Heartbreak: a model for depression

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DOI:
10.33612/diss.196900366

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2022

Citation for published version (APA):
https://doi.org/10.33612/diss.196900366

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Chapter 6

General discussion
In this chapter, we first summarize, interpret and integrate the findings of this thesis. Second, we describe possible limitations and considerations of our study designs and methods. Last, we show possibilities for future work.

6.1 Aim

The aim of this thesis was twofold: 1) to investigate whether romantic relationship breakup is a viable human experimental model to study depressive symptoms in otherwise healthy individuals and 2) use this non-clinical model to explore factors that have been indicated to play a role in clinical depression.

6.2 Summary and interpretation findings

First, we presented results from a cross-sectional study among women and men who experienced a romantic relationship breakup within the preceding six months (Chapter 2 and Chapter 3). We explored whether the effect of a romantic relationship breakup resembles a depression (-like) state. To this end, we analyzed data from a comprehensive mood-related questionnaire battery (Chapter 2). In addition, we analyzed data from an fMRI working memory task to investigate possible effects of relationship breakup on working memory functioning and the association with depressive symptom severity (Chapter 3).

In Chapter 2 we specifically investigated: 1) whether individuals who experienced a romantic relationship breakup (“heartbreak group”) demonstrate symptoms of depression, compared to individuals in a romantic relationship (“relationship group”) 2) how to describe heartbreak characteristics 3) whether this description can capture depressive symptom severity. In addition, we were interested in gender differences with regard to the above research questions. Depressive symptom severity was found to be higher in the heartbreak group compared to the relationship group and approximately a quarter of the heartbreak group reported a depressive symptom severity corresponding to mild clinical depression or more severe. Furthermore, we characterized heartbreak by two distinct descriptions; “sudden loss” and “lack of positive affect”, which were found to correlate highly with depressive symptom severity. Moreover, the findings of Chapter 2
indicate that there seems to be an effect of gender on breakup-related mood disturbances. Women of the heartbreak group reported higher depression scores than men of the heartbreak group and this cannot be explained by general gender differences, as depression scores of the men and women of the relationship group did not differ. In addition, the “lack of positive affect” description of heartbreak was more represented among heartbroken women than among heartbroken men. This carefully suggests that men are less likely to demonstrate reduced capacities to experience positive emotions during a negative period in life and this possibly relates to the considered difference in clinical depression rates between the genders (Kessler et al., 1993).

In Chapter 3 we investigated whether a romantic relationship breakup is associated with working memory alterations. Additionally, we investigated whether the possible association between working memory functioning and breakup is related to depressive symptom severity. We found differences in brain activation between the heartbreak group and the relationship group; the heartbreak group showed less activation in the precuneus at high workload. At the behavioral level, task performance did not differ between the two groups at high workload, whereas the heartbreak group performed better at moderate workload. These group-level (heartbreak versus relationship) results suggest that breakup-related effects on working memory functioning are specifically present at the neural level at high workload, while behaviorally performing similar, and affect a brain region (i.e., the precuneus) that previously was found to be important for working memory (Owen et al., 2005). Furthermore, loadings on a network of brain regions, including the precuneus, anterior cingulate and supplementary motor cortex, were found to be negatively associated with depressive symptom severity within the heartbreak group. This implies that this specific brain network is less represented in heartbroken subjects with more severe depressive symptoms. This specific working memory-related network may be of importance with regard to the transition from healthy behavior, and corresponding brain activity, to depressive behavior following a negative event such as relationship breakup. Taken together, the findings of Chapter 3 suggest that the effect of a romantic relationship breakup is, additional to elevated depressive symptom severity, associated with workload-dependent working memory alterations.
Second, in this thesis, we presented results from a longitudinal study in which women who recently experienced a romantic relationship breakup participated for a period of 30 weeks in order to explore depressive symptom trajectories and factors that are related to these trajectories (Chapter 4 and Chapter 5).

In Chapter 4 we aimed to identify distinct depressive symptom trajectories following romantic relationship breakup and investigate whether personality traits (rumination and neuroticism) and cognitive control functioning are related to these trajectories. We first grouped our total sample of women according to their consecutive depression scores during the study period of 30 weeks into distinct subgroups. Subsequently, we investigated whether the subgroups differ with regard to personality traits and cognitive control functioning. We showed that women who experienced a breakup can be divided into distinct subgroups according to their depressive symptom patterns over time. We characterized four groups, labeled as “chronic distress”, “fast recovery”, “slow recovery” and “resilience”. Neuroticism and trait rumination levels were found to differ between the groups; the “slow recovery group” and the “chronic distress group” were found to have higher neuroticism and trait rumination levels than the “resilience group” and the “chronic distress group” also had higher neuroticism levels than the “fast recovery group”. These findings suggest that especially the level of neuroticism distinguishes resilient/adaptive behavior from experiencing persistent symptoms in response to a breakup. Being highly neurotic therefore potentially puts someone at risk for developing depression following a negative event. In accordance with previous studies regarding clinical depression (Costa & McCrae, 1980; Nolan et al., 1998; Nolen-Hoeksema, 1991; Nolen-Hoeksema, 2000; Roelofs et al., 2008), the findings of Chapter 4 show that the relation between neuroticism, rumination and depressive symptoms can also be found in romantic relationship breakup. Furthermore, we displayed between-group differences in cognitive flexibility; worse overall (across all the three study visits) cognitive flexibility among the “chronic distress group” compared to the “resilience group” and worse cognitive flexibility among the “chronic distress group” compared to the “slow recovery group” at the first study visit. Taken together, in Chapter 4 we showed that distinct patterns of depressive symptom severity can be observed following romantic relationship breakup, including prolonged symptoms of depression as well as resilience. Furthermore, personality traits of rumination
and neuroticism and cognitive flexibility seem to be related to these depressive symptom patterns.

In **Chapter 5** we investigated whether processing of reward and punishment relates to depressive symptom trajectory following breakup and to personality traits that are associated with mood disturbances (rumination, neuroticism). The same sample of women as in Chapter 4 performed an fMRI monetary reward task in which the goal was to gain money and avoid losing money. At the behavioral level, our subjects reacted especially more accurate during the reward condition and the punishment condition compared to the control (neutral) condition. This indicates that our subjects were more motivated when reward or punishment was involved. Furthermore, subjects with higher levels of neuroticism were found to respond faster during the neutral condition. At brain level, we identified brain areas that coactivate (components) during anticipation of respectively reward and punishment (compared to baseline) across our total sample of women who experienced a breakup. Furthermore, we identified brain regions that coactivate when contrasting reward anticipation with punishment anticipation, representing differences in brain activation between the two conditions. The four groups did not differ with regard to any of the reward anticipation and punishment anticipation components. When contrasting reward anticipation with punishment anticipation, one of the identified components (component 4, mainly negative activation in frontal areas) differed between the groups. Specifically, the “chronic distress group” had higher loadings on this component than the “slow recovery group”. Our finding of higher loadings on a specific brain component, showing mainly negative activation in the frontal pole concerning the difference between reward and punishment, among the “chronic distress group”, suggests that people who experience prolonged symptoms following breakup show different decision-making and motivational processes at brain level. Regarding the potential association with personality traits of rumination and neuroticism, a negative association was found between one of the reward anticipation > baseline components (component 1, mainly positive activation in occipital and parietal areas) and neuroticism level. This suggests less motivation to obtain reward among highly neurotic subjects. Possibly, this relates to susceptibility for depression/anhedonia, as associated with high levels of neuroticism in the general population (Costa & McCrae, 1980; Servaas, van
der Velde et al., 2013). Furthermore, a negative association between one of the reward anticipation-punishment anticipation components (component 2, mainly negative activation in occipital, parietal and frontal areas) and trait rumination was found. So, in Chapter 5 we found specific brain activation patterns that were related to a trajectory of persistent depressive symptoms following breakup as well as to personality traits that have been linked to depression.

### 6.2.1 Heartbreak, a non-clinical model to study depressive symptomatology

The first aim of the present thesis was to explore whether romantic relationship breakup is a viable human experimental model to study depressive symptoms in individuals without a psychiatric disorder. The findings of Chapter 2 as well as the findings of Chapter 4 display that the effect of a romantic relationship breakup can lead to symptoms of depression in otherwise healthy individuals. On group-level, we found elevated depressive symptom severity among our heartbroken subjects compared to a reference group of individuals in a romantic relationship in our cross-sectional study (Chapter 2). Furthermore, our longitudinal study revealed different profiles of these elevated depression scores over time; persistent symptoms, slow recovery and fast recovery (Chapter 4). Interestingly, not everyone seemed to be affected by the breakup/reported symptoms of depression, in both of our studies. It is questionable whether those individuals show indeed resilient behavior after a negative event or whether the breakup was not that negative/stressful for them, given that it is known that the effect of a breakup partially depends on relationship variables such as perceived satisfaction and commitment (Sprecher, Felmlee, Metts, Fehr, & Vanni, 1998). Nevertheless, the presence of these different symptom profiles allows studying (risk-and protective) factors in the light of depression predisposition. So, based on the findings of this thesis, we propose that romantic relationship breakup is a good non-clinical model for depressive symptoms and using heartbroken individuals to study depressive symptomatology can provide valuable information.
6.2.2 Cognitive processes associated with depressive symptoms following breakup

The second aim of this thesis was to explore factors that have been indicated to play a role in depression among our study population of heartbroken individuals. In Chapter 3 we focused on working memory functioning among men and women who experienced a breakup within the preceding six months. This research objective was motivated by the indicated role of executive functioning, including working memory, in clinical depression (Cotrena et al., 2016; Harvey, P. O. et al., 2004; Rose & Ebmeier, 2006). In Chapter 4 we again examined executive functioning, here with the focus on inhibition and cognitive flexibility. These cognitive functions as well have been suggested to be involved in depression (Channon, 1996; Joormann et al., 2007). An interrelation between these cognitive functions and ruminative thinking processes has been suggested; possibly, people with smaller cognitive capacities are less able of suppressing negative and repetitive thoughts and switch to more adaptive thinking processes (Philippot & Brutoux, 2008; Philippot & Agrigoroaei, 2017). Although in those chapters we examined different aspects of cognition among different samples with different study designs, in both chapters alterations in cognitive functioning were found among individuals with more severe depressive symptoms following breakup compared to a reference group. Thus, we show that cognitive alterations can be observed in non-clinical populations as well, in response to a negative event. Furthermore, these findings carefully suggest that experiencing more severe and/or persistent depressive symptoms in response to a breakup relates to higher-order cognitive capacity. Interestingly, in accordance with the suggested link between maladaptive thinking processes and cognitive functioning, we also found higher levels of rumination and neuroticism among people who experienced persistent distress, in Chapter 4 of this thesis.

6.2.3 The role of dopaminergic circuits in depressive symptom trajectory following breakup

Moreover, the brain’s reward system has been implicated in clinical depression and disturbances may underlie the development of the disorder (Dunlop & Nemeroff, 2007; Gotlib et al., 2010; Rizvi et al., 2016). In Chapter
5 we focused on reward processing and relatedness with depressive symptom trajectory following breakup. We found a specific brain activation pattern (mainly negative activation in frontal areas, concerning the difference between reward anticipation and punishment anticipation) that was more represented in individuals showing a trajectory of prolonged distress. Reward-related processing can be linked to cognitive control, as both processes are known to depend on dopamine transmission in the brain. Specifically, the mesocorticolimbic pathway subserves both processes. Reward-related processing depends on dopamine transmission from the VTA to the ventral striatum, whereas cognitive control functions depend on dopamine transmission from the VTA to prefrontal brain areas (Cools, 2008; Stanton et al., 2019). In Chapter 4 we investigated cognitive control functioning among subjects with different patterns of depressive symptoms over time. We found cognitive flexibility to be associated with depressive symptom trajectory; worse cognitive flexibility among subjects who suffered from prolonged distress. So, in this thesis, both reward-related and cognitive control processes were found to be related to depressive symptom trajectory following breakup and this tentatively points towards the involvement of dopaminergic circuits in experiencing persistent distress following a negative event.

6.3 Limitations and considerations

This thesis presents a novel approach to study depressive symptoms in non-clinical individuals, which can give new insights into the transition from a healthy state to a depressive state. However, there are some potential limitations and methodological considerations to take into account.

It may be argued that the control group of our cross-sectional study, consisting of individuals in a romantic relationship, is not an ideal control group. This is because stress hormone levels were found to be increased during the first period of a new romantic relationship (Marazziti & Canale, 2004). Therefore, we only included people with a relationship duration of at least six months in our cross-sectional study. As we found significant differences in depressive symptom severity between the heartbreak group and the relationship group (higher among heartbroken individuals), we believe that the two groups differ sufficiently regarding stress-related mood disturbances. Also, using people
without a relationship (singles) as a control group would have been less ideal, as this group possibly is heterogeneous in terms of dating activity (e.g., some singles actively search for a new romantic partner whereas other do not do this) and associated stress levels (e.g., due to uncertainty and rejections) (Chin et al., 2017).

Furthermore, in the present thesis, we did not measure physiological indicators of stress such as stress hormone levels in saliva or blood. Consequently, we cannot link this information to our psychological and neural measures and say something about physiological consequences of the event. However, our psychological data indicates stress-related mood disturbances, as cross-sectional depression scores were found to be higher among individuals who experienced a breakup within the preceding six months, compared to individuals in a romantic relationship (Chapter 2). In addition, data from our longitudinal study showed elevated depression scores in the first months after the breakup in a substantial part of our sample (Chapter 4). Therefore, we believe that our subjects were indeed affected by the event.

Due to logistical reasons, and to keep the burden of the subjects as low as possible, we decided to perform only one MRI session for each subject, at the end of the longitudinal study. This way, we were not able to observe potential transitions from a “healthy brain” to a “depressive brain” in a direct way, as we do not have within-subject information regarding changes over time. Though, as our research aim mainly focused on traits (i.e., factors that are considered to be stable over time), we believe that we were still able to capture brain activity patterns of interest. However, with this study design we cannot completely distinguish trait from state, given that current depressive state varied between our subjects throughout the study period.

In our longitudinal study, we only included women, as our cross-sectional results indicated differences between the genders with regard to their heartbreak severity and mood problems (Chapter 2) and clinical depression prevalence rates are higher among women in the general population (Kessler et al., 1993). This way, we included a more homogeneous group and we did not have to take into account the effect of gender in our analyses. A drawback of this approach is that we cannot generalize our findings to the general population of people suffering from heartbreak. In addition to gender-related aspects,
we only included subjects with an age between 18 and 35 years and between 18-26 years in our longitudinal and cross-sectional study, respectively. The reason for this again relates to homogeneity. Nevertheless, we have to take this into account when interpreting our results and translating our results to the general population.

Last, because of the COVID-19 pandemic and measures taken in the Netherlands, approximately half of the initial sample of the longitudinal study could not visit our laboratory for their third study visit. Consequently, we ended up with missing MRI data and cognitive task data. This reduced the statistical power for the concerning analyses. In addition, the data from the third study visit represents a subsample of our initial sample. However, as the missingness of the data is considered to be completely unrelated to any of our outcome measures, we expect minimal influences on our outcomes.

6.4 Future work

Future studies can be conducted to follow up on the findings of the present thesis and to tackle some of the above-described limitations.

To investigate the reliability of the results of our longitudinal study, it is advisable to conduct a similar study with a larger sample in the future, including more subjects who very recently experienced a breakup. This will provide a more complete overview of the period following a negative event. In addition, including a larger sample probably will result in a larger subsample of people who suffer from prolonged distress. This way, we will be able to draw stronger conclusions and translate findings to the clinical population.

Furthermore, in future work, it will be interesting to focus on within-person differences over time and directly investigate brain activation patterns that are involved in recovery (returning from being affected to the unaffected baseline state), persistence of depressive symptoms and progression towards a clinical depressive episode. Studies can be conducted in which subjects undergo multiple fMRI sessions during a certain period of time following breakup in order to compare brain activation patterns between the sessions and relatedness with behavioral parameters, including symptoms of depression.
Moreover, in future work, we can analyze the acquired neural data of this thesis using different (statistical) approaches and gain more detailed information about underlying patterns. Decomposing the identified brain components (Chapter 5), for instance by distinguishing between the positive activation and negative activation parts, might be a future option. In addition, focusing on individual-specific patterns, instead of group averaging, might be a valuable further step.

Last, the longitudinal study of this thesis identified factors that play a role in the affectedness and recovery following breakup. Future work can subsequently focus on targeting these specific identified factors. For instance, strategies related to ruminative thinking and facilitating flexibly switching to more adaptive ways of dealing with a negative event and corresponding negative thoughts and emotions. Future studies that focus more on specific strategies and interventions to help people who experience distress following a negative event deal with their symptoms might be conducted. Potentially, mindfulness-related activities will be of value here. In addition, future (intervention) studies might focus on the reward system. For instance, it will be interesting to investigate whether inducing positive reward responses reduces potential stress-related anhedonic symptoms following a stressful/negative life-event.

6.5 Concluding remarks

In this thesis, we investigated whether romantic relationship breakup can be used as an experimental model to study depression (-like) symptoms in otherwise healthy individuals. Furthermore, we explored factors that have been indicated to play a role in clinical depression. We conclude that the effect of a romantic relationship breakup resembles a depression (-like) state and can therefore be considered a viable model to study depressive symptoms in a non-clinical population. This way, knowledge can be gained about the transition from a “healthy brain” to a “depressive brain”. Though, it should be taken into account that breakup-related effects seem to differ between men and women. Furthermore, we conclude that personality traits (rumination, neuroticism) as well as cognitive-and reward-related processes seem to be related to depressive symptom trajectory following romantic relationship breakup. Future studies are necessary to validate our results and translate our findings to other (both non-clinical and clinical) populations.