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**Institutionen för klinisk neurovetenskap**

# The Functional Neuroanatomy of Emotion Regulation in Major Depressive Disorder

AKADEMISK AVHANDLING

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## ABSTRACT

A mood-congruent processing bias toward negative emotional information is a hallmark characteristic of the pathophysiology of major depressive disorder (MDD). Previous neuropsychological studies have provided evidence of this phenomenon in memory and attention paradigms. In addition, functional neuroimaging studies consistently report increased neural responses to negative emotional stimuli, including words and faces.

The amygdala plays an essential role in the determining the salience of a stimulus and is particularly tuned to the evaluation of facial expressions. Two pathways to the amygdala have been proposed: one involving higher-order cortical regions that permits explicit stimulus perception and one involving subcortical structures that allows rapid detection of non-conscious or implicit stimuli of emotional significance.

Several studies have explored the nature of explicit emotional face processing in MDD. However, few have focused on how the brain responds to non-conscious or implicit emotional information. Altered processing of emotional information, below the level of explicit conscious awareness, may contribute to the establishment and maintenance of illness-associated symptoms involving dysfunctional conscious perceptions and social interactions. Providing further evidence, recent research suggests that the mechanisms underlying antidepressant treatment may involve a reversal of the negative emotional processing bias associated with MDD.

The purpose of this thesis was to investigate the functional anatomical neural network of structures involved in mood-congruent processing biases toward non-conscious emotional information in MDD and to evaluate differences in this network associated with antidepressant treatment.

In Study I, a novel backward masking task was developed to examine differences in the hemodynamic response of the amygdala to sad (SN), happy (HN) and neutral (NN) faces presented below the level of explicit conscious awareness using functional magnetic resonance imaging (fMRI). Participants included individuals with current major depressive disorder (dMDD), MDD in full remission (rMDD) and healthy controls (HC). A subset of dMDD participants completed the fMRI task before and after eight weeks of antidepressant treatment with sertraline hydrochloride. An amygdala region-of-interest analysis revealed a greater hemodynamic response in the amygdala to masked-sad vs. masked-happy faces (SN-HN) in dMDD vs. HC. In contrast, HC participants showed a greater response to masked-happy faces. rMDD participants also showed a negative processing bias toward masked-sad faces similar to the dMDD group. In dMDD, the negative processing bias reversed and a positive processing bias emerged following antidepressant treatment.

In Studies II and III, a regional analysis of the cortical and subcortical networks involved with the amygdala in processing emotional information was used to evaluate differences between the dMDD and HC participants and dMDD participants before and after antidepressant treatment from Study I. In Study II, dMDD participants showed a greater hemodynamic response to SN-HN in the hippocampus and anterior inferotemporal cortex. As well, participants showed a greater response to SN-NN or HN-NN in areas of the medial and orbital prefrontal cortex and superior temporal gyrus. In Study III, dMDD participants showed a greater response to SN-HN in the pre- vs. post-treatment condition in the pregenual anterior cingulate cortex, superior temporal gyrus and anterior inferotemporal gyrus. Additional regions of the sensory and visceromotor networks also showed an increased hemodynamic response to SN-NN before versus after treatment. The regions associated with these differential responses are known to participate with the amygdala in evaluating and responding to the salience of emotional stimuli.

Taken together, these studies provide insight into the underlying neurocircuitry associated with the processing of non-conscious emotional information. Furthermore, they reveal networks that are influenced by antidepressant treatment to alter brain function and establish a reversal of the negative processing bias and development of a normative positive processing bias in major depressive disorder.