Cognitive vulnerability to depression : genetic and environmental influences

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Chapter 7

General Discussion

The aim of this thesis was twofold. First, cognitive reactivity and aspects of emotional information processing were investigated as vulnerability factors or endophenotypes of depression. Secondly, the effects of an experimental manipulation, omega-3 supplementation, on emotional information processing, cognitive reactivity and mood were examined in healthy and recovered depressed individuals.

In this chapter, the main findings of the previous chapters will be briefly summarized. In addition, the results will be related to other research findings and to pertaining theories. Finally, methodological considerations will be addressed, future research will be proposed, and possible clinical implications will be highlighted.

Part A: Cognitive Vulnerability to Depression and Endophenotypes

Cognitive reactivity and suicidality

Cognitive reactivity (CR) is the tendency to respond to mild changes in mood with increased negative thinking. A large body of research has already shown that cognitive reactivity is an underlying vulnerability factor for depression. Individuals who have recovered from depression have higher CR scores than never-depressed individuals and this is linked to relapse risk (Segal et al., 2006). One recent paper had applied this concept to the area of suicidality (Williams et al., 2008). In the present thesis (chapter 2), the role of cognitive reactivity in previously depressed participants with and without history of suicidality was further examined. Distinct cognitive reactivity profiles in the group with suicidal tendencies were found. Firstly, recovered depressed participants with a history of suicidal ideation had higher hopelessness/suicidal reactivity scores than recovered depressed participants without such history. Participants with anxiety disorder comorbidity showed the same pattern. Secondly, recovered depressed individuals who had made a suicide attempt in the past not only showed higher hopelessness/suicidal reactivity but they also reported higher aggression reactivity. From all the other depressive symptoms during the past episode, only 'feelings of guilt' was also related to hopelessness/suicidal reactivity.

Whereas both hopelessness and aggression have been implicated as risk factors for suicidality in the past, the 'reactivity patterns' of these factors seems to be the key determinant of whether the underlying vulnerability is still there. The 'differential activation hypothesis' states that during a depressive episode an association is formed

between low mood and depressive cognitions. Consequently, mood fluctuations become more likely to reactivate such cognitions in the future, even when depression is in remission (Teasdale, 1988). The present findings confirm Williams et al. (2008) findings that this theory may be extended to the area of suicidality. Furthermore, individuals who have carried out a suicide attempt during their depression react with an increase of both hopelessness and aggressive thoughts when non-depressed but in a low mood. Whether this increased hopelessness and aggression reactivity increases the risk of future suicide attempts remains to be investigated.

Cognitive Reactivity as an Endophenotype

Cognitive reactivity was tested as a potential endophenotype of depression. In chapter 3, the findings show that the serotonin transporter polymorphism (5-HTTLPR) moderates the effect of childhood emotional abuse on CR. Participants homozygous for the short allele *(s)* and low emotional abuse history had significantly lower total CR scores than the other genotype groups. The same group reported higher CR when they had experienced moderate levels of childhood emotional abuse. The same differential susceptibility pattern was found for rumination reactivity.

Our findings, together with prior research, emphasize the importance of studying how genes interact with environment. They also show that, depending on environmental factors, certain genetic variants may not only increase the risk of psychopathology, but also contribute to resilience. Although our study was not designed to measure resilience, the low CR scores in the *s* homozygous participants with no history of childhood emotional maltreatment suggest that a protective interaction effect has occurred. Indeed, Chapter 3 provides stronger evidence for the differential susceptibility hypothesis (Belsky et al., 2007) than for the commonly studied diathesis-stress model (Monroe & Simons, 1991). In brief, the diathesis stress model assumes that some individuals are more likely to succumb to environmental stress due to a certain "vulnerability" or "diathesis" – which in this case would be genetic, but can also be temperamental, biological, etc. (Monroe & Simons, 1991). To date, most gene or gene-environment studies on depression are based on this model. The differential susceptibility hypothesis, on the other hand, purports that individuals who are likely to be affected by the environment in an adverse way, can also be the ones affected by a positive environment or by the absence of a negative one in a beneficial way (Belsky et al., 2007). This hypothesis

regards those individuals more *susceptible* to environmental influence and not merely more *vulnerable* than others.

Although the evidence in Chapter 3 is in favour of the differential susceptibility hypothesis, it does not mean that the diathesis-stress model was not supported. Indeed, the theories are not incompatible and may be complimentary. The low rates of maltreatment exposure in our sample inevitably favour the detection of susceptibility instead of vulnerability. Higher rates of exposure to early adversity may provide stronger support for the diathesis-stress approach. Consequently, sample differences with respect to environmental exposure may be a reason for inconsistent findings between studies.

The differential susceptibility model is also supported by evidence on genetic variants other than the 5-HTTLPR polymorphism. Recent research with the dopamine receptor gene, DRD4, has shown that children carrying 7-repeat DRD4 allele seem to benefit the most from sensitive parenting but also suffer the most from insensitive parenting (Bakermans-Kranenburg & van Ijzendoorn, 2006; Bakermans-Kranenburg et al., 2008). A number of other genes have also been studied, providing further evidence for the differential susceptibility model, and can therefore be conceived as *plasticity* genes instead of vulnerability genes (see Belsky et al., 2009 for a review). Individuals with more plasticity alleles in different genes may therefore be more susceptible to environmental influences (Belsky & Pluess, 2009). There is preliminary support of this proposition involving the DAT1 gene and the 5-HTTLPR (Sonuga-Barke et al., 2009) and five plasticity alleles from five different genes (Belsky & Beaver, 2010).

Deconstructing Cognitive Reactivity

Cognitive reactivity as measured with the LEIDS-R is comprised of several subscales that reflect different dimensions of maladaptive cognitions that characterize the vulnerable depressed mind. This thesis provides some insight in how different aspects of cognitive reactivity are differentially implicated in the "pathways" of vulnerability to depression.

Hopelessness/suicidal reactivity seems to be an underlying vulnerability mechanism activated mainly in individuals with a history of depression. In studies to date, it can be observed that recovered depressed individuals respond with higher hopelessness/reactivity levels in the face of mild mood fluctuations, compared to previously non-suicidal recovered depressed participants (Williams et al., 2008; Chapter 2). Furthermore, (Barnhofer & Chittka, 2010) investigated whether the different aspects

of cognitive reactivity (as measured with the LEIDS-R subscales) mediate the relationship between neuroticism and depressive symptoms, in previously and never-depressed individuals, and found that hopelessness/suicidal reactivity was a mediator only in individuals with a history of depression. Hence, hopelessness/suicidal reactivity seems to follow Teasdale's model of differential activation, namely that an association is formed between suicidal thinking and low mood during the depressed phase and these associations remain latent when the individual has recovered from the depression.

On the other hand, observed evidence shows that rumination reactivity can be a vulnerability factor for both onset and recurrence of depression. In our genetic study, participants with a certain genetic variant and experience of adverse emotional childhood had higher rumination reactivity, and lower if they had did have such experience. More than 50% in that group had never suffered from a depression. Rumination reactivity therefore seems to arise with experience of childhood emotional maltreatment and especially in individuals who have a genetic susceptibility (Chapter 3). Hence, the association formed between maladaptive cognitions and depressed mood may not be limited to the context of sadness, but could be generalized to any negative mood that an individual experiences intensely and repeatedly (e.g., through the experience of emotional abuse). Similarly, Barnhofer & Chittka (2010) found that rumination reactivity mediates the relationship between neuroticism and depressive symptoms not only in previously depressed participants but also in healthy controls.

Facial emotion recognition as an Endophentype

In Chapter 4, the relationship between the 5-HTTLPR gene and the identification of facial emotional expressions was examined. In this study, we observed a main effect of the 5-HTTLPR genotype on emotion recognition, as well as a gene-environment interaction with both childhood emotional abuse and recent life events as contributors. More specifically, the *s* homozygous individuals recognized negative emotions easier than the other genotype groups. Life adversity, both early and more recent, increased this vulnerability in *s* homozygote participants and specifically in females. In males, the heterozygote genotype showed a significantly easier recognition of angry and sad facial expressions. Recent life events did not have an additive effect in participants who had experienced emotional maltreatment during childhood.

These findings replicated previous research showing increased vulnerability in carriers of the *s* allele to negative stimuli as measured with behavioural endophenotypes

(Beevers et al., 2007; Perez-Edgar et al., 2009). They also extend previous research by showing that the sensitivity of the *s* homozygous individuals to negative emotional stimuli is increased by the experience of adverse life events and is more evident in females. Effects of 5-HTTLPR have been observed also along a spectrum of other behavioural and physiological endophenotyes. The *s* allele has been associated with enhanced acquisition of conditioned fear responses (Lonsdorf et al., 2009) as well as increased startle responses (Armbruster et al., 2009; Brocke et al., 2006). Another recent study found increased sensitivity of the *s* allele carriers in socio-emotional tasks. *S* allele carriers showed reduced financial risk taking, increased trait anxiety, ambiguous threat perception and greater sympathetic activity compared to the *l* homozygotes (Crisan et al., 2009). Several studies have shown increased HPA axis reactivity to negative or threatening stimuli in *s* alleles (Alexander et al., 2009; Gotlib et al., 2008; Way & Taylor, 2010). In these studies, the *s* allele is not related to baseline indices of HPA function, but is related to a greater reactivity after stress.

Similarly, an increased amygdala reactivity to threat-related information has been observed in *s* carriers of the 5HTTLPR (Munafo et al., 2008). Existing evidence shows an association between measures of complex behavioral traits that increase the risk of depression and reactivity of the amygdala to affective stimuli (Hariri, 2009). A meta-analysis concluded that there is an association between 5-HTTLPR and amygdala reactivity, explaining up to 10% of phenotypic variance (Munafo et al., 2008). A number of studies have shown increased amygdala activation in response to negative facial expressions (Canli et al., 2008; Hariri et al., 2005; Hariri et al., 2002; Pezawas et al., 2005). Furthermore, cumulative research suggests that the network communicating information from the environment to the amygdala and between the amygdala to the regulatory areas in the prefrontal cortex is affected in carriers of *s* alleles of the 5-HTTLPR (Caspi et al., 2010, for a review). Parallel to the functional differences associated with the 5-HTTLPR, structural changes have also been observed within the same networks. *S* allele carriers also showed reduced gray matter volume in the amygdala and in the anterior cingulate cortex, compared to *ll* homozygotes (Pezawas et al., 2005). The 5-HTTLPR is also related to alterations in microstructure of frontal-limbic white matter pathways, which may contribute to the observed biased regulation of emotional stimuli (Pacheco et al., 2009).

In a recent review, Caspi et al. (2010) concisely summarize the evidence of how the *s* allele of the 5-HTTLPR affects the brain's neural circuitry, and how this is mirrored

in both behavioral and physiological processes, which altogether shape the individual's risk for depression. Chapter 4 adds on this growing literature by showing that the *s* allele is involved in a perceptual bias for negative facial emotions, and that this relationship is also moderated by gender and by stressful life events.

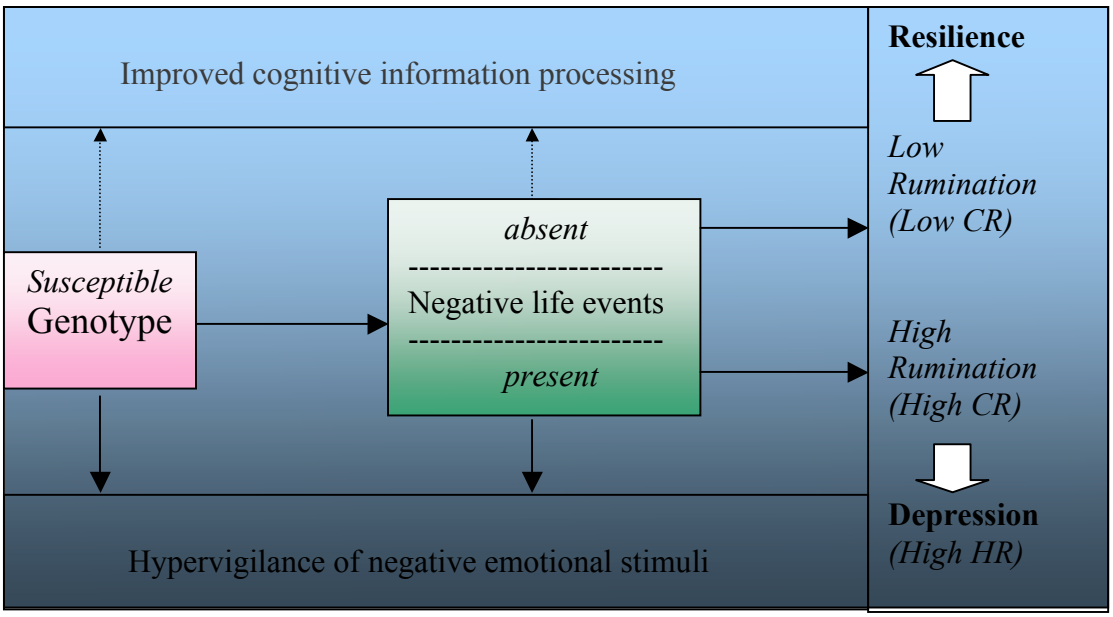
Integration of findings on Endophenotypes

In this thesis, the findings on the effects of 5HTT gene variants on plausible endophenotypes (Chapters 3 & 4) have provided new evidence of how genetic variation and environmental experiences influence vulnerability to depression. **Figure 1** depicts a schematic summary of the findings. A susceptible genotype (*s* homozygous allele of the 5-HTTLPR) in the *absence* of negative life events, such as childhood emotional maltreatment, is less likely to react with negative cognitions and ruminative thinking to mood challenges compared to other genotypes. This increases the chances of developing resilience. On the other hand, the same genotype in the *presence* of emotional maltreatment during childhood is more likely to have increased rumination tendencies and overall cognitive reactivity compared to other genotypes. This pattern increases vulnerability to depression. At a more automatic level, the susceptible genotype shows hyper-vigilance of negative emotional stimuli such as facial expressions of sadness and anger. This sensitivity is more evident in female carriers of the susceptible genotype and/or in those who have experienced negative life events (either early in childhood or more recently in life).

There is a general consensus that the *s* allele is related to increased stress sensitivity to the environment, depicted as increased cortical activation, attention to negative emotional stimuli, HPA hyperactivity and enhanced autonomic responses (Homberg & Lesch, 2010). However, there is also evidence that this increased sensitivity applies to positive environmental cues. For example, in one study, *s* homozygotes showed an attentional bias to positive images compared to other genotype groups (Beevers et al., 2009). Moreover, other cognitive functions seem to be positively affected by 5-HTTLPR variation. Preliminary evidence shows that *s* alleles have shown improved response inhibition in an affective go/no-go task (Roiser et al., 2007) and improved decision-making as evident in a gambling task (Roiser et al., 2006). Parallel to human studies, evidence in *s* allele nonhuman primates also shows superior performance on several cognitive tasks (Homberg & Lesch, 2010 for a review). The increased sensitivity to both aversive but also rewarding stimuli may constitute an evolutionary advantage,

which may explain how these common genetic variants have not become eliminated from the genetic pool through natural selection (Homberg & Lesch, 2010). Future research is clearly warranted in understanding how genes and environment influence the brain and behaviour not only in increasing the risk to psychopathology but also in promoting resilience.

Figure 1. Genetic susceptibility model to depression/resilience on the basis of findings on the 5-HTTLPR.



Bold arrows represent associations addressed in this thesis. Dark areas represent vulnerability, lighter areas represent resilience. CR: Cognitive Reactivity, HR: Hopelessness Reactivity.

Genetic sensitivity to the environment: methodological considerations

Failures to detect (or replicate) G x E interactions in depression research may be due to several reasons. Of clear importance is the definition and measurement of the (endo)phenotype. A dichotomous depression diagnosis is suboptimal since such a categorization reduces the inter-individual variability that characterizes this disorder. On the basis of the DSM-IV criteria, it is theoretically possible that two depressed patients have no symptom in common. This approach poses obvious obstacles when trying to relate a specific genetic variable to such a heterogeneous syndrome.

Neuroticism is a possible endophenotype, and indeed it was linked to the 5HTT gene earlier than depression. The literature is very inconsistent and measurement

instrument might play a role, which does not increase confidence in the robustness of the relationship. A recent meta-analysis showed no evidence for an association between the 5-HTTLPR and the scores on the Eysenck neuroticism scale, but only preliminary evidence for an association with the NEO neuroticism scale (Munafo et al., 2009). As the authors discuss, the usefulness of having one measurement instrument that is related to a gene whereas another measure of the same concept is not, is uncertain. Furthermore, only recent studies have taken the moderating effects of life adversity into account. Pluess et al. (2010) found that individuals carrying the short allele had the highest neuroticism scores when exposed to life stress and the lowest scores when exposed to positive events. These findings are line with the differential susceptibility hypothesis (Belsky & Pluess, 2009).

Another reason for unsuccessful G x E detection is due to differences in the assessment of the environmental contributor. For example, different kinds of environmental factors have been measured in G x E studies, but not all factors are known to contribute to the aetiology of depression. Two studies that did not find a G x E interaction (Gillespie et al., 2005; Surtees et al., 2006), also found weak or non-significant associations between stressful life events and depression outcomes – which is atypical. The case of childhood emotional maltreatment as an environmental pathogen is unique in its direct link with the development of depression (Chapman et al., 2004; Gibb, 2002; Gibb et al., 2001). Childhood abuse has also been associated with early changes in brain function and long-lasting effects in several biological systems, including the serotonergic system (Nemeroff, 2004) as well as structural changes in the brain (Van Harmelen, et al. 2010). In light of the inconsistent findings in G x E interaction research on depression, Brown & Harris (2008) outlined the role of including environmental pathogens that are known to predict a chronic course of depression. In a review, they concluded that the evidence for childhood maltreatment as an environmental contributor to the perpetuation of adult depression is much stronger than that for recent life events (Brown & Harris, 2008). On the other hand, another review argued that recent and acute stress is more relevant compared to chronic and distal life events (Monroe & Reid, 2008). A more appropriate question to address on this issue could be *which type of negative life event is relevant for which (endo)phenotype?* Depending on the nature of the environmental stressor, it may be possible that effects are detected on one type of endophenotypic measurement (e,g., neurobiological) but not on another type (e.g., psychological) or vice versa. For example, in G x *E* interactions, *recent* life events may be a sufficient *"E"* variable to evoke

(a) a neurophysiological response: e.g., increased startle responses (Armbruster et al., 2009) or (b) a neuropsychological response: e.g., increased perception of negative facial emotions (Chapter 4), but they may be an insufficient *"E"* variable for phenotypes such as depression diagnosis (Gillespie et al., 2005). On the other hand, childhood maltreatment seems to be a sufficient *"E"* variable not only when the (endo)phenotypic outcome is depression diagnosis or depression-related psychological measures (Eley et al., 2004; Sjoberg et al., 2006; Taylor et al., 2006; Chapter 3), but also when neuropsychological endophenotypes are used, such as facial emotion perception (Chapter 4). Such consistent observations of G x E interactions, constitute childhood abuse as a more pervasive environmental contributor, possibly closer to the gene on the genotype-phenotype continuum.

Other reasons for occasional failures to detect effects in G x E interactions are several study design limitations, such as gender ratio differences, mixed ethnicities, heterogeneous age groups, comorbid conditions and degree of exposure to the environmental pathogen (Wermter et al., 2010, for a review). In the future, well-designed studies are warranted that include sophisticated characterization of both the (endo)phenotype and environmental stressors, as well as an evidence-based rationale for their interrelation.

Future research on cognitive vulnerability to depression and endophenotypes

Research on vulnerability markers of depression typically compares remitted depressed patients with never-depressed individuals. This has the advantage that neither group is depressed at the time of testing, so abnormalities cannot be mere epiphenomena of the acute depressive episode. Some of these abnormalities cannot be observed easily in the remitted state, but are latent processes that have to be (re-)activated (e.g., by stress) to become detectable. In this thesis, cognitive reactivity was found to be a vulnerability factor to suicidality. Since these findings were based on cross-sectional data, longitudinal studies would assist in determining whether cognitive reactivity is an underlying vulnerability marker that can lead to depression onset or relapse.

Cognitive reactivity was also found to be a valuable illness endophenotype, showing that having a certain genotype makes one more susceptible to the environment and results in high or low cognitive reactivity to sad mood. Future studies should focus on investigating genetically mediated effects on both resilience and vulnerability (Wermter et al., 2010). Consequently, positive environmental contributors can also be

studied in G x E interaction research. This will increase our understanding of pathways to resilience, or reduced vulnerability to depression. This kind of research may also help to resolve inconsistencies between findings. An interesting question that arises is also if vulnerability to depression can be reversed. If a vulnerability factor has dynamic properties, can increase and decrease under certain circumstances, it would be interesting to examine if environmental influences can also change genetic expression back to their default states (Wichers et al., 2010). For example, there is preliminary research showing that experience of positive emotions during stressors can decrease the level of stress-sensitivity (Wichers et al., 2007). In that study, it was shown that genetic vulnerability to depression (expressed as having a twin with a lifetime depression diagnosis) can be attenuated when participants experience positive affect during stress in daily life (Wichers et al., 2007). At the neurobiological level, recent evidence has also shown that cognitive emotion regulation can diminish the difference in amygdala reactivity to threat-related stimuli between genotype groups of the 5-HTTLPR (Schardt et al., 2010). They also show that such volition strategies can alter prefrontal-amygdala connectivity. This is an indication that the increased sensitivity in s alleles can be reversed.

Cumulative evidence from epidemiology and evolutionary theory indicate that mental disorders such as depression are likely to be caused by gene-environment interactions and that a direct contribution by one common genetic variant is unlikely (Uher, 2009). It seems therefore that the gene-environment interaction method may yield promising advances in the understanding of the etiology of depression in the field of psychiatric genetics. In parallel, endophenotypes have been quite successful in elucidating neuropsychological and biological mechanisms that contribute to behavioural phonotypes (Meyer-Lindenberg, 2010). Finally, since a single polymorphism at one locus is probably not the only genetic pathway that shapes future cognition and behaviour, the study of interactions between risk variants holds considerable promise for the way forward in understanding the genetic architecture of depression.

Clinical Implications of cognitive reactivity and genetic research

Treatments in depression should not only focus on reducing symptoms but also vulnerability factors or "scars", in order to prevent the common perpetuating cycle that leads to recurrent episodes. For example, in a relatively new approach against relapse to depression – Mindfulness Based Cognitive Therapy, it was recently shown that mindfulness practices significantly reduced cognitive reactivity compared to a control

group (Raes et al., 2009). By detaching from one's own negative thoughts and focusing on "being in the present moment", the re-activation system of maladaptive cognitions can become weaker and less automatic. Consequently, a future possible application in clinical practice could be the assessment of decrease in cognitive reactivity (or hopelessness reactivity in previously suicidal patients).

Hence, it is not surprising that constructs embedding cognitive vulnerability to depression have been shown to be successful endophenotypes. The usefulness of endophenotypes lies in their positioning between the gene and the disorder. By unravelling the mechanisms that underlie depression vulnerability the prospects for improved personalized treatment increase. Research in the pharmacogenetics of depression is a flourishing field at the moment and a recent review concluded that several polymorphisms, including the 5-HTTLPR, modulate anti-depressant response (Kato & Serretti, 2010). In the first study to relate genetic variation to response to cognitive behavioural therapy in post-traumatic stress disorder patients, the *s* allele was related to a poorer response (Bryant et al., 2010). Additionally, the study of gene-environment interactions can help explaining individual differences in vulnerability or resilience to environmental pathogens and to the development of depression.

Part B: Modifying cognitive vulnerability to depression

In the second part, this thesis explored how cognitive vulnerability to depression can be modified by supplementation with omega-3 fatty acids. Omega-3 fatty acids may affect the brain and neuronal functioning through numerous mechanistic pathways (Owen et al., 2008). Firstly, DHA being a major structural component of the brain can affect cell membrane integrity and fluidity. Secondly, omega-3 concentrations can affect neurotrophins, such as the brain-derived neurotrophic factor (BDNF), which assists in the survival of existing neurons and encourages growth of new neurons and synapses. Thirdly, omega-3 fatty acids can influence gene expression. Finally, omega-3 (especially EPA) can decrease the production of pro-inflammatory cytokines and oxidative reactions. Although correlational studies provide some insight into the relationship between omega-3 fatty acids and depression, experimental (supplementation) studies have proven quite useful in understanding its effects on mood and cognition.

Firstly, Chapter 5 presented a double-blind placebo-controlled study, wherein effects of omega-3 supplements were tested on depression-relevant cognitive functioning in healthy individuals. The findings showed a few effects of omega-3 on cognition and mood. During the non-normative trials of decision-making, the omega-3 group made fewer risk-averse decisions than the placebo group. This only occurred in trials where there was a choice between a certain gain and 'double or nothing'. In these trials, where an overwhelming majority chooses the certain gain, participants in the omega-3 group were more likely to gamble for the larger gain. This was not accompanied by increased impulsiveness, but most likely reflected calculated thinking. No effects were found on other cognitive tasks. It cannot be ruled out, however, that the observed differences are not due to treatment with omega-3, since this task was only administered at post-test and mere group differences may explain the results. Furthermore, the omega-3 group had decreased scores on the control/perfectionism scale of cognitive reactivity, and reported lower fatigue.

Secondly, Chapter 6 presented a randomized double-blind placebo-controlled trial, wherein effects of omega-3 supplements were examined on cognitive functioning and mood of recovered depressed individuals. We again observed a group difference on the gambling task. The omega-3 group showed modulated decision-making behaviour compared to placebo: they were more likely to choose the '50-50% chance' gamble (or control gamble) compared to the variant (experimental) gamble when the expected gains were large and the expected losses were small. Participants in the omega-3 group also

showed decreased recognition of fearful faces compared to placebo, but a learning effect was also evident which makes this finding difficult to interpret. No meaningful effects were found on the other cognitive tasks. The omega-3 group also reported lower depression and tension scores compared to placebo. The findings of Chapters 5 and 6 show that omega-3 supplementation had selective effects on emotional information processing and mood in healthy and recovered depressed individuals.

These two studies used the same model that has been validated by others (Harmer et al., 2009) to examine the effects of antidepressant drug treatment. According to the cognitive neuropsychological hypothesis of antidepressant drug action, antidepressants work by remediating negative emotional cognitive biases in depression to a more positive direction, such changes not being necessarily accessible to subjective state, and which in the longer run may lead to gradual changes in social interaction, behaviour and mood (Harmer et al., 2009). Research to date has mostly focused on the effects of omega-3 fatty acids on mood improvement (Appleton et al., 2010, for a meta-analysis) and only very few studies have investigated effects of omega-3 on cognitive processing biases in depression. In a healthy group, Fontani et al., (2005) found a reduction in reaction times in two neutral cognitive tasks representing processes of vigilance and working memory. The results of that study may not be reliable though, since statistical tests were limited to pre-post supplementation t-tests conducted only for the omega-3 group. No data for the control group were reported; it is therefore unknown whether improvements in the omega-3 group were significantly larger than changes in the placebo group.

In a group of mild and moderately depressed individuals, Rogers et al., (2008) found no effects of omega-3 supplementation on a range of neutral cognitive tasks (simple reaction time, lexical decision, digit-symbol substitution, impulsivity, N-Back) and one emotional task involving physically or socially threatening words (visual probe task). In this visual probe task, anxiety disorder patients have previously shown increased attentional bias toward threat stimuli (MacLeod & Mathews, 1998) whereas evidence for such bias in depressed patients is less robust (Mogg & Bradley, 2005). Rogers et al. detected only one marginal effect on the impulsivity measure, which they interpreted as a chance finding. It is important to note that the test battery used in that study does not quite represent sensitive measures to depression vulnerability, which may explain the failure to detect significant differences.

In the two studies presented in chapters 5 and 6, we used assessments of cognitive processing that had been shown to be sensitive to cognitive biases in depression (Austin et al., 2001), or sensitive to neurotransmitter manipulations in healthy samples, tryptophan loading/depletion and anti-depressant administration (Merens et al., 2007 for a review). The main observation in both supplementation studies was the selective effect of omega-3 on decision-making behaviour. The effects of omega-3 supplementation were different in each sample: the healthy group showed increased risky choices in the non-normative trials of the task, whereas the recovered depressed group showed decreased discrimination between magnitude of possible gains and losses but shorter deliberation times. These are the first studies examining effects of omega-3 fatty acids on decision-making. The finding in the healthy group may be related to optimism (Isen & Geva, 1987), but the finding in the recovered depressed group reflects swift and cautious behaviour and is more difficult to understand. A factor that was not controlled for and may have affected the results is genetic variation. There is recent evidence that decision-making/gambling behaviour is modulated by serotonergic polymorphisms using the same task (Roiser et al., 2006). In that study, healthy participants carrying the *s* allele discriminated between high and low probabilities of winning to a greater extent than *l* homozygote participants. However, that study used a small sample (n=58) containing a subgroup of polydrug users (n=30). Other studies using different tasks have found that the 5-HTTLPR (Stoltenberg & Vandever, 2010), other serotonergic genes (Juhasz et al., 2010), and gene-gene interactions (Ha et al., 2009) are related to decision-making performance. Although genetic variation is only one of the many factors that may differentially vary between groups and affect the results, future studies would benefit in taking this parameter into account.

In the study with recovered depressed individuals (Chapter 6) we found preliminary evidence that omega-3 may affect the perception of threat-relevant material, as shown in the reduced recognition of fearful faces in the omega-3 group. This observation resembles closely the findings on the effects of repeated ('subchronic') antidepressant administration on facial emotion recognition. Seven days of citalopram also reduced the perception of fearful facial expressions in healthy volunteers (Harmer et al., 2004). Neuroimaging studies (fMRI) show effects that are congruent with these behavioural findings. Seven days of antidepressant treatment decreased amygdala activity (Harmer et al., 2006; Norbury et al., 2007) and medial prefrontal cortex activity (Harmer et al., 2006) to fearful faces. A single administration of citalopram in recovered depressed

individuals also decreased recognition of fearful expressions (Bhagwagar et al., 2004). Future studies investigating the effects of omega-3 on facial emotion recognition are worthwhile, and genetic variation would again be a valuable parameter to consider.

Finally, an effect of omega-3 supplementation was observed on mood states. The healthy omega-3 group reported lower fatigue scores and the recovered depressed omega-3 group reported lower depression (sadness) scores and lower tension scores. Mood state was a secondary outcome in both studies; nevertheless, these effects point toward beneficial effects of omega-3 supplementation. Effect sizes were small to medium in both studies. Mood effects were not detected in research with healthy volunteers who took antidepressants for seven days (Harmer et al., 2004; 2006) or tryptophan supplements for 14 days (Murphy et al., 2006). However, a four-week administration of the antidepressant paroxetine in healthy volunteers decreased their negative affect and improved their social affiliation (Knutson et al., 1998). Some studies, consistently observed improved energy levels after seven-day administration of the selective noradrenaline reuptake inhibitor reboxetine (Harmer et al., 2004; Norbury et al., 2007), which is similar to the decreased fatigue scores in the omega-3 group observed in both studies (Chapters 5 & 6). Future research elucidating on the mechanisms of omega-3 fatty acids can help identify the potential pathways that lead to improvement in mood and somatic states.

Mechanisms of omega-3 antidepressant action – what do we know so far?

As previously mentioned, there is evidence that omega-3 fatty acids have several neurochemical effects on the structure and function of the brain (Owen et al., 2008). However, the mechanistic pathways through which omega-3 may exert their anti-depressant effects have not been identified yet. New growing research on the effects of omega-3 fatty acid enriched diet either as a monotherapy or in combination with antidepressants in rodent depression models seems promising. Venna et al. (2009) found that supplementation with omega-3 fatty acid enriched diet for six weeks induced antidepressant-like effects in a mouse depression model (forced swimming test: improved performance on measures of immobility, swimming, climbing). Furthermore, significant additive effects were observed in combination with imipramine. Analysis of brain fatty acids were not different to those of the control group, but omega-3 supplementation was related to an increase in the volume of the hippocampus, enhanced

synaptogenesis, increase in newborn cells, as well as an increase in the expression of the brain-derived neurotrophic factor (BDNF) in the hippocampus. Similar underlying mechanisms have been observed with antidepressant treatments such as (SSRI's) (Dranovsky & Hen, 2006; Malberg et al., 2000; Santarelli et al., 2003).

Other animal research also supports the influence of omega-3 fatty acids on BDNF. BDNF is related to neuronal growth and plasticity and is lower in depressed patients and can be restored after antidepressant treatments (Saffet Gonul et al., 2005). DHA supplementation has been shown to increase levels of BDNF in the hippocampus, reduce oxidative damage and counteract learning disability in rodent models of brain trauma (Wu et al., 2004). Dietary deprivation of omega-3 fatty acids in rats leads to increase in depression and aggression (DeMar et al., 2006) as well as reduced frontal cortex BDNF expression (Rao et al., 2007). Moreover, synergistic effects of DHA supplementation and exercise have been shown in rodents expressed as increased BDNF synaptic plasticity and cognitive performance (spatial learning ability)(Wu et al., 2008).

In a recent study, Laino et al., (2010) examined effects of omega-3 enriched diet for 16 days on the rat depression model either as a monotherapy or in combination with antidepressants fluoxetine or mirtazapine, with varying dosages. Omega-3 enriched diet produced antidepressant-like effects similar to those shown by fluoxetine. The combined treatment had an additive effect, significantly higher than the one produced by each therapy alone. Furthermore, the combination of omega-3 fatty acids with inactive low doses of each antidepressant also showed significant antidepressant like effects. Similar to Venna et al. (2009), the changes observed were not attributable to changes in the brain membrane phospholipid composition as shown by analysis of brain phospholipids content. This finding sheds light on the mechanisms of antidepressant omega-3 action, showing that the role of DHA in the integrity and fluidity of membrane phospholipids may not be the main pathway of action and point toward effects on neurotransmission systems. The synergistic action of omega-3 with other antidepressants suggests that omega-3 may exert their effects by altering the pharmacokinetics of other drugs (Ross et al., 2007). Not surprisingly, the largest effects have been observed in trials where omega-3 was added to antidepressant ongoing treatment in depressed patients (Nemets et al., 2002; Su et al., 2003).

Although there is growing research and understanding of the neurochemical pathways of omega-3 antidepressant action, it is unknown how such changes can translate into improvement in mood in individuals who are vulnerable to depression.

Chapters 5 and 6 provide preliminary evidence that omega-3 fatty acids affect cognitive areas of decision-making and facial emotional information processing. More research is clearly warranted in understanding the cognitive neuropsychological pathways of omega-3 fatty acid mechanistic action.

Methodological considerations in Omega-3 research

Since investigation in the effects of omega-3 supplementation is relatively a young area of research, optimal study designs to detect effects are still unclear. For example, the periods of supplementation can range from 28 to 180 days, but there is no clear indication that longer supplementation is more likely to yield positive effects. Positive effects have been found with the minimum duration (4 weeks) (B Nemets et al., 2002; Chapter 5; Chapter 6) as well as longer duration periods (16 weeks) (H Nemets et al., 2006). However, very short periods of supplementation run a higher risk of failing to detect any effects, as shown in animal literature (Shaldubina et al., 2002).

On the other hand, type and dose of omega-3 fatty acid seems to play a role in efficacy. Studies using pure DHA have shown negative results (Marangell et al., 2003) whereas studies using pure EPA show higher efficacy (Jazayeri et al., 2008; Mischoulon et al., 2009; H Nemets et al., 2006). Overall, positive results have been found in studies using EPA supplementation or EPA and DHA with higher doses of EPA than DHA, in mood disorders (Freeman et al., 2010). Similarly, omega-3 supplementation in animal studies wherein antidepressant like effects were found also consisted of a higher EPA:DHA ratio (Laino et al., 2010; Venna et al., 2009). This may be counterintuitive since the DHA comprises 10-20% of total fatty acid in the brain, and EPA only 0.1% (Su, 2009). Furhtermore, decreased DHA concentrations have been observed in the brains of depressed patients (Conklin et al., 2010; McNamara, et al., 2007). EPA, however, is important in balancing the immune and inflammatory functions, as well as in regulating the synthesis of omega-6 arachidonic acid (Su, 2009). Although the mechanisms underlying the possible benefits of omega-3 on depression vulnerability remain unknown, current research findings would prescribe a high EPA to DHA ratio, at a dosage of 1g of EPA (Freeman et al., 2010).

The dosage, EPA:DHA ratio and treatment duration in the studies described in chapters 5 and 6 may be considered adequate. Although the limitations of these studies have been addressed in each chapter separately, some general points are worthy of further reflection. In both studies, the cognitive tasks were administered at baseline, after

one-week of supplementation and after four weeks. Having a baseline measure increases the power to detect treatment effects, however repeated testing increases the chance of learning effects. This has occurred in some measures (eg. facial emotion recognition task) and may have obscured the effects of the intervention. In retrospect, the one-week measurement of omega-3 effects may have been an unfortunate decision. It served the purpose of detecting short-term effects (cf. effects of single-dose antidepressants, Bhagwagar et al., 2004), however, the consequences of repeated testing seem to be of greater importance in such designs. Subsequently, testing within such short time intervals is not recommended in omega-3 research. On the other hand, the decision-making task was only administered at post-test due to previously observed order effects (Wood et al., 2006). Although any learning effect or "change in gambling strategy" was avoided in this way, it is uncertain whether the observed differences were not already there before treatment. This is not very likely, since baseline differences were not observed between the groups on other tasks. Finally, the sample size of each study (n=54 and n=71) is similar to that of other trials, and allows for the detection of medium effect sizes with a power of 80% at a one-sided alpha level of 5%. Larger studies would of course increase the generalization of the findings and would also increase the statistical power to detect small treatment effects.

Future research on omega-3 fatty acids and depression vulnerability

Investigation into how omega-3 fatty acids can affect cognitive vulnerability to depression is a new growing field of research. Most trials so far have used the intent-to-treat analysis principle to examine effects of omega-3 supplements on mood improvement. Few studies have examined effects on cognitive functioning. However, in order to get a better insight into the neuropsychological mechanisms of omega-3 action, it would be appropriate to examine effects in selected participants with abnormally low levels of omega-3. By investigating such omega-3 "depleted" participants it is possible to examine how increase in omega-3 fatty acid levels modulates emotional information processing. In such studies, it would be suitable to use measures that are known to be sensitive to depression vulnerability. Such measurements include facial emotion recognition (as in chapters 5 and 6, or the task used in chapter 4), emotional categorization and memory, as well as physiological measurements such as the emotion-potentiated startle response. Recently, in a study with healthy volunteers, (Harmer et al.,

2010) found effects on such measures of emotional cognition after a seven-day administration of agomelatine – a new antidepressant targeting melatonergic and serotonergic receptors. The authors found that agomelatine reduced recognition of sad facial expressions, improved positive affective memory and decreased startle responses to negative pictures and increased startle responses to positive pictures. Such experimental models can elucidate the mechanisms that translate neurochemical effects of omega-3 fatty acids into altered psychological and cognitive processes in depression.

Another important aspect in understanding the role of omega-3 in mental functioning is genetic variation. Omega-3 fatty acid deficits may also arise due to polymorphisms in the genes that moderate long-chain fatty acid biosynthesis from its short-chain precursors (Schaeffer et al., 2006). Genes that have been examined to date and show a relationship to concentrations of omega-3 fatty acids are mainly FADS1 and FADS2 genes (Chromosome 11, 11q12-13.1) among others (Malerba et al., 2008; Rzehak et al., 2009; Schaeffer et al., 2006). A recent study found that depressed patients showed reduced gene expression (mRNA) of FADS1 and FADS2 and other genes in the postmortem prefrontal cortex compared to controls (McNamara & Liu, 2010). Similarly, another study found that genes, such as FADS1, are down-regulated in postmortem prefrontal cortices of male depressed patients that committed suicide (Lalovic et al., 2010). Moreover, polymorphisms in those genes have been associated to increased post-partum depression risk (Xie & Innis, 2009) and increased IQ as a response to breast-feeding, indicating a gene-environment interaction (Caspi et al., 2007).

No study to date has examined the relationship between genetic variation in the 5-HTTLPR and omega-3 fatty acids. Although such an association may seem groundless at first thought, animal studies have observed similar effects of omega-3 and serotonergic antidepressants in animal models of depression (Laino et al., 2010) and evidence shows that 5-HTLLPR modulates antidepressant response (Kato & Serretti, 2010). If a serotonergic pathway is indeed involved in the mechanisms of action of omega-3 fatty acids, the 5-HTTLPR could also possibly modulate omega-3 response.

Genetic modulation of omega-3 fatty acid synthesis is a newly developing area of research, which can be combined with outcomes that are sensitive to depression vulnerability, and thereby enlighten our understanding of mechanisms that underlie this disorder. Whether such effects can be reversed by supplementation with omega-3 fatty acids and their precursors is a new exciting possibility.

Clinical Implications of Omega-3 fatty acid supplementation

Although there is less evidence of the treatment effects of omega-3 fatty acids in depression compared to that of anti-depressants, the increasing research in examining its effects can be justified for important reasons. Despite the dramatic increase in treatments during the past 30 years, a substantial proportion of patients experiencing depression do not respond to standard treatment practices. More than half of the patients do not respond to antidepressant monotherapy (Rush, 2007), some are unable to tolerate antidepressants (MacGillivray et al., 2003), and some refuse to take them (Simon et al., 1993). About 50% of the patients also relapse after cognitive therapy (Hollon et al., 2006). The inefficacy of conventional treatments of depression is inevitably felt in the patients themselves, more than 50% of whom have turned to complementary or alternative treatments, next to their standard treatment (Kessler et al., 2001). Consequently, a recent review by the American Psychiatric Association's Task Force on Complementary and Alternative medicine showed promising results for the efficacy of omega-3 supplementation treatment in major depression (Freeman et al., 2010). Few side effects from the recommended doses of omega-3 (<3g/day) have been reported and mainly include discomfort with digesting or swallowing the capsules. From both studies reported in this thesis (chapters 5 and 6) only 3 people dropped out (drop out rate: 2.4%) which shows that dosage was well tolerated and compliance was high. A promising suggestion for clinicians and researchers to consider arises from animal studies, which showed that using lower dosages of antidepressants in combination with omega-3 can improve symptoms of depression and reduce side effects, such as weight gain/loss (Laino et al., 2010). Replication of these findings in human samples is worthwhile.

Overall conclusion

In summary, it appears that cognitive vulnerability plays an important role in depression and can be moderated by genetic and environmental influences. In addition, some aspects of cognitive vulnerability can be modified via nutritional factors, such as omega-3 fatty acid supplementation. Through an interdisciplinary approach, these findings provide useful insights in understanding this multifactorial disorder and possibly open more promising roads to treatment.

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