CHAPTER 1
General introduction
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"Marja Krijnen was in her early twenties when she gradually drifted away from reality. Facing the pressure of her study and family problems, she started to hear voices, see people who were not there, and became obsessed with bizarre details, such as texts on cars like 'Auto repair company Jansen & Jansen'. She became more lonely, unhappy and started to withdraw into her own world.

'I felt very vulnerable', Krijnen says, now in her forties. 'I misjudged situations and hardly stood up for myself. For some reason, this is clearly visible to others, and I became an easy target for anyone who meant harm. Sometimes I would randomly take a train to get away from the voices, without taking the practical consequences into account. One time I stranded at Brussels station in the middle of the night, a terrible atmosphere, and I was assaulted. Another time, I ended up in Paris and I walked into a shopping street, when a man grabbed me by my arm and dragged me into a hotel. I froze and let it all happen. I never reported the sexual abuse. I lost the perception of the boundary between what is normal and abnormal.'

Not long after, she found a brick in her living room one morning, and her window was completely shattered. 'I was not sure whether this brick was meant for me personally, but a normal human being would have called the police and subsequently the glass repair service. But I wasn’t able to do so. The first thought that came to mind was: get out of here! I shut the front door behind me and went straight to my mother'.

She did not speak to anyone about these incidents. 'I think I was ashamed, and I wanted to keep up appearances. No one was to know how miserable I was, because then I would have to admit to myself that my life was a mess'.


In the movies, newspapers and other media sources, psychosis is often linked to violence and aggression. However, contrary to popular belief, people diagnosed with a psychotic disorder are more often the victim than the perpetrator of a crime (Dean et al., 2007). Although victimization can have a major impact on people's lives, no evidence-based intervention targeted at victimization is available. To prevent victimization of individuals with a psychotic disorder a body-oriented resilience therapy has been developed, based on pre-defined putative associated factors derived from the literature. In this dissertation we explored the feasibility of this therapy by means of a pilot and subsequently we performed a multicenter randomized controlled trial to investigate effects on behavioral outcomes (e.g. incidents of victimization, associated factors and generic outcomes). In addition, we conducted an MRI study to gain more insight in which brain areas or networks are associated with victimization of individuals with psychosis, and to explore the effects of the intervention on brain activation. Because the therapy contains physical exercise we also reviewed studies which have investigated the neural effects of physical exercise interventions in people with a psychotic disorder and healthy individuals.
BROADER CONTEXT: THE NWO RESEARCH PROGRAMME

Not only patients with psychosis but psychiatric patients in general are at an increased risk of victimization (Teplin, McClelland, & Abram, 2005). For example, in a large Dutch multi-site epidemiological study, almost half of the 956 included participants diagnosed with a chronic (≥ 2 years) psychotic disorder, bipolar disorder or major depressive disorder had been victim of a crime in the past year (Kamperman et al., 2014a). In addition, compared to the general population, patients with a dual diagnosis including psychotic disorder, personality disorder, mood disorder, anxiety disorder, intellectual disability and attention deficit/hyperactivity disorder reported more incidents of violent victimization (60% vs. 11%), property victimization (58% vs. 30%), and vandalism (21% vs. 14%) in the year preceding assessment (de Waal et al., 2018). Moreover, a recent longitudinal study revealed that psychiatric symptoms were prospectively associated with reporting subsequent violent victimization (Bhavsar et al., 2018). Because of the emerging evidence on victimization of psychiatric patients, the Dutch Organization of Scientific Research (NWO) launched the research program ‘Violence against psychiatric patients’ (‘Geweld tegen psychiatrische patienten’). The objective of this program was to gain more insight in the nature of victimization and in risk factors for victimization, and to develop interventions aimed at preventing victimization of psychiatric patients. To this end, five intervention studies were designed, each targeting a different patient group: the SOS study for dual diagnosis patients with substance use disorders (de Waal et al., 2015), the VICTORIA study on SMI patients (Albers et al., 2018), the VRAPT study for forensic psychiatric patients (Klein Tuente et al., 2018), the ALERT project in depressed individuals (Christ et al., 2018a) and the BEATVIC study for people with a psychotic disorder (van der Stouwe et al., 2016). This thesis concerns the BEATVIC study.

PSYCHOSIS

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM 5, APA), schizophrenia spectrum disorders concern a spectrum of mental disorders (see text box 1) that are characterized by hallucinations and delusions, negative symptoms (e.g. anhedonia, avolition and alogia), cognitive impairments and affective symptoms (American Psychiatric Association, 2013; van Os & Kapur, 2009). Hallucinations are defined as sensory perceptions in the absence of an external stimulus (e.g. hearing voices), while delusions are false beliefs or ideas often derived from misinterpretations of perceptions that are held with strong conviction and that cannot be understood in terms of a person's social or cultural background. Negative symptoms may include anhedonia, which is the loss of experienced pleasure during normally pleasant activities, avolition that is defined as decreased motivation to initiate and pursue self-directed activities, and/or alogia, which refers to reduced speech. It has been proposed that negative symptoms are best characterized by two subdomains, namely expressive deficits that refer to disturbances in the outward expression of emotion or speech, and amotivation, which is thought to reflect reduced self-initiated behaviors. This has been confirmed by factor analyses on often-used scales for the assessment of negative
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Symptoms (Liemburg et al., 2013). Cognitive impairments comprise e.g. attention deficits, impairments in memory, executive functioning and in social cognition (Owen et al., 2016). Affective symptoms may include depression or mania. People with a diagnosis in the psychotic spectrum experience one or more of these symptoms, in various compositions.

Text box 1. DSM 5 Schizophrenia Spectrum and Other Psychotic Disorders (American Psychiatric Association, 2013)

- Delusional Disorder
- Brief Psychotic Disorder
- Schizophreniform Disorder
- Schizophrenia
- Schizoaffective Disorder
- Substance/Medication-Induced Psychotic Disorder
- Psychotic Disorder Due to Another Medical Condition
- Catatonia Associated With Another Mental Disorder (Catatonia Specifier)
- Catatonic Disorder Due to Another Medical Condition
- Unspecified Catatonia
- Other Specified Schizophrenia Spectrum and Other Psychotic Disorder
- Unspecified Schizophrenia Spectrum and Other Psychotic Disorder

Worldwide, approximately one in 150 individuals is diagnosed with a psychotic disorder at some point during their lifetime (Moreno-Küstner et al., 2018). The origin of psychotic symptoms is still unclear, but it is generally assumed that an interplay between a genetic predisposition and unfavorable environmental factors determines who will be affected. Most often, symptoms manifest themselves in the early twenties for men and a few years later for women (Kirkbride et al., 2006; van Os & Kapur, 2009). Typically, incidence rates are higher in men until the mid-thirties and higher in women after the mid-forties in their meno-pause (Aleman et al., 2003; Kirkbride et al., 2012). Psychotic spectrum disorders can cause a large burden on patients, in the first place because of distressing symptoms and more indirectly because of physical health issues and/or social aspects. Compared to the general population, patients suffer more often from the metabolic syndrome (Mitchell et al., 2013), type two diabetes (Stubbs et al., 2015) and cardiovascular disease (Gardner-Sood et al., 2015). With regard to social burden, people with a psychotic disorder regularly experience problems in education, employment and relationships, and also encounter social stigma which can lead to reduced social participation and in social isolation (Rössler et al., 2005; Schulze & Angermeyer, 2003).
VICTIMIZATION IN PSYCHOSIS

Prevalence

Prevalence rates of victimization in people with a psychotic disorder vary across studies due to differences in sample characteristics, the operationalization of victimization and the examined reference period. Victimization is most often operationalized as an event in which an individual is the target of a criminal act by another individual. While in few studies participants were only asked whether they had been a victim of a crime, most studies used more extensive questionnaires and distinguished violent victimization, sexual victimization, nonviolent victimization and victimization not otherwise specified. A review by our group (de Vries et al., 2018a) on 27 studies revealed that the median year prevalence rate for sexual victimization in people with a psychotic disorder is 20%, for non-sexual violent victimization 20%, for nonviolent victimization 19% and for victimization not otherwise specified 19% when examined over a short reference period (≤ 3 years). Examination of entire adulthood resulted in higher prevalence rates, namely 66% for violent victimization, 39% for nonviolent victimization and 27% for sexual victimization. Moreover, studies that compared prevalence rates of individuals with a psychotic disorder with average prevalence rates in the general population, showed that these were between four and six times higher for people with psychosis.

Risk factors

The literature points out several risk factors that may play a role in victimization of patients with a psychotic disorder. Symptoms such as social cognitive deficits, hallucinations, delusions, manic symptoms, and personality disorder features might make patients more vulnerable (de Vries et al., 2018b; DePrince, 2005a). An offender may perceive someone with many symptoms as an easy target, and/ or symptoms may provoke anger or aggression more easily in potential offenders. Furthermore, mentioned symptoms, especially social cognitive deficits, may have a negative impact on social interactions and social functioning (Couture et al., 2006). Inadequate social behavior may hinder the development of a solid social support system and may enhance the chances of conflicting relationships. Moreover, social cognition problems, for example theory of mind (ToM) deficits and emotional face processing difficulties may directly put individuals at risk for victimization, because cues of potentially dangerous social situations such as angry or threatening facial expressions of a perpetrator might be missed (Baas et al., 2008). In section 1.5 we elaborate further on the putative association between emotional face processing and victimization.

In addition to the burden of symptoms, people with a psychotic disorder encounter stigmatization (Schulze & Angermeyer, 2003). Such stigmatization is not limited to others and society, but patients may also have self-stigmatizing thoughts. Self-stigma arises when people with a mental disorder are aware of negative stereotypes associated with their diagnosis, internalize these stereotypes and apply them to themselves (Corrigan et al., 2006). Victimization enhances self-stigma, leading to negative self-
esteem and decreased assertiveness and empowerment (Horsselenberg et al., 2016; Kleim et al., 2008; Livingston & Boyd, 2010). Consequently, patients may become more prone to victimization, leading to a vicious circle between (re)victimization, stigma and self-stigma. According to the literature, another vicious circle concerns the association between negative life experiences such as childhood abuse and previous victimization with (re)victimization. Traumatic life experiences may lead to negative beliefs about the self, self-blame or feelings of guilt which makes individuals vulnerable to revictimization (Krkovic et al., 2018; Shevlin et al., 2013). Furthermore, it has been established that exposure to threat or trauma stimulates the autonomic nervous system (ANS), resulting in sympathetic hyperarousal and parasympathetic (dorsal-vagal-mediated) hypoarousal states. This co-activation of sympathetic and parasympathetic components of the ANS lead to behavioral freeze responses (Ogden et al., 2006). Freezing is identified as one of the three behavioral responses to cope with threat, alongside fighting and flighting. In the literature it has been suggested that as a result of the failure to fight or escape during an initial threatening event, freezing becomes a conditioned behavioral response (Van Der Kolk, 2006). In subsequent threatening events, such as a potential dangerous social situation, freezing might serve as a risk factor leading to higher chances of (re)victimization. Furthermore, perpetration may be a risk factor as in some cases perpetration and victimization go hand in hand (Hodgins & Klein, 2017; Jennings et al., 2012). For example, if one individual steals property (e.g. a motor bike) of someone else which leads to violent behavior of this second person towards the first, roles of victim and perpetrator swap. Compared to people with a psychotic disorder that have not been victimized, patients that have been a victim of a crime also have been more often an offender of a crime (Fitzgerald et al., 2005; Honkonen et al., 2004). A study on murder offenders showed that those with a psychotic disorder are 3.19 times more likely to be motivated by revenge than nonpsychotic offenders and those with no diagnosis. For the offenders with a psychotic disorder the perception of having been wronged in some way was a potential risk marker for planning and committing a serious offense (Hachtel et al., 2018). For part of the individuals with a psychotic disorder in general aggression regulation problems or reduced illness insight which can be associated with aggressive behavior (Ekinci & Ekinci, 2012) may elicit conflicts eventually resulting in victimization of the patient (Witt, van Dorn, & Fazel, 2013). Other risk factors cited in the literature concern substance abuse and demographic factors such as homelessness, unemployment, and living in a disadvantaged neighborhood (de Vries et al., 2018b). These factors may expose people to potentially dangerous and criminal environments with close proximity to possible offenders.

**Victimization model**

Of the many risk factors of victimization derived from empirical studies, we could only use factors that may be amendable to change by psychosocial therapies as treatment targets. These factors were selected and incorporated in a model which formed the basis of our intervention (figure 1; van der Stouwe et al., 2016). Firstly, mentioned social cognitive deficits which may lead to social inadequate
behavior have been included in the model. Social cognition is not static and can be improved by means of training (Dodell-Feder et al., 2015). Typically, specific strategies are practiced in social cognition training (e.g. looking at certain face characteristics to see how someone else feels) (Horan et al., 2009; Roberts et al., 2014). Furthermore, the vicious circle between self-stigma and victimization via low self-esteem, decreased assertiveness and empowerment has been incorporated in the model (Horselenberg et al., 2016; Kleim et al., 2008; Livingston & Boyd, 2010). Self-stigma can be considered as an important treatment target in general as it causes a lot of burden and self-stigma serves as a predictor of adherence to psychosocial treatment (Fung et al., 2008). Also the chain reaction between previous victimization and revictimization via physiological and behavioral mechanisms has been included in the model. In body-oriented therapy interventions trauma victims can learn to recognize behavioral responses such as freeze, fight and flight and can experiment with these different types of behavior in a safe environment (Ogden et al., 2006; Van Der Kolk, 2006). And lastly, the model emphasizes the overlap between victimization and perpetration as preventing one may prevent the other (Silver et al., 2011). Aggression regulation problems or reduced illness insight were mentioned as possible pathways to social inadequate or aggressive behavior (Ekinci & Ekinci, 2012) which may elicit conflicts eventually resulting in victimization of the patient (Witt et al., 2013). Therefore, both were entered in the victimization model as potential targets of an intervention. Although it is important to test the constructed model, validation of the model is beyond the scope of this dissertation.

Figure 1. Victimization model
BEATVIC INTERVENTION

Based on the victimization model BEATVIC was developed; a body-oriented resilience therapy, in which a body-oriented approach is combined with elements of social cognition training, assertiveness training and martial arts. Because victimization often occurs and derives from factors at a non-verbal level, we chose an experiential approach which combines body awareness exercises with physical activity, in contrast to primarily verbal interventions. This approach has its origin in what in some countries is called psychomotor therapy (Probst, 2010) or body-oriented psychotherapy (Röhrich, 2015; Röhrich et al., 2009) and is typically provided by a discipline of therapists specialized in movement and body oriented interventions, in European countries referred to as psychomotor therapists (see www.psychomot.org/). A body-oriented and an experience-based approach enables patients to learn about their automatic natural tendencies and experiment with new and social adequate behavior. On the other hand, by performing exercises with a partner or by observing exercises participants also learn to interpret behavior and recognize body language or facial expressions of others, which are crucial goals in social cognition training. Studies have shown that assertiveness training has a positive effect on self-esteem, self-efficacy, perceived control and assertiveness (Brecklin, 2008; Hojjat et al., 2015). In BEATVIC, exercises derived from assertiveness training concern setting boundaries. Martial arts were chosen because of their potential to serve as a means to acquire mental resilience, self-efficacy and empowerment, and to increase aggression regulation (Hasson-Ohayon et al., 2006; Moore et al., 2018). We selected kickboxing specifically because techniques are achievable for everyone regardless of someone’s physical condition which may result in experiences of success, enhancing self-esteem. Furthermore, kickboxing enables participants to socially interact with each other and it requires continuous reading of each other’s body language and facial expression. Moreover, kickboxing is a popular form of sports in the Netherlands and is offered at many regular sports centers. Therefore, kickboxing may be appealing, non-stigmatizing and might increase therapy adherence.

BEATVIC is provided by a body-oriented therapist and an experiential expert. In mental health care, involving experiential experts have become more common in the past decades. Although more research is needed, studies thus far show that deployment of experiential experts is of important added value with regard to recovery, (self-)stigma and empowerment (Cook et al., 2012; van Vugt et al., 2012). Experiential experts can serve as a role model by showing that regardless of a long illness history it is possible to take control of certain situations and to even use this experience to support others.

NEURAL PROCESSES ASSOCIATED WITH VICTIMIZATION IN PSYCHOSIS

Up until now, research on victimization of people with a psychotic disorder has focused on personal factors (e.g. symptoms, social functioning, behavioral characteristics) and environmental factors (e.g. disadvantaged neighborhood), with little emphasis on potential related neural processes. However, information on the neural correlates of psychological processes involved can provide important insights in either underlying
mechanisms or consequences of victimization. Therefore, in the second part of this thesis we focus on neural processes, with special emphasis on social cognitive processes as a putatively associated factor of victimization and as an important outcome of the BEATVIC therapy. In the literature, four core research domains of social cognition have been identified: emotional perception and processing, social perception and knowledge, theory of mind and attributional style (Pinkham, 2014). Of these domains, deficits in facial emotion processing have been explicitly suggested to play a role in victimization of people with a psychotic disorder in previous research (Baas et al., 2008). Especially processing of angry and fearful facial expressions might be relevant. Angry expressions signal a direct and immediate threat from a potential perpetrator, while fearful expressions indicate a possible presence of a significant source of threat in the environment, as witnessed by others (Fridlund, 1994).

EMOTIONAL FACE PROCESSING & THE BRAIN

Research has consistently shown several key brain regions to be involved in the processing of emotional faces. First of all, visual areas such as occipital regions, the fusiform gyrus and the superior temporal sulcus play a role in the early perceptual processing of facial stimuli (Fox, Iaria, & Barton, 2009; Fusar-Poli et al., 2009; Gobbini & Haxby, 2007). The occipital regions are responsible for the early processing of faces, subsequently transferring information to the temporal regions, of which the superior temporal gyrus is involved in processing changing aspects of face perception and the fusiform gyrus most strongly responds to tasks focusing on facial identity (Haxby et al., 2000; Pelphrey & Morris, 2007; Winston et al., 2002). Furthermore, limbic areas such as the amygdala, the insula and the anterior cingulate cortex (ACC) are implicated in emotional face processing (Campos et al., 2016; Delvecchio et al., 2017). The amygdala responds to emotionally and socially relevant information (Adolphs, 2010), the insula is involved in processing aversive emotions such as disgust, fear and anger (Lindquist, Kober, & Barrett, 2012) and the ACC has projections to both the amygdala and the prefrontal cortex and is therefore, amongst other functions, implicated in emotion regulation and monitoring of the saliency of emotional information (Stevens et al., 2011). Finally, frontal regions also play a role in processing of emotional face stimuli. For example, the orbitofrontal cortex has been found to monitor future outcomes of social behavior (Amodio & Frith, 2006) and the ventrolateral prefrontal cortex has been found to modulate the amygdala during the process of evaluative judgments of faces (Pinkham, 2014). For a visual representation of the brain areas involved in face processing, see figure 1.

In psychotic disorders, these areas have shown aberrant activation in response to emotional face processing. A recent meta-analysis on facial emotion processing found that, compared to the general population, people with schizophrenia showed decreased activation throughout the facial affect processing areas (e.g. FG, amygdala, insula, ACC, medial frontal gyrus, para-hippocampal gyrus, right medial dorsal thalamus) (Delvecchio et al., 2017).
Emotional face processing as a risk factor

Individuals with a psychotic disorder show different brain response to emotional face processing and experience difficulties in recognizing facial expressions (Aleman & Kahn, 2005; Kohler et al. 2010). While no previous studies investigated the association between victimization and emotional faces processing, our research was based on various studies on behavioral and brain response to emotional faces in psychosis. Baas et al. (2008) showed that people with a psychotic disorder rated pictures of faces in a task as more trustworthy, especially those that were judged to be untrustworthy by healthy participants. Although this finding may seem counterintuitive at first glance with regard to paranoid symptoms, the finding of aberrant behavioral face processing is in line with neuroimaging findings of decreased activation throughout facial affect processing areas. By perceiving faces as less threatening an individual may miss an important social cue necessary to anticipate to a potential dangerous social situation. On the other hand, a couple of studies have indicated that individuals with schizophrenia tend to interpret emotional faces as more negative than healthy individuals (Kohler et al., 2010; Savulich et al., 2015), which may be associated with increased brain activation. Perceiving faces as more negative may lead to conflicts more easily which could ultimately result in victimization. Regardless of the valence of an interpretation bias, difficulties in processing faces may be a potential source of victimization.
Altered threat processing as a consequence

While difficulties in face processing may lead to victimization, victimization in turn may lead to changes in responses to threatening facial stimuli. As mentioned in the description of the victimization model, victimization is a type of trauma, in some cases leading to post traumatic stress disorder (PTSD), which may result in sympathetic hyperarousal and parasympathetic (dorsal-vagal-mediated) hypoarousal states (Corrigan et al., 2011). Although neural processes related to victimization in patients with a psychotic disorder have not been investigated yet, previous studies did explore processing of threatening stimuli in traumatized individuals. Indeed, studies found increased sensitivity to threatening information such as angry faces (Melih et al., 2017) as reflected by increased brain activation in the amygdala, the hippocampus and the ACC (Cisler et al., 2014; Garrett et al., 2012) in people that had experienced traumatic events. Other studies reported decreased brain activation of thalamus, the ACC, and the medial frontal gyrus during traumatic memories (Lanius et al., 2001) or decreased resting-state network connectivity within the default mode network, salience network, sensorimotor network and auditory network during (Zhang et al., 2015). Hagenaars et al. (2014) posit that freezing comprises a combination of the aforementioned responses: arousal and immobility. In line with this idea, based on animal research, the amygdala and the ventrolateral periaqueductal gray (PAG) seem to be implicated in the freezing response (Roelofs, 2017).

In summary, the brain response to threatening facial expressions as a putatively relevant factor for victimization is insufficiently understood at present, but gaining knowledge regarding this relationship may provide more insight in victimization and may ultimately have clinical implications.

NEURAL EFFECTS OF BEATVIC

Neural response to threatening emotional faces was also investigated as an outcome measure of BEATVIC since emotional face processing and social cognition as a whole were important targets of the intervention. Unraveling the neural correlates of effects of therapeutic interventions such as BEATVIC can have important implications for our understanding of the mechanisms of therapeutic change (Brenner et al., 2006; Van Der Gaag, 2006). While we were the first to investigate this specific therapy, several previous studies looked at neural effects of social cognition training (SCT), which also targets emotional face processing. A review on neural effects of SCT reported increased activation in regions that typically show decreased activation in response to emotional faces in psychosis, namely in the insula and amygdala, in occipital areas and in frontal areas. These neural changes were related to improvements in social cognitive performance (Campos et al., 2016).

Because BEATVIC combines elements of different approaches and also contains physical exercise it was considered worthwhile to also investigate the neural effects of other physical exercise interventions in psychotic disorder to gain insight in the specific effect of this element of the therapy. In the past decade, studies on exercise interventions in psychotic disorders emerged reporting promising effects on positive
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and negative symptoms, cognition, depression, social withdrawal, self-esteem and fitness (Dauwan et al., 2016; Firth et al., 2015). It has been suggested that exercise interventions may be important complementary interventions because they target symptoms that are addressed insufficiently in existing treatments, such as negative symptoms, cognitive deficits and cardiac metabolic factors such as fitness.

OUTLINE

We address two general objectives in this dissertation. In the first part, we aim to investigate the effect of BEATVIC on the behavioral level. In Chapter 2, we examine the feasibility of the BEATVIC intervention in preparation of a larger randomized controlled trial. More specifically, we explore the feasibility of the intervention, to improve the intervention protocol and to explore suitable outcome measures for a subsequent RCT. In Chapter 3, we describe the study protocol of our multi-center RCT. Lastly, in Chapter 4 we investigate the effect of the BEATVIC intervention on victimization, associated factors of victimization (e.g. social cognition, interpersonal behavior, internalized stigma) and more generic outcomes (e.g. quality of life, recovery).

The second part of this thesis emphasizes the neural level: we aim to investigate neural correlates of victimization, neural effects of exercise interventions in general and more specific the neural effects of BEATVIC. In Chapter 5 we focus on the domain 'face processing' of social cognition as a possible associated factor of victimization. We report an MRI study to determine whether victimized patients with a psychotic disorder show differences in brain activation and brain connectivity during processing of angry facial expressions compared to patients that have not been victimized. In preparation of the study on neural effects of the BEATVIC intervention, in Chapter 6 we investigate neural effects of exercise interventions as BEATVIC also contains exercise. In Chapter 7 we report a study on the neural effects of BEATVIC using two face processing task, of which one was also used in Chapter 4. Finally, the main findings are summarized, and clinical implications, methodological considerations, and directions for future research are discussed in Chapter 8.