	cong	yazar	happy_f_1.bmp
incong	idrar	happy_m_1.bmp	cong	gözyaşı	sad_f_1.bmp
cong	koşu	happy_m_1.bmp	incong	salata	sad_m_1.bmp
cong	kokteyl	happy_m_2.bmp	cong	yara	sad_m_1.bmp
incong	kırık	happy_m_2.bmp	incong	tütün	happy_f_2.bmp
cong	gübre	sad_f_2.bmp	incong	okyanus	sad_f_1.bmp
incong	bulut	sad_f_1.bmp	cong	mikrop	sad_m_2.bmp
incong	çöplük	happy_f_1.bmp	incong	konser	sad_m_2.bmp
cong	posta	happy_f_2.bmp	incong	masraf	happy_f_2.bmp
cong	ilaç	sad_m_2.bmp	incong	bebek	sad_f_1.bmp

APPENDIX C: Faces from Minear & Park Face Database (2004)

Sad Faces: Wmale18sad, TMWfemale21-2sad, Wfemale24-2sad



Happy Faces: WWmale20-3happy, TSFWmale23happy, WWfemale22happy, EMWfemale22happy

APPENDIX D: AFNI command scripts

APPENDIX D1: Pre-processing commands

Script for Warp & Interpolation (3dWarp):

```
#!/bin/bash

DIR=/home/zeynep/Documents/SAGLIKLI_RAW/S22

if [ -e $DIR/anatomik+orig.BRIK ] ; then

        3dWarp -deoblique -prefix anat_warped anatomik+orig.
        3dWarp -deoblique -prefix run1_warped wfs_run1+orig.
        3dWarp -deoblique -prefix run2_warped wfs_run2+orig.
        3dWarp -deoblique -prefix run3_warped wfs_run3+orig.
        3dWarp -deoblique -prefix run4_warped wfs_run4+orig.

fi
```

Script for checking the outliers and determining the sub-brick (3dToutcount) & plotting them (1dplot):

```
#!/bin/bash

DIR=/home/zeynep/Documents/SAGLIKLI_RAW/S22

        if [ -e $DIR/run1_warped+orig.BRIK ] ; then

        3dToutcount -automask run1_warped+orig>outlier1.1D
        3dToutcount -automask run2_warped+orig>outlier2.1D
        3dToutcount -automask run3_warped+orig>outlier3.1D
        3dToutcount -automask run4_warped+orig>outlier4.1D

        1dplot outlier1.1D
        1dplot outlier2.1D
        1dplot outlier3.1D
        1dplot outlier4.1D

        fi
```

Script for registering anatomical image to the chosen sub-brick (3dAllineate) & registering functional images to the chosen sub-brick (3dvolreg):

```
#!/bin/bash

DIR=/home/zeynep/Documents/SAGLIKLI_RAW/S22

    if [ -e $DIR/run1_warped+orig.BRIK ] ; then

        3dAllineate -base anat_warped+orig -source run1_warped+orig'[35]'

        3dvolreg -verbose -base run1_warped+orig'[35]' -prefix
run1_warped_volreg -heptic -zpad 4 -1Dfile motionfile1.1D -1Dmatrix_save
matrix1.1D run1_warped+orig'[0..99]'

        3dAllineate -base anat_warped+orig -source run2_warped+orig'[60]'

        3dvolreg -verbose -base run2_warped+orig'[60]' -prefix
run2_warped_volreg -heptic -zpad 4 -1Dfile motionfile2.1D -1Dmatrix_save
matrix2.1D run2_warped+orig'[0..99]'

        3dAllineate -base anat_warped+orig -source run3_warped+orig'[40]'

        3dvolreg -verbose -base run3_warped+orig'[40]' -prefix
run3_warped_volreg -heptic -zpad 4 -1Dfile motionfile3.1D -1Dmatrix_save
matrix3.1D run3_warped+orig'[0..99]'

        3dAllineate -base anat_warped+orig -source run4_warped+orig'[65]'

        3dvolreg -verbose -base run4_warped+orig'[65]' -prefix
run4_warped_volreg -heptic -zpad 4 -1Dfile motionfile4.1D -1Dmatrix_save
matrix4.1D run4_warped+orig'[0..99]'

        1dplot motionfile1.1D
        1dplot motionfile2.1D
        1dplot motionfile3.1D
        1dplot motionfile4.1D

    fi
```

Script for checking whether motion parameters are as expected (3dToutcount); low-pass filtering (3dFourier); spatial smoothing (3dmerge); removing non-brain areas (3dAutomask); calculating mean values per voxel (3dTstat) & finally normalizing the data (3dcalc):

```
#!/bin/bash

DIR=/home/zeynep/Documents/SAGLIKLI_RAW/S22

	if [ -e $DIR/run1_warped+orig.BRIK ] ; then

		3dToutcount -automask run1_warped_volreg+orig>aftermc1.1D

		3dFourier -prefix run1_warped_volreg_fourier -lowpass 0.2 -retrend 
run1_warped_volreg+orig

		3dmerge -1blur_fwhm 6 -doall -prefix 
run1_warped_volreg_fourier_merged run1_warped_volreg_fourier+orig

		3dAutomask -prefix mask_run1 
run1_warped_volreg_fourier_merged+orig

		3dTstat -prefix mean_run1 run1_warped_volreg_fourier_merged+orig

		3dcalc -a run1_warped_volreg_fourier_merged+orig -b 
mean_run1+orig -c mask_run1+orig -expr '(c*(a-b)/b*100)' -prefix prep_run1

		3dToutcount -automask run2_warped_volreg+orig>aftermc2.1D

		3dFourier -prefix run2_warped_volreg_fourier -lowpass 0.2 -retrend 
run2_warped_volreg+orig

		3dmerge -1blur_fwhm 6 -doall -prefix 
run2_warped_volreg_fourier_merged run2_warped_volreg_fourier+orig

		3dAutomask -prefix mask_run2 
run2_warped_volreg_fourier_merged+orig

		3dTstat -prefix mean_run2 run2_warped_volreg_fourier_merged+orig

		3dcalc -a run2_warped_volreg_fourier_merged+orig -b 
mean_run2+orig -c mask_run2+orig -expr '(c*(a-b)/b*100)' -prefix prep_run2

		3dToutcount -automask run3_warped_volreg+orig>aftermc3.1D

		3dFourier -prefix run3_warped_volreg_fourier -lowpass 0.2 -retrend 
run3_warped_volreg+orig
```

3dmerge -1blur_fwhm 6 -doall -prefix run3_warped_volreg_fourier_merged run3_warped_volreg_fourier+orig

3dAutomask -prefix mask_run3 run3_warped_volreg_fourier_merged+orig

3dTstat -prefix mean_run3 run3_warped_volreg_fourier_merged+orig

3dcalc -a run3_warped_volreg_fourier_merged+orig -b mean_run3+orig -c mask_run3+orig -expr '(c*(a-b)/b*100)' -prefix prep_run3

3dToutcount -automask run4_warped_volreg+orig>aftermc4.1D

3dFourier -prefix run4_warped_volreg_fourier -lowpass 0.2 -retrend run4_warped_volreg+orig

3dmerge -1blur_fwhm 6 -doall -prefix run4_warped_volreg_fourier_merged run4_warped_volreg_fourier+orig

3dAutomask -prefix mask_run4 run4_warped_volreg_fourier_merged+orig

3dTstat -prefix mean_run4 run4_warped_volreg_fourier_merged+orig

3dcalc -a run4_warped_volreg_fourier_merged+orig -b mean_run4+orig -c mask_run4+orig -expr '(c*(a-b)/b*100)' -prefix prep_run4

fi

APPENDIX D2: 1st level Analysis Command

Script for creating a statistical map of voxels correlated with the task (3dConvolve):

#!/bin/bash

DIR=/home/zeynep/Documents/SAGLIKLI_RAW/S22

if [-e $DIR/prep_run1+orig.BRIK] ; then

3dDeconvolve -polort 3 -input prep_run1+orig prep_run2+orig prep_run3+orig prep_run4+orig -num_stimts 4 -stim_file 1 "GAMwaver_congpos_4runs_eStroop.txt" -stim_label 1 congpos -stim_file 2 "GAMwaver_congneg_4runs_eStroop.txt" -stim_label 2 congneg -stim_file 3 "GAMwaver_incongpos_4runs_eStroop.txt" -stim_label 3 incongpos -stim_file 4 "GAMwaver_incongneg_4runs_eStroop.txt" -stim_label 4 incongneg -num_glt 4 -gltsym "SYM: congpos -incongpos" -glt_label 1 congposVSincongpos -gltsym "SYM: congneg -incongneg" -glt_label 2 congnegVSincongneg -gltsym "SYM:

congpos -congneg" -glt_label 3 congposVScongneg -gltsym "SYM: incongpos -incongneg" -glt_label 4 incongposVSincongneg -tout -fout -bucket eStroop_stats -fitts eSTroop_fits

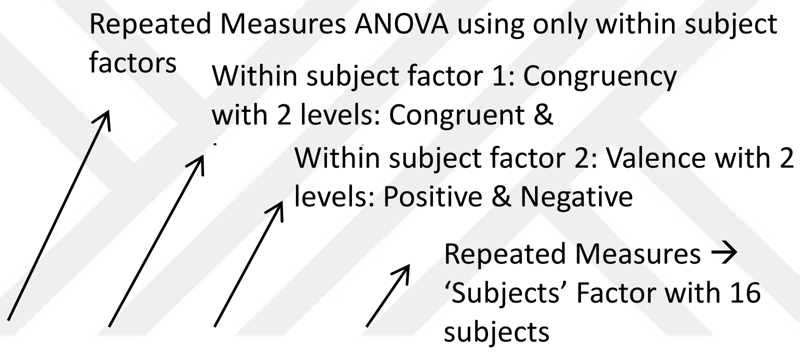
fi

<u>The code that resamples the statistical maps on a talairach space according to the talairached anatomic image:</u>

adwarp -apar anat_warped+tlrc -dpar eStroop_stats+orig -overwrite -prefix S??_eStroop_stats_tlrc

APPENDIX D3: 2nd Level Analysis Commands

<u>Depressed ANOVA</u>



3dANOVA3 -type 4 -alevels 2 -blevels 2 -clevels 16 -dset 1 1 1 H2_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 2 H4_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 3 H5_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 4 H6_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 5 H7_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 6 H8_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 7 H9_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 8 H10_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 9 H12_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 10 H13_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 11 H14_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 12 H15_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 13 H16_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 14 H17_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 15 H18_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 16 H19_eStroop_stats_tlrc+tlrc'[2]' -dset 1 2 1 H2_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 2 H4_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 3 H5_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 4 H6_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 5 H7_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 6 H8_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 7 H9_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 8 H10_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 9 H12_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 10 H13_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 11 H14_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 12 H15_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 13 H16_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 14 H17_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 15 H18_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 16 H19_eStroop_stats_tlrc+tlrc'[5]' -dset 2 1 1 H2_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 2 H4_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 3 H5_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 4 H6_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 5 H7_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1

6 H8_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 7 H9_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 8 H10_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 9 H12_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 10 H13_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 11 H14_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 12 H15_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 13 H16_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 14 H17_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 15 H18_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 16 H19_eStroop_stats_tlrc+tlrc'[8]' -dset 2 2 1 H2_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 2 H4_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 3 H5_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 4 H6_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 5 H7_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 6 H8_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 7 H9_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 8 H10_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 9 H12_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 10 H13_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 11 H14_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 12 H15_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 13 H16_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 14 H17_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 15 H18_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 16 H19_eStroop_stats_tlrc+tlrc'[11]' -fa CongruencyEffect -fb ValenceEffect -fab CongValInteraction -adiff 1 2 congVSincong -bdiff 1 2 posVSneg -aBcontr 1 -1 : 1 congposVSincongpos -aBcontr 1 -1 : 2 congnegVSincongneg -abmean 1 1 depressedcongpos -abmean 1 2 depressedcongneg -abmean 2 1 depressedincongpos -abmean 2 2 depressedincongneg -Abdiff 1 : 1 2 DepcongposDifneg -Abdiff 2 : 1 2 DepincongposDifneg -aBdiff 1 2 : 1 DepposcongDifincong -aBdiff 1 2 : 2 DepnegcongDifincong -bucket EXTDepressedANOVAmain

Control ANOVA

3dANOVA3 -type 4 -alevels 2 -blevels 2 -clevels 16 -dset 1 1 1 S8_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 2 S9_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 3 S10_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 4 S12_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 5 S13_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 6 S14_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 7 S15_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 8 S17_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 9 S20_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 10 S21_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 11 S22_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 12 S23_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 13 S24_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 14 S25_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 15 S27_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 16 S28_eStroop_stats_tlrc+tlrc'[2]' -dset 1 2 1 S8_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 2 S9_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 3 S10_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 4 S12_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 5 S13_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 6 S14_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 7 S15_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 8 S17_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 9 S20_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 10 S21_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 11 S22_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 12 S23_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 13 S24_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 14 S25_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 15 S27_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 16 S28_eStroop_stats_tlrc+tlrc'[5]' -dset 2 1 1 S8_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 2 S9_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 3 S10_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 4 S12_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 5 S13_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 6 S14_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 7 S15_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 8 S17_eStroop_stats_tlrc+tlrc'[8]' -dset 2

1 9 S20_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 10 S21_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 11 S22_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 12 S23_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 13 S24_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 14 S25_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 15 S27_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 16 S28_eStroop_stats_tlrc+tlrc'[8]' -dset 2 2 1 S8_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 2 S9_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 3 S10_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 4 S12_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 5 S13_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 6 S14_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 7 S15_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 8 S17_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 9 S20_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 10 S21_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 11 S22_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 12 S23_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 13 S24_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 14 S25_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 15 S27_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 16 S28_eStroop_stats_tlrc+tlrc'[11]' -fa CongruencyEffect -fb ValenceEffect -fab CongValInteraction -adiff 1 2 congVSincong -bdiff 1 2 posVSneg -aBcontr 1 -1 : 1 congposVSincongpos -aBcontr 1 -1 : 2 congnegVSincongneg -abmean 1 1 controlcongpos -abmean 1 2 controlcongneg -abmean 2 1 controlincongpos -abmean 2 2 controlincongneg -Abdiff 1 : 1 2 ContcongposDifneg -Abdiff 2 : 1 2 ContincongposDifneg -aBdiff 1 2 : 1 ContposcongDifincong -aBdiff 1 2 : 2 ContnegcongDifincong -bucket EXTControlANOVAmain

congposVScongneg (Group Comparison)

Mixed design ANOVA using both between & within subject factors

Between subject factor: Group with 2 levels: Depressed & Healthy

Within subject factor: Valence on Congruency with 2 levels: Congruent-positive & Congruent-negative

Repeated Measures → 'Subjects' Factor with 16 subjects

3dANOVA3 -type 5 -alevels 2 -blevels 2 -clevels 16 -dset 1 1 1 H2_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 2 H4_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 3 H5_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 4 H6_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 5 H7_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 6 H8_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 7 H9_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 8 H10_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 9 H12_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 10 H13_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 11 H14_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 12 H15_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 13 H16_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 14 H17_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 15 H18_eStroop_stats_tlrc+tlrc'[2]' -dset 1 1 16 H19_eStroop_stats_tlrc+tlrc'[2]' -dset 1 2 1 H2_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 2 H4_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 3 H5_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 4 H6_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 5 H7_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 6 H8_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 7 H9_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 8 H10_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 9 H12_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 10 H13_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 11 H14_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 12 H15_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 13 H16_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 14 H17_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 15 H18_eStroop_stats_tlrc+tlrc'[5]' -dset 1 2 16 H19_eStroop_stats_tlrc+tlrc'[5]' -dset 2 1 1 S8_eStroop_stats_tlrc+tlrc'[2]' -dset 2 1 2 S9_eStroop_stats_tlrc+tlrc'[2]' -dset 2 1 3 S10_eStroop_stats_tlrc+tlrc'[2]' -dset 2 1 4 S12_eStroop_stats_tlrc+tlrc'[2]' -dset 2 1 5 S13_eStroop_stats_tlrc+tlrc'[2]' -dset 2 1 6 S14_eStroop_stats_tlrc+tlrc'[2]' -dset 2 1 7 S15_eStroop_stats_tlrc+tlrc'[2]' -dset 2 1 8 S17_eStroop_stats_tlrc+tlrc'[2]' -dset 2 1 9 S20_eStroop_stats_tlrc+tlrc'[2]' -dset 2 1 10 S21_eStroop_stats_tlrc+tlrc'[2]' -dset 2 1 11 S22_eStroop_stats_tlrc+tlrc'[2]' -dset 2 1 12 S23_eStroop_stats_tlrc+tlrc'[2]' -dset 2 1 13 S24_eStroop_stats_tlrc+tlrc'[2]' -dset 2 1 14 S25_eStroop_stats_tlrc+tlrc'[2]' -dset 2 1 15 S27_eStroop_stats_tlrc+tlrc'[2]' -dset 2 1 16 S28_eStroop_stats_tlrc+tlrc'[2]' -dset 2 2 1 S8_eStroop_stats_tlrc+tlrc'[5]' -dset 2 2 2 S9_eStroop_stats_tlrc+tlrc'[5]' -dset 2 2 3 S10_eStroop_stats_tlrc+tlrc'[5]' -dset 2 2 4 S12_eStroop_stats_tlrc+tlrc'[5]' -dset 2 2 5 S13_eStroop_stats_tlrc+tlrc'[5]' -dset 2 2 6 S14_eStroop_stats_tlrc+tlrc'[5]' -dset 2 2 7 S15_eStroop_stats_tlrc+tlrc'[5]' -dset 2 2 8 S17_eStroop_stats_tlrc+tlrc'[5]' -dset 2 2 9 S20_eStroop_stats_tlrc+tlrc'[5]' -dset 2 2 10 S21_eStroop_stats_tlrc+tlrc'[5]' -dset 2 2 11 S22_eStroop_stats_tlrc+tlrc'[5]' -dset 2 2 12 S23_eStroop_stats_tlrc+tlrc'[5]' -dset 2 2 13

S24_eStroop_stats_tlrc+tlrc'[5]' -dset 2 2 14 S25_eStroop_stats_tlrc+tlrc'[5]' -dset 2 2 15 S27_eStroop_stats_tlrc+tlrc'[5]' -dset 2 2 16 S28_eStroop_stats_tlrc+tlrc'[5]' -fa GroupEffect -fb CongruentValEffect -fab GroupCongInteraction -adiff 1 2 depVScont -bdiff 1 2 congposVScongneg -aBcontr 1 -1 : 1 depcongposVScontcongpos -aBcontr 1 -1 : 2 depcongnegVScontcongneg -bucket EXTANOVAcongposVScongneg

<u>incongposVSincongneg (Group Comparison)</u>

3dANOVA3 -type 5 -alevels 2 -blevels 2 -clevels 16 -dset 1 1 1 H2_eStroop_stats_tlrc+tlrc'[8]' -dset 1 1 2 H4_eStroop_stats_tlrc+tlrc'[8]' -dset 1 1 3 H5_eStroop_stats_tlrc+tlrc'[8]' -dset 1 1 4 H6_eStroop_stats_tlrc+tlrc'[8]' -dset 1 1 5 H7_eStroop_stats_tlrc+tlrc'[8]' -dset 1 1 6 H8_eStroop_stats_tlrc+tlrc'[8]' -dset 1 1 7 H9_eStroop_stats_tlrc+tlrc'[8]' -dset 1 1 8 H10_eStroop_stats_tlrc+tlrc'[8]' -dset 1 1 9 H12_eStroop_stats_tlrc+tlrc'[8]' -dset 1 1 10 H13_eStroop_stats_tlrc+tlrc'[8]' -dset 1 1 11 H14_eStroop_stats_tlrc+tlrc'[8]' -dset 1 1 12 H15_eStroop_stats_tlrc+tlrc'[8]' -dset 1 1 13 H16_eStroop_stats_tlrc+tlrc'[8]' -dset 1 1 14 H17_eStroop_stats_tlrc+tlrc'[8]' -dset 1 1 15 H18_eStroop_stats_tlrc+tlrc'[8]' -dset 1 1 16 H19_eStroop_stats_tlrc+tlrc'[8]' -dset 1 2 1 H2_eStroop_stats_tlrc+tlrc'[11]' -dset 1 2 2 H4_eStroop_stats_tlrc+tlrc'[11]' -dset 1 2 3 H5_eStroop_stats_tlrc+tlrc'[11]' -dset 1 2 4 H6_eStroop_stats_tlrc+tlrc'[11]' -dset 1 2 5 H7_eStroop_stats_tlrc+tlrc'[11]' -dset 1 2 6 H8_eStroop_stats_tlrc+tlrc'[11]' -dset 1 2 7 H9_eStroop_stats_tlrc+tlrc'[11]' -dset 1 2 8 H10_eStroop_stats_tlrc+tlrc'[11]' -dset 1 2 9 H12_eStroop_stats_tlrc+tlrc'[11]' -dset 1 2 10 H13_eStroop_stats_tlrc+tlrc'[11]' -dset 1 2 11 H14_eStroop_stats_tlrc+tlrc'[11]' -dset 1 2 12 H15_eStroop_stats_tlrc+tlrc'[11]' -dset 1 2 13 H16_eStroop_stats_tlrc+tlrc'[11]' -dset 1 2 14 H17_eStroop_stats_tlrc+tlrc'[11]' -dset 1 2 15 H18_eStroop_stats_tlrc+tlrc'[11]' -dset 1 2 16 H19_eStroop_stats_tlrc+tlrc'[11]' -dset 2 1 1 S8_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 2 S9_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 3 S10_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 4 S12_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 5 S13_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 6 S14_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 7 S15_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 8 S17_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 9 S20_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 10 S21_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 11 S22_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 12 S23_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 13 S24_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 14 S25_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 15 S27_eStroop_stats_tlrc+tlrc'[8]' -dset 2 1 16 S28_eStroop_stats_tlrc+tlrc'[8]' -dset 2 2 1 S8_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 2 S9_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 3 S10_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 4 S12_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 5 S13_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 6 S14_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 7 S15_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 8 S17_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 9 S20_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 10 S21_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 11 S22_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 12 S23_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 13 S24_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 14 S25_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 15 S27_eStroop_stats_tlrc+tlrc'[11]' -dset 2 2 16 S28_eStroop_stats_tlrc+tlrc'[11]' -fa GroupEffect -fb IncongruentValEffect -fab GroupIncongInteraction -adiff 1 2 depVScont -bdiff 1 2 incongposVSincongneg -aBcontr 1 -1 : 1 depincongposVScontincongpos -aBcontr 1 -1 : 2 depincongnegVScontincongneg -bucket EXTANOVAincongposVSincongneg

Valence of the Face comparison between the groups

3dANOVA3 -type 4 -alevels 2 -blevels 2 -clevels 16 -dset 1 1 1
H2_eStroop_statsFACE_tlrc+tlrc'[2]' -dset 1 1 2
H4_eStroop_statsFACE_tlrc+tlrc'[2]' -dset 1 1 3
H5_eStroop_statsFACE_tlrc+tlrc'[2]' -dset 1 1 4
H6_eStroop_statsFACE_tlrc+tlrc'[2]' -dset 1 1 5
H7_eStroop_statsFACE_tlrc+tlrc'[2]' -dset 1 1 6
H8_eStroop_statsFACE_tlrc+tlrc'[2]' -dset 1 1 7
H9_eStroop_statsFACE_tlrc+tlrc'[2]' -dset 1 1 8
H10_eStroop_statsFACE_tlrc+tlrc'[2]' -dset 1 1 9
H12_eStroop_statsFACE_tlrc+tlrc'[2]' -dset 1 1 10
H13_eStroop_statsFACE_tlrc+tlrc'[2]' -dset 1 1 11
H14_eStroop_statsFACE_tlrc+tlrc'[2]' -dset 1 1 12
H15_eStroop_statsFACE_tlrc+tlrc'[2]' -dset 1 1 13
H16_eStroop_statsFACE_tlrc+tlrc'[2]' -dset 1 1 14
H17_eStroop_statsFACE_tlrc+tlrc'[2]' -dset 1 1 15
H18_eStroop_statsFACE_tlrc+tlrc'[2]' -dset 1 1 16
H19_eStroop_statsFACE_tlrc+tlrc'[2]' -dset 1 2 1
H2_eStroop_statsFACE_tlrc+tlrc'[5]' -dset 1 2 2
H4_eStroop_statsFACE_tlrc+tlrc'[5]' -dset 1 2 3
H5_eStroop_statsFACE_tlrc+tlrc'[5]' -dset 1 2 4
H6_eStroop_statsFACE_tlrc+tlrc'[5]' -dset 1 2 5
H7_eStroop_statsFACE_tlrc+tlrc'[5]' -dset 1 2 6
H8_eStroop_statsFACE_tlrc+tlrc'[5]' -dset 1 2 7
H9_eStroop_statsFACE_tlrc+tlrc'[5]' -dset 1 2 8
H10_eStroop_statsFACE_tlrc+tlrc'[5]' -dset 1 2 9
H12_eStroop_statsFACE_tlrc+tlrc'[5]' -dset 1 2 10
H13_eStroop_statsFACE_tlrc+tlrc'[5]' -dset 1 2 11
H14_eStroop_statsFACE_tlrc+tlrc'[5]' -dset 1 2 12
H15_eStroop_statsFACE_tlrc+tlrc'[5]' -dset 1 2 13
H16_eStroop_statsFACE_tlrc+tlrc'[5]' -dset 1 2 14
H17_eStroop_statsFACE_tlrc+tlrc'[5]' -dset 1 2 15
H18_eStroop_statsFACE_tlrc+tlrc'[5]' -dset 1 2 16
H19_eStroop_statsFACE_tlrc+tlrc'[5]' -dset 2 1 1
S8_eStroop_statsFACE_tlrc+tlrc'[2]' -dset 2 1 2 S9_eStroop_statsFACE_tlrc+tlrc'[2]' -dset 2 1 3 S10_eStroop_statsFACE_tlrc+tlrc'[2]' -dset 2 1 4
S12_eStroop_statsFACE_tlrc+tlrc'[2]' -dset 2 1 5
S13_eStroop_statsFACE_tlrc+tlrc'[2]' -dset 2 1 6
S14_eStroop_statsFACE_tlrc+tlrc'[2]' -dset 2 1 7
S15_eStroop_statsFACE_tlrc+tlrc'[2]' -dset 2 1 8
S17_eStroop_statsFACE_tlrc+tlrc'[2]' -dset 2 1 9
S20_eStroop_statsFACE_tlrc+tlrc'[2]' -dset 2 1 10
S21_eStroop_statsFACE_tlrc+tlrc'[2]' -dset 2 1 11

S22_eStroop_statsFACE_tlrc+tlrc'[2]' -dset 2 1 12
S23_eStroop_statsFACE_tlrc+tlrc'[2]' -dset 2 1 13
S24_eStroop_statsFACE_tlrc+tlrc'[2]' -dset 2 1 14
S25_eStroop_statsFACE_tlrc+tlrc'[2]' -dset 2 1 15
S27_eStroop_statsFACE_tlrc+tlrc'[2]' -dset 2 1 16
S28_eStroop_statsFACE_tlrc+tlrc'[2]' -dset 2 2 1
S8_eStroop_statsFACE_tlrc+tlrc'[5]' -dset 2 2 2 S9_eStroop_statsFACE_tlrc+tlrc'[5]' -dset 2 2 3 S10_eStroop_statsFACE_tlrc+tlrc'[5]' -dset 2 2 4
S12_eStroop_statsFACE_tlrc+tlrc'[5]' -dset 2 2 5
S13_eStroop_statsFACE_tlrc+tlrc'[5]' -dset 2 2 6
S14_eStroop_statsFACE_tlrc+tlrc'[5]' -dset 2 2 7
S15_eStroop_statsFACE_tlrc+tlrc'[5]' -dset 2 2 8
S17_eStroop_statsFACE_tlrc+tlrc'[5]' -dset 2 2 9
S20_eStroop_statsFACE_tlrc+tlrc'[5]' -dset 2 2 10
S21_eStroop_statsFACE_tlrc+tlrc'[5]' -dset 2 2 11
S22_eStroop_statsFACE_tlrc+tlrc'[5]' -dset 2 2 12
S23_eStroop_statsFACE_tlrc+tlrc'[5]' -dset 2 2 13
S24_eStroop_statsFACE_tlrc+tlrc'[5]' -dset 2 2 14
S25_eStroop_statsFACE_tlrc+tlrc'[5]' -dset 2 2 15
S27_eStroop_statsFACE_tlrc+tlrc'[5]' -dset 2 2 16
S28_eStroop_statsFACE_tlrc+tlrc'[5]' -fa GroupEffect -fb FaceEffect -fab GroupFaceInteraction -adiff 1 2 depVScont -bdiff 1 2 posfaceVSnegface -aBcontr 1 -1 : 1 depposfaceVScontposface -aBcontr 1 -1 : 2 depnegfaceVScontnegface -abmean 1 1 depressedposface -abmean 1 2 depressednegface -abmean 2 1 controlposface -abmean 2 2 controlgnegface -Abdiff 1 : 1 2 DepposDifneg -Abdiff 2 : 1 2 ContposDifneg -aBdiff 1 2 : 1 PosdepDifcont -aBdiff 1 2 : 2 NegdepDifcont -bucket EXTFACEANOVA

APPENDIX D4: Post-Processing Command to determine the optimum voxel size and p value to make our statistics Bonferroni corrected

```
# Program:        AlphaSim
# Data set dimensions:
# nx =    64   ny =    64   nz =    34   (voxels)
# dx =  3.00   dy =  3.00   dz =  4.00   (mm)

# Gaussian filter widths:
# sigmax =  2.55   FWHMx =  6.00
# sigmay =  2.55   FWHMy =  6.00
# sigmaz =  2.55   FWHMz =  6.00

# Cluster connection radius: rmm =  5.50
# Threshold probability: pthr = 1.000000e-03
# Number of Monte Carlo iterations = 10000

# Cl Size  Frequency  CumuProp     p/Voxel       Max Freq      Alpha
     1      460337     0.569319     0.00109136       0           1.000000
```

2	184481	0.797475	0.00076081	0	1.000000
3	75557	0.890919	0.00049587	1	1.000000
4	41401	0.942122	0.00033311	82	0.999900
5	20202	0.967106	0.00021420	570	0.991700
6	11255	0.981026	0.00014167	1484	0.934700
7	6317	0.988838	0.00009317	1875	0.786300
8	3748	0.993474	0.00006142	1882	0.598800
9	2119	0.996094	0.00003989	1408	0.410600
10	1239	0.997627	0.00002620	965	0.269800
11	775	0.998585	0.00001730	639	0.173300
12	427	0.999113	0.00001118	393	0.109400
13	290	0.999472	0.00000750	278	0.070100
14	159	0.999669	0.00000479	157	**0.042300**

→the cluster size should be chosen as '14' according to alpha<0.05, corresponding to a threshold of Bonferroni corrected p<0.001 as specified in the code below.

15	104	0.999797	0.00000320	102	0.026600
16	61	0.999873	0.00000208	61	0.016400
17	39	0.999921	0.00000137	39	0.010300
18	29	0.999957	0.00000090	29	0.006400
19	15	0.999975	0.00000052	15	0.003500
20	8	0.999985	0.00000032	8	0.002000
21	2	0.999988	0.00000020	2	0.001200
22	2	0.999990	0.00000017	2	0.001000
23	0	0.999990	0.00000014	0	0.000800
24	5	0.999996	0.00000014	5	0.000800
25	1	0.999998	0.00000006	1	0.000300
26	1	0.999999	0.00000004	1	0.000200
27	1	1.000000	0.00000002	1	0.000100

Code: AlphaSim -nxyz 64 64 34 -dxyz 3 3 4 -iter 10000 -pthr 0.001 -fwhm 6 -rmm 5.5 -quiet -fast -approx -out alpha_p0.001.out

CURRICULUM VITAE

PERSONAL INFORMATION

Surname, Name: Başgöze, Zeynep
Nationality: Turkish (TC)
Date and Place of Birth: 14.01.1982, Ankara
Gender: Female
Marital Status: Single

EDUCATION

Degree	Institution	Year of Graduation
MS	METU Cognitive Sciences	2008
BS	Boğaziçi University Philosophy	2005
High School	Ankara Anatolian High School	2000

WORK EXPERIENCE

Year	Place	Enrollment
September 2014- …	Baskent University, Ankara	Lecturer in Psychology Department
March 2014-December 2015	EU-CIP Project MASTERMIND, Ankara	Project Assistant
February 2014-January 2015	Bilkent University, Ankara	Part-time lecturer in Psychology Department
October 2012-October 2013	Center for Magnetic Resonance Research, Minneapolis	Visiting Scholar
February 2007-September 2012	METU Department of Informatics Institute, Ankara	Research Assistant
October 2006-February 2007	METU Department of Informatics Institute, Ankara	Teaching Assistant
June-July 2004	Klan EURO RSCG Advertising Agency, Istanbul	Trainee copywriter
March-June 2004	Esenkent Yön Dershanesi, Istanbul	Philosophy and Turkish Language Teacher

PUBLICATIONS

1. Başgöze, Z., Gönül, A. S., Başkak B. , Gökçay, D. (2015). Valence-based Word-Face Stroop task reveals differential emotional interference in patients with major depression, *Psychiatry Research, 229(3)*,960-7.
2. Musgrove, D. R., Eberly, L. E., Klimes-Dougan, B., Başgöze, Z., Thomas, K. M., Mueller, B. A., Houri, A., Lim, K. O., Cullen, K. R. (2015). Impaired bottom-up effective connectivity between amygdala and subgenual anterior cingulate cortex in unmedicated adolescents with major depression: results from a dynamic causal modeling analysis, *Brain Connectivity, 5(10), 608-19.*
3. Başgöze, Z., Cullen, K., Gokcay, D. (2014). The contribution of word-face stroop task to measure emotional interference and to specify the level of depression. *Journal of Istanbul Medical School. Vol: 77, Supplement 1*.
4. Basgoze, Z., & Inam, A. (2011). Epilogue: a philosophical perspective on incorporating emotions in human computer interaction. In D. Gokcay, & G. Yildirim, Affective computing and interaction: psychological, cognitive and

neuroscientific perspectives (pp. 359-363). New York: Information Science Reference.

5. Basgöze Z and Gökçay D (2008). Measuring the emotional conflict with a word-face stroop task. *Frontiers in Human Neuroscience. Conference Abstract: 10th International Conference on Cognitive Neuroscience*. doi: 10.3389/conf.neuro.09.2009.01.206

LANGUAGES

- Turkish (Native)
- English (Advanced)
- French (Advanced)
- German (Elementary)

COMPUTING SKILLS:

- Applications: Microsoft Office Suite, GIMP, NVU
- Operating Systems: Windows, Linux
- Other: AFNI, FSL, SPM, SPSS, E-Prime

HONORS & AWARDS:

- METU Best Thesis of Informatics Institute Award (May 2009)
- Turkish Psychopharmachology Association Poster award (2nd Place): 2007, Turkish Psychopharmachology Congress, Istanbul, Turkey
  Poster titled 'Volumetric morphology analysis of compartments of the anterior cingulate cortex in major depressive disorder'
- Came second in graduation from Philosophy Dept., Boğaziçi University (June 2005)

INTERESTS
Ballet, playing cello, knitting, photography, poetry, painting