Chapter 7
Discussion
Main findings of this thesis

In Chapter 2 we measured heart rate variability and skin conductance level in participants with different levels of psychosis susceptibility during exposure to virtual reality (VR) social stressors. Both the number of VR stressors and level of psychosis susceptibility significantly affected levels of nominal heart rate, heart rate variability, and skin conductance. The VR social stress model was able to elicit an autonomic stress response, namely an increase in sympathetic activity and a decrease in parasympathetic activity. In the high psychosis susceptibility group, we found a decreased parasympathetic activity and unaltered sympathetic input. The response to increasing virtual stress was similar in both susceptibility groups. Participants with high psychosis susceptibility were characterized by higher arousal both before and during exposure.

In Chapter 3 we examined the influence of childhood trauma in participants with low and high psychosis susceptibilities on paranoia and distress in response to social stress. We found that childhood trauma was associated with higher levels of (subclinical) psychotic and affective symptoms at baseline and more subjective distress to virtual social stress exposure. The effects of childhood trauma on paranoia and subjective distress were significantly stronger in the high psychosis susceptibility groups and in the more stressful VR environments. Thus, we showed childhood trauma is associated with heightened social stress sensitivity and may contribute to psychotic and affective dysregulation later in life, through a sensitized paranoid and stress response to social stressors.

In Chapter 4 we examined effects of psychosis susceptibility and childhood trauma on serum levels of BDNF, CCL-2, CRP, IFN-γ, IGFBP2, IL-6, PDGF, SCF and TNF-α. We did not find any statistically significant effects of psychosis susceptibility or childhood trauma on concentrations of cytokines or growth factors in peripheral blood, nor were there any statistically significant interaction effects of psychosis susceptibility with childhood trauma on serum levels of cytokines or growth factors. These negative findings are not fully supported by meta-analytic work.

In Chapter 5 we report on Natural Killer and T cell populations in relation to psychosis liability, childhood trauma, and subjective stress during exposure to VR stressors. We found that childhood trauma was associated with increased Th17 cell numbers in the high psychosis susceptibility group only. Moreover, in this group, increased T regulator and decreased NK cell numbers predicted stress experience during exposure to virtual social stressors.

The work in chapters 4 and 5 is placed in a broader perspective in Chapter 6, in which we systematically reviewed studies on associations between psychosis risk factors (childhood trauma, ethnicity and urbanicity) and inflammatory markers in patients with psychosis. Multiple studies have found associations of childhood trauma with individual inflammatory markers in psychosis patients, although these are often without replication and the results of the most commonly measured markers (IL-6, CRP and TNF-α) are somewhat inconsistent. For ethnic minority status and urbanicity, the available literature on patients with psychosis is very limited. Findings from general population studies support associations with inflammation levels and both race/ethnicity and neighbourhood characteristics.

Discussion

The main topics of interest considered in this thesis were associations of childhood trauma, stress sensitization, and inflammation in patients with psychosis and these are discussed more elaborately below. Virtual reality was used as an experimental method to explore these associations, which was an innovative method when this study was started in 2013. Since then, VR has developed rapidly and new applications in psychiatry are discussed below.

Virtual reality (VR)

We designed a VR experiment to expose participants to social stress. They were exposed to daily experiences of minor psychosis risk factors by manipulating the number, ethnic appearance and facial expressions of avatars. This exposure induced subjective stress and paranoid thoughts [1]. With an increasing number of social stressors, we saw the level of subjective stress and paranoia also increase [1]. Furthermore, exposure to virtual social stress was able to elicit an autonomic stress response, namely an increase in sympathetic activity and a decrease in parasympathetic activity (Chapter 1). Again, the level of subjective stress in the VR environments was seen to affect the autonomic stress response (Chapter 1). These findings confirmed that the levels of social stress could be manipulated in VR in a meaningful way and strengthened the validity of our VR model for social stress.

We used our VR model to study determinants of stress reactivity and found high psychosis susceptibility, and pre-existing (minor) affective and psychotic symptoms to be associated with more paranoia and distress in social environments [1]. Participants with a history of childhood trauma responded with more subjective distress to virtual social stress exposures (Chapter 2). The model is particularly well-suited for studying
interaction effects between participant characteristics and levels of social stress. We found that the effects of pre-existing symptoms and childhood trauma on paranoia and subjective distress were significantly stronger when the number of virtual environmental stressors was increased (Chapter 2).

Our VR model of social stress exposure adds to two other commonly used research paradigms for social stress: the experience sampling method (ESM) and the Trier Social Stress Test (TSST). ESM is a structured diary method. Typically, patients carry a mobile device that signals multiple times a day to answer brief, specific questions about e.g. their social interactions and symptoms while they go about their daily life. Its naturalistic approach and large number of repeated measure in the same person have proved advantageous in studying relations between the environment and symptoms, in general, and the concept of stress sensitivity in psychosis, in particular [2,3]. In ESM, exposure is different for each participant and rating of exposure is subjective. In virtual reality environments, their exposure can be controlled. Virtual reality is also more suited to measure implicit effects, such as interpersonal distance regulation.

In the Trier Social Stress Test, participants are asked to prepare and present a speech in front of a jury of actors, followed by a mental arithmetic task. This laboratory setting is highly controlled and consistently evokes a stress response. The TSST uses multiple time-points during baseline, exposure and recovery, which make it particularly suitable for unravelling the physiological stress response, including the hypothalamic-pituitary-adrenal (HPA) axis [4]. The use of actors is, of course, rather cumbersome. In fact, VR jury panels of avatars have been developed, but the response in these virtual TSST is lower than in traditional TSST [5]. This points to the strength and weakness of the TSST: it is the combination of multiple elements (public speaking, social evaluation, anticipation, mental arithmetic) that provides a very robust psychological stressor. Whereas our VR social stress model uses daily, minor social stressors and is more suited to manipulating the intensity and type of social stressors in the model.

**Virtual reality treatments**

Virtual reality has also been used for treatment. The first VR treatments focused on exposure therapy for specific phobias, e.g. spiders or flying. Exposing patients to VR allows therapists to be present at the same time without needing a plane ticket or pet spiders. Furthermore, it is thought to be more acceptable to patients, as they know ‘it is not real.’ Virtual reality exposure therapy was shown to be equally effective as in vivo exposure [6] and, importantly, exposure to virtual spiders reduced anxiety for real spiders [7]. Other VR treatments were developed for anxiety disorders, psychosis, eating disorders, depression, and substance-related disorders [6]. The focus is still mostly on exposure, with VR exposure often being part of a cognitive behaviour therapy (CBT).

For patients with psychosis, exposure is seen as particularly challenging. Patients with specific phobias generally recognize their anxiety is excessive or unreasonable, although this is no longer given as a criterion in DSM-5. Patients with psychosis tend to be more convinced of their paranoid fears and are reluctant to undergo exposure. Negative symptoms can also hinder homework assignments of exposure in CBT. Anxiety in psychosis often involves social situations and psychosis is characterized by behavioural symptoms, which is perhaps more likely to elicit negative reactions in social situations. Thus, patients may not receive positive feedback on in vivo exposure, which makes subsequent exposure even more difficult. To overcome these barriers, a VR cognitive behaviour therapy was developed in parallel to the experimental study described in this thesis [8]. The VR environment included a café and other situations commonly avoided by patients, e.g. a street, a bus and a supermarket. Exposure sessions could be personalized, for example, by letting avatars say pre-recorded sentences. Virtual reality exposure took place during the therapy session, allowing the therapist to guide the exposure, help challenge cognitions, and address safety behaviour. Common safe behaviour included avoiding eye contact and maintaining distance. After 16 sessions, paranoia and anxiety was significantly reduced compared to treatment as usual [8]. Reduced safe behaviours mediated the treatment effect and it is possible that reducing safe behaviours allowed patients to have more positive social interactions in real life.

Virtual reality training to alleviate aggression in a forensic setting was also developed [9]. Aggressive behaviour in forensic patients is difficult to treat and previous studies had suggested role-playing as a key component of effective behaviour training. VR allowed therapists to role-play through avatars using voice morphing. Patients and therapists were mostly positive about this VR training in follow-up interviews. For example, patients recalled that they had gained insights into their triggers and were more aware of their physiological arousal, whereas therapists indicated that participants appeared to be immersed in the VR environments and were able to practise new skills. Positive treatment effects of were found on self-reported direct aggression and hostility, anger control skills, anger expression index, and non-planning impulsiveness [9]. Unfortunately, these effects were not maintained in the longer term and no improvements on staff-rated aggressive behaviour or self-reported aggression were made.
Virtual reality allows for the swapping of perspectives, replaying from another perspective, and role playing. For example, in AVATAR therapy [10], an avatar of the presumed persecutor is created to interact with the patient and, gradually, the avatar concedes power to the patient. Patients reported a lower intensity of hallucinations and less distress from them. In another example, VR helped patients with eating disorders to experience how it would be to have a healthy body weight, with subsequent positive effects [11].

Other applications of VR in mental health, including symptom assessment, were suggested some time ago [12]. For psychosis, VR assessment could be especially helpful in distinguishing unfounded paranoia from genuine hostility, which is a common clinical dilemma. When patients are presented with neutral faces, they develop paranoid thoughts. With regard to the virtual social environments we used in the research design, it would be interesting to repeat the study after treatment to evaluate its effect on subjective stress, paranoia and/or physiological stress response.

We also used VR in a 2018 study on interpersonal distance regulation [13]; two years later, “social distancing” suddenly became an everyday concept with completely different associations. Before 2020, most people were only rarely aware of their interpersonal space, with a mild feeling of discomfort when it was intruded into, perhaps when travelling to a country with slightly different cultural norms. Our study confirmed that the size of interpersonal boundaries depended on (social) context and personal characteristics, and we also found that this size was independent of psychosis susceptibility. We could not have foreseen how soon and how drastically the context would change with the appearance of Covid-19 corona virus in 2020, affecting what is considered an appropriate interpersonal space, and how regulating our interpersonal distance would suddenly become a necessary and conscious process for nearly everyone. Now we feel mild discomfort when seeing “pre-corona” films or photos, where the new norms of interpersonal spaces are largely violated. I would now expect participants to handle their interpersonal space differently in virtual environments. Perhaps the VR environment could even be helpful in determining the effects of interventions on interpersonal distancing. A much-debated question in the Netherlands (and elsewhere) in the summer of 2020 was whether wearing face masks would make people more or less careful in their interactions and more or less likely to maintain their social distance. This could be investigated by having participants wear face masks themselves and/or by including avatars with face masks.

Since the start of this thesis in 2013 and the development of the virtual reality café, VR technology has advanced. Our set-up already appears old-fashioned, with an uncomfortable looking headset, connected to a computer using cables and with navigation by joystick. Some participants suffered from “cybersickness” due to a slight delay between the vestibular input of the actual movement and the visually-induced perception of self-motion. Virtual reality experiences are now even more immersive, headsets are more advanced, more comfortable, and less likely to induce sickness. Meanwhile, the hardware costs of a VR set-up have drastically decreased, although software and licencing costs are still high. If these could be reduced in the future, it would open up possibilities for upscaling and home use. This could be very helpful for patients who experience barriers to treatment centres and the first results of stand-alone exposure therapy for anxiety are promising [14,15].

**Childhood trauma**

Our study once again confirms an important role for childhood trauma in psychosis. We found childhood trauma was highly prevalent among the group with a high psychosis susceptibility. A staggering 80% of ultra-high risk (UHR) patients and 49% of patients with psychosis in our sample reported childhood trauma. All types of trauma measures by the CTQ were more likely to be reported by the high susceptibility group (UHR and patients with psychosis) compared to the low susceptibility group (healthy controls and siblings). Our findings are in line with other studies, for which a meta-analysis found a mean prevalence rate of 86% for trauma in UHR patients [16].

Childhood trauma increased the risk of psychosis with an OR of 2.8 [17]. Furthermore, our findings emphasize the clinical relevance of childhood trauma in patients with psychosis. In our sample, childhood trauma was associated with a higher level of subclinical and clinical psychotic and affective symptoms (Chapter 2). Participants with a history of childhood trauma responded with more subjective distress to virtual social stress exposures (Chapter 2).

This is in line with the literature that links childhood trauma to more severe affective and positive psychotic symptoms, both in psychosis patients [18,19] and in UHR patients [20–22]. Furthermore, childhood adversity was associated with a higher persistence of psychotic experiences in clinical samples, as well as in the general population [23]. Childhood trauma has also been associated with increased rates of transition to psychosis [24]. However, a meta-analysis showed only the effect between sexual abuse specifically and transition to psychosis, and this effect was based on only one, large study [25]. It is possible that the adverse effects of childhood trauma are more widely associated with general, comorbid psychopathology than with a transition to
psychosis. Childhood trauma predisposes to a wide range of mental health problems, including depression, anxiety and self-harm. A network analysis in psychosis also suggested that the effects of childhood trauma on psychosis symptoms are seen in general psychopathology [26]. Our findings in Chapter 3 suggest that increased stress sensitivity may be involved and this is discussed further in the next section.

Unfortunately, there was, and still is, a large gap between the scientific knowledge on the importance of childhood trauma and clinical practice [27]. It was long thought that it was best not to ask psychosis patients about their traumatic experiences for fear of destabilizing them. This is in contrast to patients’ wishes to address their social circumstances and trauma [28]. PTSD (post-traumatic stress disorder) is often underdiagnosed in patients with severe mental illness [27]. Psychosis has long been accepted as a contra-indication for trauma-focused therapy. This widespread belief was only tested in 2009: cognitive behaviour therapy that included imaginary exposure intervention in patients with chronic psychosis and PTSD was found to significantly reduce their PTSD symptoms and improve their general mental health [29]. No adverse events were observed. In a randomized controlled trial in 2016, eight sessions of prolonged exposure or Eye Movement Desensitization and Reprocessing (EMDR) for psychosis patients with PTSD were compared to waiting list controls [30]. Treatment was found to be safe. Revictimization was less likely to occur in those receiving trauma-focused therapy. Participants given courses of prolonged exposure or EMDR were less likely to fulfil PTSD criteria and their psychosis symptoms were reduced. Thus, the evidence now shows that fears of exacerbating symptoms are ungrounded and trauma-focused therapy is effective in patients with psychosis and PTSD.

It would be interesting to find if trauma-focused treatment, e.g. EMDR, is beneficial for patients with psychosis who report childhood trauma but who do not fit the full criteria for PTSD. Our virtual environments might be helpful in evaluating the effectiveness of trauma therapy. The increased subjective distress seen in participants with childhood trauma who are exposed to virtual social stresses may decrease after trauma therapy.

**Stress sensitization**

We hypothesized that previous and repeated exposure to social stress leads to stress sensitization, an increased response to small social stressors in daily life, with cumulative effects resulting in lasting susceptibility in emotional and psychotic reactivity. We found that paranoia and subjective distress were higher in a high psychosis susceptibility group than a low susceptibility group and that both aspects increased with the degree of social stress experienced in the virtual environment [1]. We did not find an interaction effect between social stress exposure and psychosis susceptibility, expect for a stronger increase in paranoia with increasing social stress for the UHR group [1]. High psychosis susceptibility was associated with higher subjective stress and paranoia across all model conditions (virtual environments), including a low social stress "baseline" condition. This is similar to our results from the autonomic stress response study (Chapter 2). In the high psychosis susceptibility group, we found decreased parasympathetic activity and unaltered sympathetic input. The responses to increasing virtual stress were similar in both susceptibility groups. The high susceptibility group reported higher arousal both before and during exposure. This suggests that high susceptibility participants are chronically stressed rather than hyper-responsive to increases in social stress.

A recent large ESM study found early and chronic psychosis patients had higher baseline levels of negative affect, tension and suspiciousness compared to healthy volunteers in the absence of stressful events [31]. They reported an increased affective reactivity to stressful events only in the early psychosis group, but not in the chronic psychosis group. We also found an increased paranoia response to stress in our UHR group, but not in our "recent onset" psychosis group [1]. (We defined recent onset as start of treatment less than five years ago.) It is possible that hyper-responsiveness to social stress is a feature of the very early stage of psychosis and that the majority of our sample had already progressed beyond this stage.

Interestingly, ESM studies point to delayed recovery of negative affect and suspiciousness after stressful events in the early psychosis group [31]. Elevated "baseline" levels of subjective stress, paranoia and arousal may reflect impaired recovery, perhaps even from the stress elicited by participating in a research study, interactions with researchers, or filling in questionnaires. Our design was not well-suited to investigate this aspect and we recommend that multiple time points should be included in future studies to address this issue.

In contrast to psychosis susceptibility, we found pre-existing symptoms had a stronger impact on paranoia when the (virtual) environmental social stress increased [1]. This was especially the case for affective symptoms, suggesting "an affective route" to psychosis. Childhood trauma was also associated with heightened social stress sensitivity and may well contribute to psychotic and affective dysregulation later in life through a sensitized paranoid and stress response to social stressors. These findings...
have been confirmed in ESM studies. In adolescents seeking help, childhood trauma was associated with increased negative affect and more psychotic experiences in response to momentary stresses in daily life. Controls appeared resilient against such minor daily stressors [32].

We did not investigate the effects of affective symptoms or a personal history of childhood trauma on autonomic stress response. Nor did we take any measurements of the endocrine stress response, such as cortisol. Recent theories propose that different stages of psychosis illness may be associated with different patterns of HPA axis regulation or dysregulation [33]. Blunting of the cortisol response to laboratory psychosocial stressors was found in psychosis patients, especially in those with chronic schizophrenia [34,35]. A recent meta-analysis found poor concordance between naturally occurring psychosocial stressors (childhood trauma, life events, perceived stress) and cortisol measurements (hair, cortisol awakening response, basal levels in morning and evening, diurnal levels) in individuals on the psychosis spectrum and healthy individuals [36]. Interestingly, stressors were associated with "basal" cortisol measurements if they were completed on the same day, suggesting that distress associated with recalling these events might elicit a cortisol response that enables a significant association to be observed [37]. This pattern resembles our findings on the subjective and autonomic stress responses: psychosis may be associated with an abnormal 'set point' of a patient's stress systems, while childhood trauma is associated with an abnormal response to social stressors.

Childhood trauma contributes to general psychopathology. The hyper-responsive stress system may reflect a general psychopathology factor in psychosis, rather than something that is psychosis-specific. This idea is further supported by our findings that affective symptoms predict stress responses in virtual reality. In this regard, the finding that stress hyper-responsiveness is limited to early psychosis is also interesting. The early stages of psychosis often display a rather mixed range of symptoms and may reflect general psychopathology factors more than psychosis-specific factors.

If we speculate about translating our results to clinical practice, we would suggest interventions should be targeted toward reducing social stress, and treating trauma symptoms and general psychopathology symptoms in very early psychosis. In the later stages, interventions directed at baseline or recovery from stress might be more effective for patients with psychosis. Such interventions could be directed at promoting general well-being, both physically and mentally, a healthy life style, increased physical exercise, a daily rhythm and meaningful activities.

**Inflammation**

We examined the main and interaction effects of psychosis susceptibility and childhood trauma on serum levels of BDNF, CCL-2, CRP, IFN-γ, IGFBP2, IL-6, PDGF, SCF and TNF-α and on Natural Killer and T cell populations in our participants. We found a significant interaction effect of psychosis susceptibility x childhood trauma on Th17 cell numbers. In the high susceptibility group, the experience of childhood trauma was associated with increased Th17 cell numbers. In the low susceptibility group, Th17 cells were lower in those who had experienced childhood trauma. We did not find any other main or interaction effects of psychosis susceptibility or childhood trauma on serum levels of the other cell types.

Our mostly negative findings should be interpreted within a framework of meta-analysis studies. Since the start of the research presented in this thesis, new studies and meta-analyses of the relationship between psychosis and inflammation have been published. Four recent meta-analyses are of particular interest: Pillinger et al. (2019) because of their exclusive focus on first-episode, antipsychotic-naive patients, rigorous method, and inclusion of analysis of variability and modal distribution [38]; Goldsmith et al. (2016) who compared cytokine alterations across psychotic disorders and clinical status [39]; Fernandes et al. (2016) who focused on C-reactive protein (CRP) only and analysis of its moderators [40]; and Park and Miller (2019) who performed the first meta-analysis of high-risk psychosis patients [41].

**Meta-analyses of patients with psychoses**

Pillinger et al. (2019) found increased levels of IFN-γ, IL-17, IL-6, TGF-β and TNF-α in first-episode, antipsychotic-naive patients, but no significant differences in CRP, IL-10, IL-1β, IL-2, IL-4, IL-8 or sIL-2R [38]. Only 8 out of 32 included studies controlled for age, gender, BMI and smoking. In this subset, IL-6, IL-17 and IFN-γ remained elevated and IL-10 and IL-1β remained at similar levels. TNF-α was no longer significant, suggesting it could be influenced by confounding factors.

Goldsmith et al. (2016) found that levels of IFN-γ, IL-1RA, IL-1β, IL-6, IL-8, IL-10, IL-12, sIL-2R, TGF-β and TNF-α were all significantly increased, levels of IL-4 were significantly decreased, and levels of IL-2, IL-17 and IL-18 were unaltered in first-episode psychosis patients vs. controls [39]. Following treatment of psychosis, there were significant decreases observed in IL-1β, IL-4 and IL-6 levels and significant increases in IL-12. Levels of IFN-γ, IL-1RA, IL-1β, IL-6, IL-8, IL-12, sIL-2R, TGF-β and TNF-α were all significantly increased, levels of IL-4 and IL-10 were significantly decreased and IL-2 was unaltered in acutely ill patients with chronic schizophrenia vs. controls. In chronically ill patients, levels of IL-6, TNF-α, sIL-2R, IL-1β, IFN-γ were significantly increased, while IL-2, IL-4 and IL-10 were unaltered compared to controls.
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Meta-analysis of CRP only, by Fernandes et al. (2016), showed a moderate increase of CRP levels in patients with schizophrenia vs. controls, regardless of use of antipsychotics and duration of illness (<1 year vs. >1 year) [40]. This effect remained significant when only studies paired by BMI and age were considered. However, these within-group analyses included only a few studies.

In a meta-analysis of UHR patients, IL-6 levels were significantly higher and IL-1β levels significantly lower vs. controls [41]. Age, sex and BMI were unrelated to the association between IL-6 and high-risk of psychosis. The number of studies was limited and sample sizes were small. There were no differences in IL-6 and IL-1β between converters and non-converters. IL-12 was higher in converters vs. non-converters.

Although all the meta-analyses report differences between patients with psychosis and controls, their results are inconsistent. All the meta-analyses reported considerable heterogeneity and controlling for age, sex, BMI and smoking was limited to a minority of the studies. There was also no consensus on which markers should be measured, nor whether future studies should focus on the markers most commonly replicated or invest in finding new markers. Nonetheless, the meta-analyses do support the notion of elevation of inflammatory cytokines in patients with psychoses, in general. This means we should consider different reasons to explain our negative findings.

Immune subtype

Some authors think that inconsistent findings could be explained by the existence of inflammation subtypes in psychosis, with immune alterations only evident in a proportion of patients. This would provide an explanation for our negative findings if this immune subtype was for some reason relatively underrepresented in our sample. However, if there is an immune subtype, one would expect to see a bimodal distribution of immune parameters in patients and, consequently, an increased variability of immune parameters in patient groups vs. controls. However, Pillinger et al.’s meta-analysis of first-episode, antipsychotic naive psychosis patients showed the opposite [38]: immune measures follow skewed unimodal distributions in both first-episode psychosis patients and controls. Moreover, variability of IL-1β, IL-4, IL-6, IL-8 and TNF-α was significantly reduced in patients compared to controls. Their findings argue against there being an inflammatory subtype in psychosis patients.

Dynamic course of anti-inflammatory markers

Our sample of patients with psychosis does not quite fit into any of the groups specified by Pillinger et al., Goldsmith et al., or Fernandes et al. [38-40]. We included patients with recent-onset psychosis who had been treated at an outpatient clinic for less than five years. They were treated naturalistically and given antipsychotics. They may thus represent a patient group between the acute, first-episode psychosis and chronic schizophrenia. Goldsmith et al.’s analysis suggests the course of anti-inflammatory markers is dynamic, with increased levels of inflammatory cytokines seen in first-episode psychosis patients, decreasing after treatment, and increasing again in chronically ill patients, especially those with acute episodes [39]. It is therefore possible that our sample was taken at the lowest point of inflammation, just after the first episode and before development of a chronic disease state. Furthermore, our sample was part of a virtual reality environment study, a procedure that took 3 hours and also included taking blood samples and filling in questionnaires. It is quite likely that this was perceived as too demanding by the most severely ill patients, which may have led to a selection bias of relatively stable and well-functioning patients. Indeed, their levels of symptoms were relatively low compared to UHR patients, for example.

Assay sensitivity

Another possibility is that our results were affected by assay sensitivity. Although we used highly sensitive assays, a proportion of values were either too low to detect or were detected but extrapolated under the lower limit of quantification. These values are still meaningful, but carry an increased measurement error, which might have decreased the power of our analysis and contributed to our negative findings. It seems unlikely that these issues are unique to our study, as cytokines tend to have a positively skewed distribution and peripheral concentrations are low in healthy individuals. Nonetheless, it is rare to find reports on assay sensitivity and data reliability in studies of cytokines in psychosis. Moreover, mean and standard deviations are often reported, even though this may not be the best way to describe skewed distributions. Log-transformation to reduce the effects of positive skew on analyses are not uniformly applied.

The role of obesity

Our sample was characterized by an, on average, healthy BMI, with no statistically significant differences in BMI between groups. In general, obesity rates are, on average, higher in psychosis patients [43,44], making our study group a notable exception. Adipose tissue shows endocrinological and immunological activity, with excessive nutrient accumulation and obesity resulting in low-grade inflammation [45,46]. Increased levels of IL-6 and CRP, for example, are observed in obesity [47]. Low-grade inflammation in psychosis patients may depend on obesity and our negative findings could therefore be explained by a lack of obesity in our study group. In support of this idea, Keinänen et al. (2018) found CRP levels that were similar in patients with psychosis and controls at baseline. However, they observed a 2.5-fold increase in CRP
Furthermore, drugs with known primarily immunomodulatory effects (e.g., NSAIDs, 
minocycline, fingolimod and tocilizumab) were compared with drugs with potential 
immunomodulatory effects (e.g., oestrogens and melatonin). Both these categories of 
drugs (primary effects and potential effects) displayed similar effects to primarily anti-
inflammatory drugs, which raises the question whether the treatment effect was due 
to anti-inflammatory properties or other pharmacological mechanisms [49].

However, findings do highlight that psychosis has systemic effects: patients with 
psychosis are not only characterized by hallucinations and delusions, but are also 
chronically stressed, there is evidence of low-grade inflammation and metabolic 
dysregulation. In this light, it is hardly surprising that patients often have comorbidities 
and a lower life expectancy [50,51]. This highlights the need for life-style interventions, 
even though life style has proven difficult to influence [52,53]. More intensive coaching 
programs, including performing physical exercise with patients instead of just giving 
advice on physical exercise and targeting the early stages of psychosis may hold the 
most promise [54,55].

Low-grade inflammation is likely to be a more general mechanism of psychopathology 
than specific for psychosis. Indeed, Goldsmith et al. found similarities in cytokine 
alterations across various disorders and in the pattern of change occurring in 
different phases of psychiatric illness [39]. Levels of IL-6, TNF-α, sIL-2R and IL-1RA were 
significantly increased in acutely ill patients with schizophrenia, bipolar disorder, and 
major depressive disorder (MDD) compared to controls. Following treatment of acute 
ilness, IL-6 levels significantly decreased in both schizophrenia and MDD. In chronically 
il patients, IL-6 levels were significantly increased in schizophrenia, euthymic bipolar 
disorder and MDD compared to controls. This suggests that dysregulation of the 
immune network may be a common underlying pathway for severe psychiatric 
disorders, rather than specific for psychotic disorders.

At the other end, multiple risk factors may predispose to low-grade inflammation. 
As discussed in chapter 6, there is evidence to suggest psychosis risk factors such 
as childhood trauma, ethnic minority status, and urbanicity are associated with low-
grade inflammation. And again, obesity may play a central role in the pathway. Other 
stressors, both genetic and environmental, and psychological and biological in nature 
are known to affect the immune system.

Dysregulation of the immune system is likely to predispose to multiple (adverse) 
outcomes, ranging from autoimmune disorders to cardiovascular disease and 
psychiatric symptoms. However, these stressors also occur in individuals who do not 
have adverse outcomes. It would be interesting to study the resilience of such groups.
Connections between social stress, immune dysregulation and psychosis

I started the work for this thesis with the somewhat over-ambitious goal of integrating two lines of research: one focused on low-grade inflammation in psychosis and one on the social environment of psychoses. Looking at this thesis now, the two lines run largely separately through different chapters. They touch here and there, sometimes intertwining or getting tangled up.

The findings from this thesis, combined with the literature, suggest that psychosis is best characterized by an abnormal ‘set point’ of stress systems, namely a chronic (over)activation independent of social stress. Childhood trauma is associated with an hyper-responsive reaction to social stressors. This is especially relevant since childhood trauma is extremely common among psychosis patients and deserves adequate attention in their treatment. Social stress and psychosis are both linked to immune dysregulation by literature reports, although we could not confirm this link in our own sample group. Obesity may play a central role in associations between social stress, immune dysregulation and psychosis.

In conclusion, we are still far from determining an all-explanatory model or a well-defined pathophysiological pathway to psychosis in general or to any particular subtype. There are abundant links between social stress, immune dysregulation and psychosis but they are subtle and how they work is still largely unclear. I sincerely hope the complex nature of the links will inspire future clinicians and researchers to perform studies to find more leads towards improving treatments for patients with psychotic and other psychiatric disorders.

References


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