Cognitive vulnerability to depression : genetic and environmental influences

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Summary

Title: Cognitive Vulnerability to Depression: Genetic and Environmental Influences

This thesis explores cognitive vulnerability to depression and the interplay between genetic and environmental influences. A large percentage of people suffer from depression and will most likely experience another episode at some point in life. Determining the mechanisms that make an individual prone to depression (or its recurrence) remains a challenge.

From a cognitive science perspective, cognitive vulnerability to depression is characterized by negative patterns of information processing. These patterns may be formed during the depressive state and/or may be latent and re-activated in the face of mild mood fluctuations. One type of cognitive vulnerability is *cognitive reactivity (CR)*: the ease with which maladaptive cognitions are triggered by non-pathological low mood. Another type of cognitive vulnerability involves information processing biases in attention, decision-making, facial emotion recognition, and other cognitive processes that are crucial in how one processes personal and socially relevant affective information. Such factors are known to play an important role in the development and maintenance of depression. Due to their specificity, they have been recently proposed as potential endophenotypes, lying in between genes and complex phenotypes such as depression.

The aim of this thesis was twofold. In the first part, the role of cognitive reactivity and emotional information processing as vulnerability factors or endophenotypes of depression were investigated. In the second part, effects of experimental manipulations on emotional cognition were examined.

In chapter 1, the theoretical framework of this thesis is described and the research questions are introduced, which are then investigated in chapters 2 to 6. In **chapter 2**, the role of cognitive reactivity (CR) in recurrent depression was studied within the context of suicidality. It is suggested that suicidal ideation arises as part of the negative thinking patterns during the first episodes and an association is formed between depressed mood and suicidal thoughts such that future mood fluctuations may re-activate such thinking. A subtype of individuals that have suffered from suicidal tendencies during their depression was examined within the longitudinal research project: the Netherlands Study of Depression and Anxiety. Using a self-report measure of CR, the Leiden Index of Depression Sensitivity-Revised (LEIDS-R), which contains several subscales, the CR profile of recovered depressed individuals with/without suicidal ideation/behaviour was examined. The results showed that history of suicidal ideation was associated with a distinct CR profile during remission: elevated hopelessness

reactivity scores. This relationship was independent of anxiety disorder co-morbidity. Moreover, a history of suicide *attempt(s)* was associated with both higher hopelessness reactivity and higher aggression reactivity. This study demonstrated that suicidal ideation and suicidal behavior were associated with distinct CR patterns. Since CR is a potentially treatable vulnerability marker of depression recurrence, this has important clinical implications.

In **Chapter 3**, the plausibility of CR as an endophenotype of depression was investigated. The relationship between genetic variation on the serotonin transporter gene (5HTTLPR) and childhood adversity (a gene-environment interaction) was examined on CR, on the personality trait of neuroticism and on depression diagnosis as comparable (endo)phenotypes. The findings showed that participants with the homozygous low expressing genotype (*ss*) had the highest CR if they had experienced childhood emotional maltreatment but the lowest CR if they did not have such experience. This interaction was strongest on the Rumination subscale of CR. No significant results were found with neuroticism or depression diagnosis, and no direct effect of genotype was found. The pattern of the results provides support for a differentially susceptible genotype rather than a vulnerable genotype: absence of maltreatment yielded the lowest CR scores in the *ss* genotype group.

In **Chapter 4**, facial emotion perception was examined as another plausible endophenotype of depression. Biases in the perception of emotional face expressions can influence social and emotional adaptation, and contribute to depression vulnerability. The association of the 5HTTLPR gene, stressful life events and gender with facial emotion perception was investigated. *S* homozygous participants recognized negative facial expressions (anger, sadness, fear) at a lower intensity than the other genotype groups. This effect was more evident in female participants and in participants who had experienced negative life events. The increased sensitivity of the *s* homozygous genotype is assumed to be related to a heightened neurobiological response to threat (as also shown in neuroimaging studies) and subsequent increased vulnerability to emotional disorders.

In Part B (Chapter 5 & 6), biases in emotional cognition were manipulated experimentally. Most research to date has examined how alternative treatment approaches, such as omega-3 fatty acid supplementation, affect mood; there is little research on cognitive effects. In **Chapter 5**, the effects of omega-3 supplementation on

depression-relevant cognitive functioning were explored. Fifty-four healthy volunteers were randomized to receive either omega-3 supplements or placebo for four weeks in a double-blind design. Results revealed that the omega-3 group made fewer risk-averse decisions than the placebo group and this behavior was not accompanied by increased impulsiveness. The omega-3 group also had lower scores on the control/perfectionism CR subscale, and reported reduced fatigue. No effects were found on the other cognitive tasks and on mood.

In **Chapter 6,** the effects of omega-3 supplementation on cognition and mood were examined in a more vulnerable sample, that of recovered depressed individuals. Seventy-one participants with history of depression were randomized to receive either omega-3 or placebo for 4 weeks in a double-blind design. Results showed an effect of omega-3 supplementation on emotional decision-making and on states of depression and tension. Participants in the omega-3 group also showed decreased recognition of fearful faces compared to placebo, but this result was confounded by a learning effect. No meaningful effects were observed on the attentional tests, memory, cognitive reactivity and depressive symptomatology. Since the neuropsychological mechanisms of action of omega-3 fatty acids are yet unknown, future research is warranted in this field.

Finally, **Chapter 7** is the concluding chapter of this thesis. It contains a summary and integration of the main findings in the context of the related theoretical frameworks. In brief, cognitive reactivity is a valuable measure of depression vulnerability. Together with facial emotion perception, these two vulnerability measures constitute plausible endophenotypes of depression, influenced by gene-environment interactions. Some aspects of cognitive vulnerability can be modified by omega-3 fatty acid supplementation. For each part of the thesis, methodological considerations are outlined, clinical implications are addressed and future directions in the field are suggested.