# CLINICAL PSYCHOLOGICAL ASPECTS OF GENETIC NEURODEVELOPMENTAL DISORDERS

## A DIALECTICAL BEHAVIOR THERAPY APPROACH TO EMOTION REGULATION IN NEUROFIBROMATOSIS TYPE 1

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DONDERS SERIES

# Clinical psychological aspects of genetic neurodevelopmental disorders

## A Dialectical Behavior Therapy approach to emotion regulation in Neurofibromatosis Type 1

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## Content

“The way I describe the situation is that Mother saw me as a tulip and desperately wanted to make me into a rose. She thought I’d be happier as a rose. But I did not have what it took to be a rose, not then and not now. This tulip/rose conflict eventually became part of the way I talk to my clients in DBT. This is what I tell them:

*If you’re a tulip, don’t try to be a rose. Go find a tulip garden.*

All of my client are tulips, and they’re trying to be roses. It doesn’t work. They drive themselves crazy trying. I recognize that some people don’t have the skills to plant the garden they need. But everybody can learn how to garden.”

Marsha Linehan, Building a life worth living (2021, p. 54)

# 1

# Introduction

Understanding the etiology, presentation, and treatment of neurodevelopmental disorders (NDDs) is becoming more pertinent to clinical psychology and psychiatry. Neurodevelopmental disorders form a heterogeneous group of early-onset conditions characterized by impairments in cognitive, social, and motor functioning that interfere with daily life. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), NDDs include intellectual disability (ID), communication disorders, autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), specific learning disorders, and motor disorders such as tic disorders (American Psychiatric Association, 2022). It has become increasingly recognized that conditions that arise early in life affecting cognition, behavior, and emotion are a significant and often underestimated as a cause of lasting mental health challenges. Neuro-developmental disorders tend to be implicated in complex interplay among environmental influences and genetic vulnerabilities, and these play a role not only in the presentation of NDD symptoms but also in how they are treated. Despite the progress in diagnostic frameworks and neurobiological research, individuals with NDDs still often do not receive the care they need, especially when their problems involve cognitive, affective, and behavioral domains that do not fit in traditional diagnostic categories.

Traditionally, NDDs have been classified as distinct categories based on observable behavioral symptoms. However, accurately diagnosing mental disorders and identifying their etiological mechanisms remains a central challenge in clinical psychology and psychiatry. Dimensional classification systems such as the Hierarchical Taxonomy of Psychopathology (HiTOP) aim to improve diagnostic precision by conceptualizing psychopathology as a hierarchy of transdiagnostic spectra based on empirical data (Kotov et al., 2017; Kotov et al., 2018). In parallel, efforts to better understand the causes of NDDs have accelerated through rapid advances in genetics, molecular biology, and neuroscience. The Research Domain Criteria (RDoC), developed by the National Institute of Mental Health, promotes a multidimensional approach to psychopathology that integrates genetic, neuro-biological, cognitive, and behavioral levels of analysis (Cuthbert & Insel, 2013; Insel et al., 2010). Increasingly, studies have identified specific gene variants and biological pathways associated with neurodevelopmental conditions, supporting a biological model of their etiology (Morris-Rosendahl & Crocq, 2022). Dimensional models allow for a more nuanced characterization of symptom severity and variation across domains. This is especially relevant in NDDs, where comorbidities are common, symptom profiles are heterogeneous, and developmental trajectories vary widely. A dimensional perspective and more integrative approach, one that acknowledges the interaction between genetic, psychological, and environmental influences, would offer a more complete understanding of NDDs and better support the needs of individuals affected by them.

One of the genetic conditions associated with neurodevelopmental disorders (NDDs) is Neurofibromatosis Type 1 (NF1). Neurofibromatosis type 1 (NF1) is a genetic disorder that affects the skin and the nervous system. It is caused by a change in the NF1 gene (Gutmann et al., 2017). People with NF1 usually receive care in general hospitals, where the focus is on physical symptoms like café-au-lait spots, Lisch nodules, and neurofibromas. Even though emotional and behavioral problems are becoming more recognized, people with NF1 are still rarely referred to mental health services (Bottessi et al., 2020; Domon-Archambault et al., 2018; Reichardt et al., 2013). In cases where referral to mental health services does occur, it is typically because psychological symptoms are present that warrant diagnostic assessment, or because there are somatically unexplained complaints, such as fatigue, for which comprehensive (neuro)psychological evaluation is requested to explore potential psychological explanations. Subsequent treatment is frequently absent or symptom-specific only (Copley-Merriman et al., 2021). This makes sense given the categorical diagnostic approach that has prevailed in recent years, rather than a transdiagnostic perspective. The preceding information highlights the potential need for a more integrated approach that addresses the broader cognitive, behavioral, and emotional challenges faced by individuals with NF1, while also underscoring the importance of tailored treatment options to effectively address the needs.

A critical first step in addressing this unmet need is to comprehensively map the cognitive, behavioral, and psychopathological profiles of individuals with NF1. Understanding of these psychological factors is important for a targeted, effective therapeutic intervention. Rare genetic syndromes present unique challenges due to the complex interplay between genetics, physical symptoms, and behavior. This highlights the necessity of a treatment framework that is comprehensive and adaptable. A treatment approach based on behavioral therapeutic principles could be considered, as many individuals with neurodevelopmental disorders (NDDs) often exhibit reduced intellectual capacities (Bos-Roubos et al., 2020), and interventions focusing on behavioral change offer a promising framework by analysing the function of behaviors and their reinforcing consequences. Subsequently, it is essential to involve a systemic approach in the treatment process, as relatives play a role in both the consequences of behavior and the reinforcement mechanisms that sustain it. This functional approach enables clinicians and patients to identify maladaptive behavioral patterns and learn strategies for sustainable change. Additionally, it is important to acknowledge the chronic, unchanging component inherent to a genetic condition, where acceptance alongside change is considered essential.





Dialectical Behavior Therapy (DBT) emerges as a suitable therapy for this purpose. Its dialectical nature lies in the balance between change and acceptance. When individuals are exclusively oriented towards change, it may inadvertently convey the message that they are not good enough as they are. For individuals with NF1, understanding the function of their behavior in light of their genetic condition and learning history can contribute to self-validation, which indicates an understanding of the logical relationship between antecedents and consequences of behavior. Validation for the broad spectrum of symptoms can emerge when the full picture is acknowledged and systematically assessed by encompassing both somatic and psychological issues. As a transdiagnostic intervention, DBT addresses core challenges by teaching skills related to emotion regulation, distress tolerance, mindfulness, and interpersonal effectiveness (Linehan, 2002; 2016). Its adaptability and emphasis on the natural mixture of acceptance and behavioral change make DBT accessible and relevant for individuals with a range of intellectual and cognitive abilities (Brown et al., 2013; McNair et al., 2017). These characteristics underscore the rationale for exploring the applicability of DBT to genetic neurodevelopmental disorders, and specifically to NF1, where treatment has not previously focused on emotion regulation problems as an underlying transdiagnostic construct associated with symptom-specific complaints, such as anxiety or depression (Caspi & Moffit, 2018; Mulay et al., 2019; Ruggero et al., 2019; Sloan et al., 2017).

This introductory chapter continues by reviewing current knowledge about the cognitive, behavioral and psychological profiles of individuals with NF1, then outlining the principles of DBT, followed by an exploration of its transdiagnostic applicability and its relevance for neurodevelopmental disorders, particularly NF1. It concludes with an outline of the thesis structure.

## Neurofibromatosis type 1 (NF1)

Neurofibromatosis type 1 (NF1) is a genetic condition that affects the skin and nervous system. It is caused by changes in a specific gene called the NF1 gene, which is found on chromosome 17. This gene normally helps control cell growth and development through a process known as the Ras/Mitogen-activated protein kinase pathway. When there are variations in the NF1 gene, this control is disrupted, leading to the symptoms and complications associated with NF1 (Gutmann et al., 2017). With an estimated worldwide prevalence of 1:2,500 to 1:3,000 (Williams et al., 2009), NF1 presents a spectrum of clinical manifestations that are both diverse and unpredictable, varying even within families. Between 40 and 75 percent of these genetic variations arise de novo, which means that the genetic changes that cause NF1 happen spontaneously and are not inherited from either parent (Evans et al., 2010; van Minkelen et al., 2014).

Clinically, NF1 is characterized by a range of symptoms including pigmentary lesions such as café-au-lait macules, skinfold freckling, and Lisch nodules, as well as dermal neurofibromas, skeletal abnormalities, and various tumors of the peripheral nerves and brain (Gutmann et al., 2017). Diagnosis typically follows the criteria established by the National Institutes of Health (NIH) in 1987, requiring the presence of at least two specific manifestations, such as:

- Six or more café-au-lait macules (>0.5 cm in children or >1.5 cm in adults)
- Two or more cutaneous or subcutaneous neurofibromas or one plexiform neurofibroma
- Freckling in the axillary or inguinal regions
- Optic pathway glioma
- Two or more Lisch nodules
- Bony dysplasia
- A first-degree relative with NF1

Genetic testing is employed when the clinical diagnosis is inconclusive, during prenatal testing, or to differentiate NF1 from other conditions. To assess the severity of NF1, specialists often use the Riccardi scale, which classifies the severity as minimal, mild, moderate, or severe based on the impact of specific complications (Riccardi, 1992).

The symptoms of NF1 can vary widely. Most patients have café-au-lait spots and small skin tumors called cutaneous neurofibromas, which mainly affect appearance. However, larger tumors under the skin, known as subcutaneous and plexiform neurofibromas, occur in 20-44% of people with NF1 and can lead to serious nerve problems and potentially become cancerous. These plexiform neurofibromas are particularly tedious, causing pain and other issues (Ferner & Evans, 2011; Mautner et al., 2008). People with NF1 have a 7-13% chance of developing a type of cancer called malignant peripheral nerve sheath tumours (MPNST) (Ferner, 2007). These tumours, along with heart-related problems, can shorten life expectancy by 8-15 years (Stewart et al., 2018).

NF1 can also lead to a variety of other health issues. About 45% of people with NF1 have larger than average heads (macrocephaly), and 30% are shorter than average. Scoliosis, or curvature of the spine, occurs in 10% of cases, while 15% develop tumours on the optic pathway, called optic pathway gliomas. Epilepsy affects 6-7% of people with NF1, early puberty occurs in 2-3%, and 2-3% develop brain tumours known as cerebral gliomas (Ferner, 2007). Severe fatigue is also common (Rosenberg et al., 2024), as are vitamin D deficiency, heart problems,





high blood pressure, and seizures (Gutmann et al., 2017). Additionally, NF1 can cause various brain abnormalities, including unexplained bright spots, increased brain size, changes in the volume of the corpus callosum, brain asymmetries, and differences in white and grey matter volume (Rauen, 2013; Payne et al., 2010). Although these brain abnormalities are frequent, they do not always correlate clearly with cognitive issues. However, some fMRI studies suggest that problems with executive functions might be linked to dysfunction in certain frontal brain areas. Difficulties with visual-spatial skills might be related to issues in the visual cortex, especially within a specific pathway called the magnocellular pathway (Baudou et al., 2020). Connectivity studies have also shown reduced connectivity between front and back brain regions and issues with deactivating the default mode network during cognitive tasks (Baudou et al., 2020).

The symptoms of NF1 can change as a person gets older (Jett & Friedman, 2010). Although there is no cure for NF1, treatment aims to manage the widespread symptoms. As a result, some people with NF1 may have only minor issues, while others may experience serious problems (Potter & Mendoza, 2019; Rosenberg et al., 2021).

NF1 is not just about physical symptoms; it also brings many cognitive and behavioral challenges. Most research has focused on children, with less known about adults. Generally, people with NF1 have slightly lower IQs, ranging from the high 80s to low 90s (Descheemaeker et al., 2013; Hyman et al., 2005; Lehtonen et al., 2015). Children with NF1 often struggle with visual-spatial skills, learning, attention, working memory, planning, and other executive functions (Lehtonen et al., 2015; Schwetye & Gutmann, 2014; Torres-Nupan et al., 2017; Beaussort et al., 2018). These difficulties continue into adulthood, though problems with executive function are less severe (Descheemaeker et al., 2013). Children with NF1 also tend to have lower academic achievements and motor skills (Lehtonen et al., 2015; Torres Nupan et al., 2017). Speech and language development issues are common in children and have been noted in adults as well (Alivuotila et al., 2010; Rietman et al., 2018).

Social cognition issues, like trouble recognizing facial emotions, face perception, and understanding others' thoughts and feelings, are frequently reported in children with NF1 (Huijbregts et al., 2015; Lewis et al., 2016; Payne et al., 2016). These difficulties contribute to a higher occurrence of a diagnosis of autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD) in these children (Chisholm et al., 2018; McNeill et al., 2019; Payne et al., 2020). Similar social cognitive deficits have been found in adults, particularly in recognizing emotions and understanding others' mental states (Pride et al., 2013; 2014).

Behavioral problems, such as emotional distress and social difficulties, are common in people with NF1 of all ages. These issues, along with the high burden of the disease and reduced quality of life, significantly affect individuals with NF1 and their families (Domon-Archambault et al., 2018; Doser et al., 2020; Foji et al., 2021). Adults with NF1 often report higher levels of anxiety and depression than the general population, even more so than patients with life-threatening diseases like cancer (Doser et al., 2020; Wang et al., 2012). The mood and anxiety issues in NF1 are linked to the unpredictable course of the disorder, the risk of developing cancer, uncertainty about the future, concerns about passing NF1 to children, social stigma, reduced social activity, deficits in prosocial behavior, lower self-esteem (Bottessi et al., 2019; Copley-Merriman et al., 2021; Foii et al., 2021), and loneliness (Rietman et al., 2018).

In children and adolescents, there are common concerns about social skills, school performance, psychological disorders, and developmental issues (ASD, ADHD), which also impacts their parents' well-being (Cipoletta et al., 2018; Domon-Archambault et al., 2018; Rietman et al., 2018).

## Dialectical Behavior Therapy (DBT)

The early experiences of emotional suffering and the inadequacy of existing treatments for individuals with severe emotional dysregulation and suicidality became the foundation for Marsha Linehan to create a therapeutic approach that would both validate patients' experiences and help them change behaviors, a synthesis that would eventually become Dialectical Behavior Therapy.

One of Linehan's early contributions came in 1987 with the publication of her article, "Cognitive-behavioral treatment of chronically parasuicidal borderline patients,". In this seminal paper, Linehan detailed her initial attempts to apply cognitive behavioral therapy (CBT) to individuals with chronic suicidality and borderline personality disorder. She noted that the focus on behavioral change in traditional CBT often exacerbated emotional distress in these patients, who felt invalidated by the lack of attention to their intense emotional experiences.

In response to these challenges, Linehan introduced the concept of dialectics, the idea that two seemingly opposing truths can coexist. This insight marked a significant shift in her therapeutic approach, as she recognized the necessity of balancing the need for behavioral change with an emphasis on validating and accepting the patient's emotional state. This synthesis of opposites, embodied in the dialectical principle, became the cornerstone of DBT. It highlighted the dual





emphasis on both change and acceptance, which was important for addressing the complex emotional and behavioral patterns seen in patients with severe emotion dysregulation.

DBT is a behavioral treatment program, not so much an individual psychotherapy approach. It is a combination of individual sessions, group training, telephone coaching, a therapist consultation team, and the opportunity to help change the client's social or family situation as well (for example, with family interventions). DBT is an evidence-based treatment program specifically designed for addressing emotion regulation problems. DBT is initially created for people dealing with emotional dysregulation and high-risk impulsive or chronic suicidal behavior (Linehan et al., 1991; Linehan, 2002, 2016; Linehan & Sayrs, 2020; Van den Bosch et al., 2002). Over thirty years of clinical studies have shown that DBT has evolved into a flexible intervention that can be adapted to meet the needs of diverse populations and settings (Sinnaeve et al., 2018; Swales, 2018; Van Leeuwen et al., 2021).

A significant aspect of the adaptability of DBT is found in Marsha Linehan's biosocial theory. This theory redefines psychological maladaptive behaviors, including impulsive high risk behavior such as suicidal behavior and non-suicidal self-injury (NSSI), as coping mechanisms for emotion dysregulation (Linehan, 2002; 2016). Linehan posits that persistent dysregulation arises from the transaction between an emotionally vulnerable individual and an invalidating environment. Vulnerability factors include heightened impulsivity, a predisposition to negative emotions, and an elevated baseline tension (Linehan, 2016). An invalidating environment lacks sufficient understanding or attention to an individual's thoughts, emotions, and/or behaviors, which hinders the development of the ability to take one's own emotions seriously and impairs the acquisition of skills to adequately manage one's inner emotional experiences. This environment includes primary caregivers, family members, peers, educators, partners, colleagues, mental health professionals, and can also involve traumatic situations such as emotional, physical, and sexual abuse (Fruzzetti et al., 2005; Linehan, 2002). While the specific biological and social factors and their interplay are unique to each individual, the common outcome is a lack of trust in one's experiences and insufficient emotion regulation skills to build a fulfilling life.

It makes sense that biological vulnerabilities make it more complex for the environment to match the emotional and/or interpersonal needs of someone. Individuals with a structurally heightened baseline arousal are more sensitive to external stimuli. They tend to notice stress-inducing events more quickly. Additionally, their emotional response to these situations is more intense compared to those

without such dysregulation and the accompanying biological vulnerability. And then, when their emotional tension increases, it takes significantly longer for it to subside compared to individuals without structural emotional dysregulation. Because their stress level is already high, even small events can quickly add more tension and lead to strong emotional distress. This escalation can be fuelled by a series of seemingly minor events, thoughts, or emotions, ultimately resulting in a peak where the emotional tension becomes intolerable. At this point, impulsive behavior like suicidal behavior, non-suicidal self-injury (NSSI) or other life threatening behavior may be viewed as the only immediate means to reduce the emotional tension back to baseline levels.

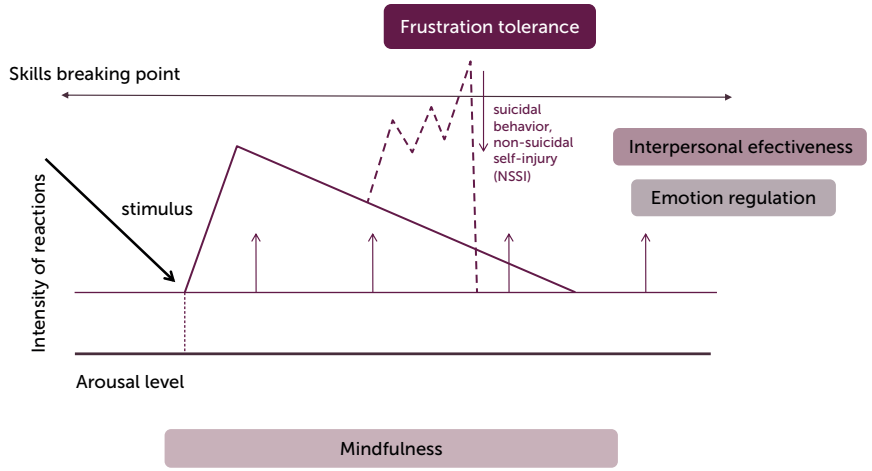



**Figure 1.** Application of the Biosocial Model in DBT, Adapted with permission from Wies van den Bosch, unpublished figure.

The primary focus of DBT is to first stop the life-threatening behaviors. This corresponds to the peak in the graph above, where such behaviors are perceived as a direct escape from the intense emotional distress that is experienced. Frustration tolerance and mindfulness skills are essential to reduce emotional arousal and create psychological distance from the overwhelming distress, allowing for a clearer assessment of the situation. Subsequently, it is crucial to improve the individual's circumstances and optimize their interactions with both their environment and themselves.
Furthermore, recognizing and addressing emotions, as well as reducing emotional vulnerability, are essential to prevent emotional intensity from escalating excessively and to develop timely awareness of emotional build-up.





DBT focusses on **mindfulness** as a foundational skill. The importance of mindfulness is understood as the ability to remain in the present moment, thereby interrupting the connection with a preceding impulse. Through mindfulness, individuals learn to observe reality as it is, connect with their internal experiences, reflect on their values and goals, and gain control over their attention in a compassionate and non-judgmental manner. These mindfulness skills are essential for the successful application of all subsequent DBT modules.

The **emotion regulation** module teaches individuals how to observe, describe, and modify their emotions if necessary, using techniques such as opposite action. It also focuses on building resilience and developing strategies to manage intense emotions. By enhancing emotional awareness and naming emotions early in their escalation, individuals can take timely action to prevent emotional overload. If emotional tension has already escalated to the point where clear thinking becomes difficult and self-injury feels like the only option, Linehan refers to this as a "skills breakdown point." At this stage, it is crucial to intervene directly at the physiological level using **distress tolerance** skills, which are designed to lower emotional tension without requiring conscious thought. These skills focus on surviving crises, accepting reality, and managing addictive behaviors.

Finally, Linehan emphasized the importance of effective communication in emotion regulation, leading to the development of the **interpersonal effectiveness** module. This module teaches individuals to clarify their personal goals, assert themselves in pursuit of those goals, build and end relationships, validate others, and find a middle path in interactions. By improving interpersonal effectiveness, individuals can better navigate emotional challenges in their relationships, contributing to greater emotional stability overall.

These four modules are trained in a structured skills training. The skills training sessions follow a consistent structure: welcome, mindfulness practice, brief announcements, homework review, introduction of a new skill with theoretical background, discussion and practice, orientation to the next homework assignment, and session closure. Typically, a standard DBT skills training involves 24 sessions delivered over a six-month period, with weekly meetings. In addition to the skills training, the generalization of learned skills to everyday life is important. This is facilitated through individual therapy. During individual sessions, the therapist reviews the events of the previous week based on a diary card kept by the client. A detailed chain analysis is conducted to understand and validate the underlying factors of problematic behaviors, followed by a solution analysis to explore how the client can respond differently in the future, using newly acquired skills,

contingency management, and exposure techniques. Furthermore, DBT offers 24/7 telephone coaching which is intended to prevent problem behaviors, support skill generalization, or repair ruptures in the therapeutic relationship. Equally important is the DBT consultation team, which acts as a support system for therapists. This team provides weekly consultations, helping therapists enhance their clinical skills and share responsibility for all program participants. Finally, DBT interventions may extend into the client's environment, including engaging their support network or offering network training to ensure that the client's progress is supported beyond therapy. The before mentioned modalities (skills training, individual therapy, consultation team) are mostly performed face to face. however, ensuring accessible healthcare services is critical due to geographical barriers and limited expertise in specialized care.

The DBT skills manual is written for both DBT clients and therapists, providing a comprehensive guide to the skills and concepts central to Dialectical Behavior Therapy. It includes detailed explanations of the various skills, as well as descriptions of the different DBT programs that can be followed (Linehan, 2002, 2016). The book chapter of de Ruiter, Sinnaeve and Witteveen (2023) gives an account of the DBT skills training and exposit that DBT is not a rigid, protocol-bound treatment limited to a specific psychiatric diagnosis but a flexible framework that helps practitioners address the changing and complex needs of individuals seeking help. The curriculum and pace can be tailored to the needs of the target group and the context in which the training is organized (Delaquis et al., 2022; Linehan, 2016; van den Bosch et al., 2014; Sinnaeve et al., 2018). For individuals with severe and persistent emotional dysregulation, this cycle is typically repeated twice. Recent studies indicate that even a six-month skills training can lead to significant improvement (McMain et al., 2022).

## Blended DBT

Blended treatment approaches, combining face-to-face interventions with digital technologies, provide accessible pathways to care that transcend geographical boundaries. By integrating telehealth platforms and online consultations, blended treatments enable remote access to expert care, reducing the need for extensive travel. This not only enhances accessibility for individuals in remote areas but also disseminates expertise beyond geographical boundaries. Furthermore, blended treatments might improve patient experience by reducing travel burdens and accommodating diverse needs.





## DBT as a transdiagnostic treatment program

Emotion regulation is considered a transdiagnostic and dimensional construct, playing a key role in a wide range of mental illnesses (Caspi & Moffit, 2018; Mulay et al., 2019; Ruggero et al., 2019; Sloan et al., 2017). The DBT skills training, initially focused on suicidal patients with borderline personality disorder (BPD), has evolved into a transdiagnostic intervention (Linehan, 2016; Swales, 2018). Although DBT was primarily designed for suicidal and self-harming behavior, with a possible comorbidity such as substance abuse, post-traumatic stress disorder and eating disorders, it remains effective when tailored for other clinical populations, age groups, or treatment settings (Delaquis et al., 2022; Linehan, 2016).

The DBT skills training, a core component of DBT, has emerged as a versatile intervention designed to teach individuals skills for managing emotions, coping with distress, and improving interpersonal relationships. Increasingly, it is being implemented as a standalone treatment across diverse clinical settings and populations, with a growing body of evidence supporting its utility. Recent studies have explored its applications in various contexts, yielding promising but nuanced findings.

In individuals with substance use disorders (SUD), a systematic review of nine studies found DBT skills training to be generally feasible and acceptable, with preliminary evidence for reducing substance use and improving emotion regulation (Warner & Murphy, 2022). A mixed-methods study from Flynn and colleagues (2019) reported significant decreases in binge drinking and drug use within 64 participants, along with improved mindfulness skills and emotion regulation, while a trial of Maffei and colleagues (2018) demonstrated a 73.2% abstinence rate after a three-month DBT program with 244 alcohol-dependent patients. Improved emotion regulation mediated these outcomes. Similarly, a secondary analysis involving 186 participants found reductions in addictive behaviors linked to better emotion regulation and decreased experiential avoidance (Cavicchioli et al., 2020).

For individuals with borderline personality disorder (BPD), the DBT skills training has been effective in community mental health settings. A study with 100 adults reported reductions in emotion dysregulation and dysfunctional coping after a 24-week intervention (Kells et al., 2020). In Malaysia, a 14-week DBT group for BPD patients showed decreases in depressive symptoms, stress, and emotion regulation difficulties, alongside increased self-compassion and well-being (Keng et al., 2021).

Among adolescents and their families, a feasibility study on the DBT skills training for suicidal behaviors found similar completion and dropout rates compared to standard DBT for Adolescents, supporting its viability without individual therapy (White et al., 2023).

Outside of psychiatric contexts, DBT skills training has been explored in chronic physical health conditions. In 40 individuals with multiple sclerosis (MS) and their support system, a randomized controlled trial showed reductions in anxiety and depression compared to peer support, though these effects were not sustained at follow-up, highlighting the need for strategies to maintain long-term benefits (Hughes et al., 2022).

The transdiagnostic nature of DBT makes it particularly suitable for conditions where emotional dysregulation is a central feature. Given the established efficacy of DBT in populations with complex comorbidities, it is logical to explore its application in individuals with NF1. The dual emphasis of DBT on acceptance and change aligns well with the needs of this population, who must learn to navigate the lifelong challenges of an incurable condition alongside its associated psychosocial burdens. This alignment highlights the potential of DBT as a therapeutic model for addressing the unique needs of individuals with NF1.





## Aim and Outline

The aim of this thesis is to deepen the understanding of the psychological challenges faced by adults with Neurofibromatosis Type I (NF1) and to explore the potential of the Dialectical Behavior Therapy (DBT) skills training as a targeted intervention to address these challenges. By examining the cognitive, behavioral, and emotional profiles of individuals with NF1, this research seeks to identify their unique psychological needs and search for a contextually sensitive treatment framework. The focus is on addressing core issues such as emotion regulation difficulties and systemic factors that influence psychological well-being, while also evaluating the feasibility and effectiveness of DBT as a therapeutic approach.

In **Chapter 2**, A detailed description is provided of the neuropsychological phenotype of adults with NF1, based on comprehensive clinical examinations of cognition, emotion, and behavior across multiple functions. Despite increased knowledge over the past decade, no comprehensive description of cognition and behavior in a large cohort of adults with NF1 currently exists. This precise understanding is essential for identifying the psychological treatment needs of this population.

In **Chapter 3**, Two individuals with NF1 are presented for whom by means of specialized clinical neuropsychological assessment, participation in a Dialectical Behavior Therapy (DBT) skills training was indicated. These case studies describe how individuals develop skills during treatment and how their significant others perceive the impact of the treatment.

**Chapter 4** focuses on the importance of involving significant others in treatment. We identify contextual factors that might enhance treatment effects by altering perceived criticism through a treatment targeting emotion regulation problems.

During the investigation of a possible psychological treatment (Dialectical Behavior Therapy) for people with NF1, covid-19 occurred. **Chapter 5** focuses on the best available research evidence regarding the availability, efficacy, and clinical utility of telepsychology in Dialectical Behavior Therapy (DBT). The emergence of the Covid-19 pandemic necessitated a shift to online treatment modalities. This review aims to stimulate empirically supported decisions about the use of telepsychology during and after the pandemic, and to anticipate the evolving digital needs of patients and DBT therapists, thus guiding both into a new digital age.

**Chapter 6** investigates the suitability of Dialectical Behavior Therapy skills training as a treatment option for addressing underlying emotion regulation mechanisms in people with NF1. It assesses the feasibility and acceptability of a DBT skills group training and explores initial patient experiences. The primary aim is to determine if individuals can complete the DBT skills training from start to finish and remain present throughout. Secondary aims include exploring changes in emotional experiences from the first DBT session to three months post-intervention.

The thesis concludes in **Chapter 7** with a summary and discussion, integrating the results of the individual studies in terms of theoretical and clinical considerations, as well as formulating implications and recommendations for future follow-up research on treatment.

# 2

## Cognition and Behavior in Adults with Neurofibromatosis Type 1

Bos-Roubos, A.*, Van Leeuwen, H.*, Wingbermühle, E., Van Den Bosch, L., Ossewaarde, L., Taal, W., de Graaff, L., & Egger, J. (2024). Cognition and behavior in adults with neurofibromatosis type 1. *Frontiers in Neurology*, *15*, 1476472. https://doi.org/10.3389/fneur.2024.1476472

*These authors contributed equally to this work and share first authorship

## Abstract

Neurofibromatosis Type 1 (NF1) is a congenital neurocutaneous disorder. As NF1 is incurable and presents with a wide range of physical and mental symptoms, knowledge of neurocognitive and behavioral functioning can be an important aid in understanding their functional impact, and developing treatment options. To date, studies in children with NF1 have shown dysfunction in several domains, but much less is known about cognition and behavior in adults with NF1. The present study describes the neuropsychological phenotype of adults with NF1 based on comprehensive clinical examination of cognition and behavior across multiple functions. In this study, 62 adults with NF1 (mean age 38.2 years; *SD* 13.4) underwent individual clinical neuropsychological assessment at the Center of Excellence for Neuropsychiatry as part of regular care. Scores on all individual measures were standardized into z-scores based on the corresponding normative group data. The proportions of mean z-scores in the NF1 study group were calculated according to cut-off points (±1 to ±1.5 SD; > ±1.5 SD) and compared to the expected proportions in the normal population distribution. Cognition and behavior was tested against population means constructed by bootstrapping. Performance on the cognitive measures oral reading speed, visuospatial copying, visuospatial immediate recall, visual learning/imprinting, and visual memory immediate recall in the NF1 group were lower than normative means. The behavioral measures indicated higher levels of dysfunction, including psychopathology. The proportions of the NF1 study group with lower cognitive performance and higher levels of behavioral dysfunction were larger than in the normal population distributions. In addition, domain-level results revealed that intelligence, attention/speed, memory, and social cognition reflect cognitive dysfunction. Moreover, levels of emotion perception problems, experienced executive dysfunction, internalizing psychopathology (e.g., anxiety, depression), and severe fatigue were significantly higher compared to the simulated population sample. The mean level of emotion regulation (coping strategies) did not differ significantly from the population. Identified cognitive and behavioral dysfunction in multiple domains indicates high vulnerability in adults with NF1 and underscores the importance of individualized neuropsychological assessment and treatment. Further research on the relationships between cognition and behavior (including fatigue) in NF1 is warranted.



## Introduction

Neurofibromatosis type 1 (NF1) is an autosomal dominant neurocutaneous disorder caused by variations in the *NF1* gene on chromosome 17q11.2 (Gutmann et al., 2017). This gene encodes Neurofibromin, which functions as a tumor suppressor by inhibiting activity of the *Ras/Mitogen-activated protein kinase (MAPK) pathway.* The estimated worldwide prevalence is 1:2,500-3,000 (Ferner, 2007; Williams et al., 2009). Between 40 and 75 percent of the variations arise *de novo* (Evans et al., 2010; van Minkelen et al., 2014).

The diagnosis of NF1 is often made clinically, in accordance with the international consensus on the diagnostic criteria (Legius et al., 2021; National Institutes of Health Consensus Development Conference Statement, 1988). Genetic testing may be needed if the clinical diagnosis is inconclusive, in the context of prenatal testing or in order to distinguish from other conditions.

NF1 is highly variable in its physical expression, and may manifest with pigmentary lesions (café-au-lait macules, skinfold freckling, and Lisch nodules), dermal neurofibromas, skeletal abnormalities (e.g., shortness of stature, scoliosis), peripheral nerve tumors (spinal neurofibromas, plexiform neurofibromas, and malignant peripheral nerve sheath tumors), and brain tumors (optic pathway gliomas and other pilocytic astrocytomas) (Gutmann et al., 2017). Specific structural and functional brain abnormalities include focal areas of signal intensity (FASI), increased brain volume, altered corpus callosum volume, cerebral asymmetries, and differences in white and gray matter volume (Gutmann et al., 2017; Payne et al., 2010; Rauen, 2013). Other co-occurring physical symptoms may include hydrocephalus, seizures, headaches, cardiac abnormalities, cardiovascular disease, hypertension, vitamin D deficiency, and fatigue (Jett & Friedman, 2010; Rosenberg et al., 2024). The progressive physical symptom profile of individuals with NF1 can change throughout their lives (Jett & Friedman, 2010). As NF1 cannot be cured, medical treatment remains symptomatic. Due to the variety of signs and symptoms, some individuals with NF1 have little disease burden or are even unaware of their condition, while others suffer severely (Potter & Mendoza, 2019; Rosenberg et al., 2024).

People with NF1 may experience several neurocognitive and behavioral difficulties. Neurocognitive research to date has focused primarily on the pediatric NF1 population, with limited attention paid to adults. Nevertheless, a slightly lower than average full-scale Intelligence Quotient (IQ) has consistently been found across all ages, ranging from higher 80s to lower 90s (Descheemaeker et al., 2013; Hyman et al., 2005; Lehtonen et al., 2013; Lehtonen et al., 2015).

In addition, deficits in visuospatial processing, visuospatial learning, attention, (nonverbal) working memory, planning, and other executive functioning have been widely reported in children (Beaussart et al., 2018; Lehtonen et al., 2013; Lehtonen et al., 2015; Schwetye & Gutmann, 2014; Torres-Nupan et al., 2017). Lower visuospatial abilities and visuospatial memory have also been found in adults (Descheemaeker et al., 2013). Dysexecutive functioning (e.g., poor cognitive flexibility) has been reported in adults (Descheemaeker et al., 2013), but to a much lesser extent. One study has shown deficits in the executive control and no deficits in attentional function in adults (Wang et al., 2019). Lower academic achievement and poorer motor function have also been found in children (Lehtonen et al., 2015; Torres Nupan et al., 2017). In addition, deficits in language and speech development are common in children, and have been reported to some extent in adults (Alivuotila et al., 2010; Rietman et al., 2018). In the pediatric population, deficits in social cognition and social functioning are commonly reported, in line with the increased prevalence of autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD) (Chisholm et al., 2018; McNeill et al., 2019; Payne et al., 2020). In children, there is some evidence for deficits in facial emotion recognition, face perception (Huijbregts et al., 2015; Lewis et al., 2016), and theory-of-mind (Payne et al., 2016). Studies of social-cognitive functioning in adults indicate potential deficits in emotion recognition and mentalizing (Pride et al., 2013; 2014).

Despite the prevalence of brain abnormalities in NF1, brain imaging studies could not establish strong and consistent correlations between this morphology and cognitive functioning in NF1. Some functional magnetic resonance imaging (fMRI) research suggests possible associations between executive function deficits and dysfunction in the right inferior frontal areas and the middle frontal areas. In addition, visuospatial deficits may be related to dysfunction in the visual cortex, particularly in the magnocellular pathway involved in low spatial frequency and high temporal frequency processing (Baudou et al., 2020). Furthermore, some connectivity studies have shown a reduction in anterior-posterior “long-range” connectivity and a deficit in the deactivation of the default mode network (DMN) during cognitive tasks (Baudou et al., 2020).

Behavioral difficulties in NF1 include emotional distress and impaired social functioning. These challenges, along with high disease burden and reduced quality of life, affect individuals with NF1 of all ages, as well as their relatives (Domon-Archambault et al., 2018; Doser et al., 2020; Foji et al., 2021). Significantly more symptoms of anxiety and depression have been reported in adults with NF1 compared to the population norm, even more than in patient groups with life-





threatening diseases such as cancer (Doser et al., 2020; Wang et al., 2012). Mood and anxiety problems in individuals with NF1 have been linked to the unpredictable course of NF1, the predisposition to develop malignancies, concerns about passing on NF1 to offspring, stigma, reduced social activity, deficits in prosocial behavior, lower self-esteem (Botessi et al., 2020; Copley-Merriman et al., 2021; Foii et al., 2021), and loneliness (Rietman et al., 2018). In children and adolescents with NF1, concerns about sociability, school performance, psychological disorders, developmental (ASD, ADHD), emotional, and behavioral problems have been described; which also affect the well-being of their parents (Cipoletta et al., 2018; Domon-Archambault et al., 2018; Rietman et al., 2018a).

To summarize from the above, NF1 is not curable and is associated with a wide range of symptoms, both physical and mental. Previous studies in children and adolescents with NF1 have shown a variable neurocognitive phenotype with dysfunction in several domains, including attention, visuospatial processing, executive function, language, social cognition, developmental and behavioral problems. However, much less detailed information is known about cognition and behavior in adults with NF1 in one overview and study group.

To our knowledge, no detailed description of cognition and behavior in a large cohort of adults with NF1 exists to date. Knowledge of neurocognitive and behavioral functioning can be an important aid in analyzing symptom patterns, understanding their functional impact, and developing targeted treatment options. This study aims to describe the neuropsychological phenotype of adults with NF1 based on comprehensive, clinical examination of cognition and behavior across multiple functions.

Because behavior and psychopathology can be viewed as overlapping concepts, in this study we define behavior as the broader concept, referring to both functional and dysfunctional behavior. Psychopathology is defined as specific dysfunctional aspects of behavior in terms of mental and/or psychiatric illness.

In terms of expectations, based both on the literature as presented and on clinical practice, we hypothesize, first, that performance on individual cognitive tests in the NF1 group will be lower than the normative means of the instruments administered. Second, we expect higher levels of (experienced) behavioral problems compared to the normative means. Third, we expect the proportions in the NF1 group reflecting lower levels of cognitive performance and higher levels of behavioral problems compared to normal population distributions. Fourth, as in children, we expect the adult NF1 group to have cognitive function deficits and

behavioral dysfunction across all cognitive and behavioral domains. In particular, we expect psychopathology (e.g., anxiety, depression) and high levels of fatigue.

## Materials and Methods

### Participants

This study included 62 Dutch-speaking adults with NF1 with a mean age of 38.2 years (*SD* = 13.4; range 18-62). **Table 1** shows sex and education of the participants. Data were collected between September 2017 and October 2022, as part of regular care. All participants underwent a comprehensive neuropsychological assessment at the Centre of Excellence for Neuropsychiatry, Vincent van Gogh Institute for Psychiatry, The Netherlands. Prior to their assessments, all participants or their legal representatives gave voluntary written informed consent for their data to be used anonymously for research purposes. No participants were excluded.

**Table 1.** Sex and education participants NF1.

| | *n* | % |
|---|---|---|
| | 62 | |
| **Sex** | | |
| Female | 36 | 58.1 |
| Male | 26 | 41.9 |
| **Education**[a] | | |
| 1 | 3 | 4.8 |
| 2 | 0 | - |
| 3 | 9 | 14.5 |
| 4 | 18 | 29.0 |
| 5 | 20 | 32.3 |
| 6 | 10 | 16.1 |
| 7 | 2 | 3.2 |

*Note.* [a] For level of education, we used a seven-point scale ranging from 1 *(primary school not completed)* to 7 *(academic degree)* according to the Dutch educational system (Verhage, 1964). This scale is comparable to the International Standard Classification of Education (UNESCO, 2011).

In accordance with the diagnostic standards (Legius et al., 2021) the diagnosis of NF1 was clinically established in all participants; and, if medically indicated, also reconfirmed by DNA analysis. Of the participants 97% were referred to the Centre of Excellence for Neuropsychiatry after visiting the outpatient Center for Adults with Rare Genetic Syndromes, or the outpatient Clinic for Neurology/Neuro-oncology,





both at the Erasmus University Medical Center, Rotterdam. The others (3%) were referred by their specialist at the Radboud University Medical Center, Nijmegen. All patients were referred because of symptoms of fatigue or psychosocial complaints without a (direct) physical explanation. None of the patients had known brain malformations according to the medical referral information.

The study was conducted according to the principles of the Declaration of Helsinki and was approved by the Vincent van Gogh Institutional Review Board (CWOP-EM/hl/2019.00.02/RvB/19.01818).

### Materials

A comprehensive set of widely accepted standardized (neuro)psychological tests and questionnaires was administered to assess cognitive and behavioral abilities, distinguished by (11) domains, according to the classification of Lezak et al. (2012): intelligence, attention/speed, executive function, verbal fluency, memory and learning, and social cognition, as well as levels of emotion perception problems, emotion regulation, subjective dysexecutive functioning, general psychopathology in terms of internalizing and externalizing psychopathology, and fatigue complaints. The Supplement (Supplementary Figure 1 and Supplementary Table 1) provides an overview of the domains, the instruments administered, and corresponding references to normative data (appropriate for age, sex, and/or educational or intelligence level, if available).

### Data collection

All of the cognitive and behavioral domains (including psychopathology) were assessed for each patient. The battery of tests used was variable on an individual level and tailored to the clinical questions of both the referring clinician and the patient. All tests were administered by trained psychologists, typically over a two-day period. There was no evidence of reduced mental effort during test administration for any of the participants. The following performance validity tests were administered: the Dutch test for short-term memory, i.e., Amsterdamse Korte Termijn Geheugen Test (AKTG; Schmand, De Sterke & Lindeboom, 1998), the Test of Memory Malingering (TOMM; Tombaugh, 1996), or the Visual Association Test – Extended (VAT-E; Meyer & De Jonghe, 2019). See also Supplementary Table 1, including the applied cut-off scores. Regarding symptom validity, we systematically analyzed all the embedded validity indicators of the Minnesota Multiphasic Personality Inventory (MMPI) following the procedure as described in Ben-Porath & Tellegen (2008), and there was no indication for violation of the validity.

Informed consent forms were kept confidential and stored separately from test data in a locked cabinet at the Centre of Excellence for Neuropsychiatry. Transcripts linking a subject to a subject number were stored separately. Raw test data were obtained anonymously from a database at the Centre of Excellence for Neuropsychiatry. The data files at the Centre are accessible only to the researchers involved in the data collection and analysis of this study (AB-R, HVL, WO).

## Statistical analysis

The data were analyzed at three levels: (1) at the level of outcome measures of the instruments administered; (2) at the level of proportions relative to the normal population distribution; (3) at the level of cognitive and behavioral domains to determine the presence or absence of dysfunction, using bootstrapping.

### *Outcome measures*

Participants' scores on each individual test and questionnaire were calculated based on the normative data for each instrument (Dutch Advanced Neuropsychological Diagnostics Infrastructure (ANDI) or data as presented in the respective test manuals). Raw scores on all tests and questionnaires were standardized to z-scores, using the normative group data (mean and standard deviation). Mean standardized scores for the NF1 study group were reported on each measure. For the Wechsler test battery, a two-tailed paired t-test of the means of the four indices was performed.

### *Proportions*

In addition, chosen cut-off points and corresponding classifications were 0 to ±1 SD ('average'), ±1 to ±1.5 SD ('below average' or 'above average'), and > ±1.5 SD ('low' or 'high'). Both wide and narrow cut-off point ranges were chosen to detect not only robust but also subtle differences in the NF1 study group compared to normative groups, and to avoid under- and over-estimation of their functioning. The percentages of the NF1 study group scores were then calculated according to the selected cut-off points. We calculated the proportions of the NF1 study group scores relative to the proportions of the theoretical normal distribution of the population.

### *Domains*

The convention in clinical neuropsychological practice is that a judgment about whether a function is impaired or not can only be made if it has been assessed with at least two tests (Bouma et al., 2012). Therefore, in order to test our fourth hypothesis, we defined and compiled domains (Strauss et al. 2006; Tate, 2010). 27 Outcome measures from 13 cognitive tests administered were grouped into 6





different cognitive domains. Similarly, 22 outcome measures from 11 questionnaires administered were grouped into 5 different behavioral domains.

To test whether the NF1 study group differed from the general population, the observed z-scores of each participant were averaged per domain, resulting in mean domain z-scores per participant ($N$ = 62), which were subsequently bootstrapped. Bootstrapping is an iterative replacement sampling procedure in which the observed scores are used to create proxy samples ("simulated population scores"). To construct the proxy sample (per domain), an observed mean domain score (from the NF1 study group subject) was randomly selected and copied. This process was repeated 1000 times. The proxy samples have the same values but a slightly different composition than the NF1 study sample, as the observed scores are replaced in the study group pool to be selected again for simulation. A histogram of the means of a proxy sample approximates a standard distribution of means. The mean of this standard distribution is approximately equivalent to the mean of the observed study sample. However, the objective was not to determine whether the observed sample of participants with NF1 had the same mean as the "simulated population." Rather, the aim was to determine whether the observed sample of participants with NF1 had the same mean as the general population of healthy controls. Since all scores of each instrument administered were previously compared to the corresponding normative controls and rescaled to z-scores (with a mean of 0 and a standard deviation of 1), we now assumed that the current domain scores also had a mean of 0. Therefore, the question was whether the observed mean was approximately equal to 0. This was tested by centering the standard distribution of the means of the created proxy samples around 0 and point estimating if our observed mean was still part of the 95% of proxy means around 0. If the observed mean falls outside this 95% interval, it can be assumed with sufficient certainty that the observed sample is not the same as a sample of healthy controls and that the domain score reflects either a strength or a weakness compared to healthy controls. The probability that the observed mean was part of the simulated population distribution with a mean of 0 was determined for each domain. Statistical analyses were performed in R Statistical Software (v.4.3.1; R Core Team 2023).

## Results

**Table 2** presents all results in terms of the mean z-scores of the NF1 study group and the proportions of z-scores according to the cut-off points compared to the expected proportions based on normal population distributions. All scores are also shown graphically in **Figure 1**. The results are described in detail below, according to the table layout.

As to intelligence, the mean Full-Scale Intelligence Quotient (FSIQ) on the Wechsler Adult Intelligence Scale IV-NL (WAIS-IV-NL) was 86.82 (*SD* = 16.67), ranging from 48 to 119 (median FSIQ 88.00). The level of the mean observed FSIQ was approximately one standard deviation lower than the mean FSIQ of the normative population (*M* = 100; *SD* = 15). The means of the four indices of the WAIS-IV-NL of the NF1 group were: Verbal Comprehension Index (VBI) 91.91 (*SD* = 15.93), Perceptual Reasoning Index (PRI) 87.74 (*SD* = 17.23), Working Memory Index (WMI) 85.19 (*SD* = 19.00), and Processing Speed Index (PSI) 87.95 (*SD* = 17.55). The mean VBI was significantly higher than the mean WMI ($t$ = 2.42, $df$ = 56, $p$ = .019), and higher than the mean PRI ($t$ = 3.67, $df$ = 56, $p$ < .001). In addition, all mean WAIS-IV-NL z-scores of the NF1 study population were overrepresented at the lower end of the normal distribution. They were also underrepresented at the upper end of the normal distribution.

With respect to attention/speed, 6 of the 7 measures composing this domain, had mean z-scores below zero, but remained within the average range (-1.0 to 0). The mean z-score of one measure, related to oral reading speed (Stroop test trial 1), was below average. In addition, almost half of the z-scores on this measure in the entire NF1 sample (46.8%) were low ($z \leq$ -1.5). Moreover, the observed attention/speed scores in the NF1 sample were overrepresented at the lower end of the normal distribution compared to the normative group. There was also an under-representation of observed scores at the higher end of the normal distribution.

In the executive functioning domain, the mean z-scores of 2 (Stroop interference, Trail-Making-Test interference) of the 4 measures were above zero. These two measures relate to interference sensitivity. The proportion of these observed z-scores was over-represented at the upper end of the normal distribution in the normative group. This means that the performance of the study group was remarkably good at this point. The results of the other 2 (Rey-Complex Figure Test Copy; Rey-CFT Copy, and Behavioural Assessment of the Dysexecutive Syndrome; BADS) of the 4 executive function measures were negative. These two measures relate to several cognitive functions, such as planning and organization, fine motor





coordination, and visuospatial perception. In particular, the mean z-score of the test condition related to fine-motor coordination and visuospatial perception (Rey-CFT Copy) reflected below average performance. Almost three-quarters (71.9%) of the z-scores of the entire NF1 sample on this test condition were in the below average and low range ($z$ < -1). In addition, the observed scores on the Rey-CFT Copy were overrepresented at the lower end of the normal distribution relative to the normative group. Underrepresentation of scores at the upper end of the normal distribution was also observed for both the Rey-CFT Copy and the BADS.

Regarding verbal fluency, the mean z-scores of the 3 function measures in this domain were all below zero, but still in the average range (between -1 and 0). However, the observed scores were again overrepresented at the lower end of the normal distribution compared to the normative group. Also, the observed scores were predominantly underrepresented at the upper end of the normal distribution.

Within the learning and memory domain, the mean z-scores of the 6 measures were all below zero, ranging from -0.58 to -2.08. In particular, the mean z-score of the visual learning test (Location Learning Test, Learning; LLT Learning) was low ($z$ = -2.08). On this visual learning test, 85% of the total NF1 sample had a z-score below -1.5, indicating low performance in the majority of the NF1 sample. Regarding the (3) memory measures in the immediate recall condition (requiring preceding learning and imprinting), the mean z-scores of the two visual conditions (LLT Immediate Recall, CFT-Rey Immediate Recall) were below average. In contrast, the mean z-score of the auditory condition (Auditory Verbal Learning Test, Immediate Recall; AVLT Immediate Recall) was in the average range, although below zero ($z$ = -0.58). The observed z-scores on all (3) Immediate Recall memory tests were overrepresented in both the below-average and the low ranges. More specifically, a total of 60% of the NF1 sample had z-scores lower than -1 on the LLT Immediate Recall. A total of 51.8% of the NF1 sample had z-scores lower than -1 on the CFT-Rey Immediate Recall. The immediate recall performance of the NF1 sample was also underrepresented at the upper end of the normal distribution, particularly on the two visual immediate recall tests, both in the above average and in the high range. With respect to the Delayed Recall condition of memory (indicating the ability to retain and recall stored information) of which the performance is related to the amount of imprinted information, mean z-scores on these two tests were both below zero, but still within the average range. On the visual delayed recall condition (CFT-Rey Delayed Recall) (mean $z$ = -0.93), a total of 54.17% of the NF1 sample had z-scores lower than -1. On the auditory delayed recall condition (AVLT Delayed Recall), a total of 35.71% of the NF1 sample had

**Table 2.** Results NF1 study group.

**Table 2a.** Cognition.

| Classification of z-scores | *N* | Mean z (SD) | Min. z | Max. z | Median z | % z ≤ -1.5 | % z > -1.5 to -1.0 | % z ≥ -1.0 to 0 | % z ≥ 0 to 1.0 | % z ≥ 1 to 1.5 | % z ≥ 1.5 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Low | Below average | Average | Average | Above average | High |
| Expected % based on normal distribution in population | | | | | | 7% | 9% | 34% | 34% | 9% | 7% |
| **Measure** | | | | | | | | | | | |
| **Intelligence** | | | | | | | | | | | |
| WAIS-IV FSIQ | 57 | -0.88 (1.11) | -3.47 | 1.27 | -0.80 | 29.83 | 10.53 | 36.84 | 19.30 | 3.51 | 0.00 |
| WAIS-IV VCI | 57 | -0.54 (1.06) | -2.67 | 1.93 | -0.47 | 21.05 | 12.28 | 31.58 | 29.83 | 1.75 | 3.51 |
| WAIS-IV PRI | 57 | -0.82 (1.15) | -3.27 | 1.93 | -0.73 | 33.33 | 7.02 | 35.09 | 21.05 | 1.75 | 1.75 |
| WAIS-IV WMI | 57 | -0.99 (1.27) | -3.47 | 1.47 | -0.73 | 35.09 | 7.02 | 36.84 | 14.04 | 7.02 | 0.00 |
| WAIS-IV PSI | 58 | -0.80 (1.17) | -3.67 | 1.13 | -0.73 | 18.97 | 18.97 | 34.48 | 24.14 | 3.45 | 0.00 |
| **Attention/speed** | | | | | | | | | | | |
| Stroop trials 1 | 47 | -1.26 (1.52) | -4.44 | 1.5 | -1.00 | 46.81 | 2.13 | 31.92 | 14.89 | 2.13 | 2.13 |
| Stroop trials 2 | 47 | -0.76 (1.52) | -3.96 | 2.16 | -0.66 | 27.66 | 14.89 | 23.40 | 23.40 | 4.26 | 6.38 |
| Stroop trials 3 | 46 | -0.37 (1.05) | -2.64 | 1.96 | -0.57 | 13.04 | 6.52 | 45.65 | 23.91 | 6.52 | 4.35 |
| TMT A | 44 | -0.35 (1.19) | -3.77 | 2.29 | -0.29 | 11.36 | 15.91 | 38.64 | 20.46 | 6.82 | 6.82 |
| TMT B | 37 | -0.50 (1.17) | -2.84 | 1.75 | -0.25 | 24.32 | 10.81 | 21.62 | 35.14 | 2.70 | 5.41 |
| D2 Tn | 38 | -0.44 (4.05) | -2.00 | 2.00 | -0.40 | 15.79 | 13.16 | 39.47 | 26.32 | 0.00 | 5.26 |
| D2 Tn-F | 38 | -0.53 (4.12) | -2.00 | 1.60 | -0.50 | 15.79 | 15.79 | 39.47 | 23.68 | 2.63 | 2.63 |
| **Executive function** | | | | | | | | | | | |
| Rey-CFT Copy | 32 | -1.15 (0.78) | -2.06 | 1.32 | -1.31 | 37.50 | 34.38 | 18.75 | 6.25 | 3.13 | 0.00 |
| BADS battery total | 26 | -0.36 (0.95) | -2.29 | 1.22 | -0.32 | 11.54 | 7.69 | 42.31 | 30.77 | 7.69 | 0.00 |
| Stroop interference | 46 | 3.23 (0.84) | 0.07 | 3.87 | 3.38 | 0.00 | 0.00 | 0.00 | 6.52 | 0.00 | 93.48 |
| TMT interference | 37 | 0.41 (1.71) | -4.89 | 2.57 | 0.40 | 10.81 | 5.41 | 8.11 | 43.24 | 0.00 | 32.43 |
| **Verbal fluency** | | | | | | | | | | | |
| Letters | 44 | -0.67 (1.36) | -3.92 | 1.68 | -0.52 | 22.73 | 15.91 | 29.55 | 20.46 | 9.09 | 2.27 |
| Animals | 52 | -0.64 (1.16) | -3.60 | 2.00 | -0.66 | 15.39 | 21.15 | 38.46 | 17.31 | 3.85 | 3.85 |
| Occupations | 52 | -0.45 (1.30) | -3.84 | 2.49 | -0.34 | 21.15 | 15.39 | 23.08 | 30.77 | 1.92 | 7.69 |
| **Learning and memory** | | | | | | | | | | | |
| **Immediate recall** | | | | | | | | | | | |
| Rey-ALVT – IR | 56 | -0.58 (1.13) | -2.83 | 2.75 | -0.69 | 19.64 | 16.07 | 30.36 | 28.57 | 1.79 | 3.57 |
| LLT – IR | 40 | -1.12 (1.07) | -3.04 | 1.92 | -1.16 | 37.50 | 22.50 | 27.50 | 7.50 | 2.50 | 2.50 |
| Rey-CFT – IR | 27 | -1.00 (0.93) | -2.78 | 0.86 | -1.18 | 40.74 | 11.11 | 33.33 | 14.82 | 0.00 | 0.00 |

**Table 2a.** Continued.

| Classification of z-scores | *N* | Mean z (SD) | Min. z | Max. z | Median z | % z ≤ -1.5 | % z > -1.5 to -1.0 | % z ≥ -1.0 to 0 | % z ≥ 0 to 1.0 | % z ≥ 1 to 1.5 | % z ≥ 1.5 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Low | Below average | Average | Average | Above average | High |
| Expected % based on normal distribution in population | | | | | | 7% | 9% | 34% | 34% | 9% | 7% |
| **Delayed recall** | | | | | | | | | | | |
| Rey-ALVT – DR | 56 | -0.59 (1.19) | -3.62 | 1.39 | -0.43 | 19.64 | 16.07 | 25.00 | 30.36 | 8.93 | 0.00 |
| LLT Learning | 40 | -2.08 (1.35) | -3.35 | 1.40 | -2.48 | 85.00 | 0.00 | 0.00 | 7.50 | 7.50 | 0.00 |
| Rey-CFT DR | 24 | -0.93 (0.80) | -2.58 | 0.80 | -1.07 | 29.17 | 25.00 | 33.33 | 12.50 | 0.00 | 0.00 |
| **Social cognition** | | | | | | | | | | | |
| ERT | 52 | -0.80 (0.95) | -2.71 | 1.62 | -0.83 | 17.31 | 25.00 | 42.31 | 11.54 | 1.92 | 1.92 |
| ToM-test-R | 26 | -0.35 (1.25) | -2.10 | 2.10 | 0.38 | 26.92 | 3.85 | 15.39 | 46.15 | 3.85 | 3.85 |

*Note. Abbreviations: WAIS-IV-NL: Wechsler Adult Intelligence Scale-IV Dutch translation; FSIQ: Full Scale Intelligence Quotient; VCI: Verbal Comprehension Index; PRI: Perceptual Reasoning Index; WMI: Working Memory Index; PSI: Processing Speed Index; TMT: Trail Making Test; D2: D2 Test of Attention; Tn: Total number; F: Faults; Rey-CFT; Rey Complex Figure Test; BADS: Behavioural Assessment of the Dysexecutive Syndrome; Stroop: Stroop Color and Word Test; Rey-ALVT: Rey-Auditory Verbal Learning Test; IR: Immediate Recall; LLT: Location Learning Test; DR: Delayed Recall; ERT: Emotion Recognition Task; ToM-test-R: Theory of Mind test Revised.*

**Table 2b.** Behavior.

| Classification of z-scores | N | Mean z (SD) | Min. z | Max. z | Median z | % z ≤ -1.5 | % z > -1.5 to -1.0 | % z ≥ -1.0 to 0 | % z ≥ 0 to 1.0 | % z ≥ 1 to 1.5 | % z ≥ 1.5 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Low | Below average | Average | Average | Above average | High |
| Expected % based on normal distribution in population | | | | | | 7% | 9% | 34% | 34% | 9% | 7% |
| **Measure** | | | | | | | | | | | |
| **Emotion perception problems** | | | | | | | | | | | |
| TAS-20 self | 44 | 1.13 (1.26) | -1.22 | 3.66 | 1.00 | 0.00 | 6.82 | 11.36 | 31.82 | 6.82 | 43.18 |
| TAS-20 proxy | 44 | 1.58 (1.67) | -1.64 | 4.92 | 1.81 | 2.27 | 2.27 | 15.91 | 20.46 | 2.27 | 56.82 |
| **Emotion regulation** | | | | | | | | | | | |
| FEEL-E adaptive | 33 | -0.60 (3.70) | -3.00 | 3.00 | -0.60 | 21.21 | 15.15 | 33.33 | 24.24 | 0.00 | 6.06 |
| FEEL-A maladaptive | 33 | 0.26 (3.56) | -3.00 | 3.00 | 0.30 | 15.15 | 3.03 | 21.21 | 36.36 | 6.06 | 18.18 |
| CISS Task-oriented | 17 | -0.92 (0.81) | -2.00 | 0.46 | -1.22 | 35.29 | 23.53 | 17.65 | 23.53 | 0.00 | 0.00 |
| CISS Emotion-oriented | 17 | 0.52 (0.72) | -0.58 | 2.40 | 0.36 | 0.00 | 0.00 | 29.41 | 47.06 | 17.65 | 5.88 |
| CISS Avoidance-oriented | 17 | 0.19 (1.23) | -2.61 | 2.29 | 0.18 | 5.88 | 5.88 | 29.41 | 41.18 | 0.00 | 17.65 |
| **Subjective dysexecutive functioning** | | | | | | | | | | | |
| DEX total self | 13 | 1.26 (1.75) | -0.97 | 5.13 | 1.08 | 0.00 | 0.00 | 23.08 | 23.08 | 23.08 | 30.77 |
| BRIEF-A total self | 44 | 1.37 (3.91) | -0.60 | 4.10 | 1.20 | 0.00 | 0.00 | 11.36 | 31.82 | 15.91 | 40.91 |

**Table 2b.** Continued.

| Classification of z-scores | N | Mean z (SD) | Min. z | Max. z | Median z | % z ≤ -1.5<br>Low | % z > -1.5 to -1.0<br>Below average | % z ≥ -1.0 to 0<br>Average | % z ≥ 0 to 1.0<br>Average | % z ≥ 1 to 1.5<br>Above average | % z ≥ 1.5<br>High |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Expected % based on normal distribution in population | | | | | | 7% | 9% | 34% | 34% | 9% | 7% |
| **Psychopathology** | | | | | | | | | | | |
| SCL-90 Psychoneuroticism | 13 | 1.58 (1.57) | 0.00 | 5.59 | 1.12 | 0.00 | 0.00 | 0.00 | 30.77 | 30.77 | 30.77 |
| BDI-II total | 26 | 2.98 (2.47) | -1.00 | 7.97 | 2.29 | 0.00 | 3.85 | 7.69 | 11.54 | 7.69 | 69.23 |
| BDI-II affective | 26 | 2.45 (2.46) | -0.60 | 9.47 | 2.09 | 0.00 | 0.00 | 7.69 | 19.23 | 19.23 | 53.85 |
| BDI-II cognitive | 26 | 2.63 (2.64) | -0.60 | 8.06 | 2.22 | 0.00 | 0.00 | 19.23 | 15.39 | 3.85 | 61.54 |
| BDI-II somatic | 26 | 2.52 (2.07) | -1.12 | 6.53 | 2.14 | 0.00 | 3.85 | 7.69 | 11.54 | 15.39 | 61.54 |
| ABCL total self-report | 11 | 0.54 (4.02) | -0.60 | 2.70 | 0.30 | 0.00 | 0.00 | 27.27 | 54.55 | 0.00 | 18.18 |
| ABCL internalizing self-report | 11 | 0.96 (3.95) | -0.20 | 3.00 | 0.80 | 0.00 | 0.00 | 9.09 | 72.73 | 0.00 | 18.18 |
| ABCL externalizing self-report | 11 | -0.07 (4.24) | -1.20 | 1.10 | -0.30 | 0.00 | 9.09 | 54.55 | 18.18 | 18.18 | 0.00 |
| MMPI-2-RF internalizing (rEID) | 29 | 1.63 (3.81) | -0.90 | 3.90 | 1.50 | 0.00 | 0.00 | 3.57 | 35.71 | 17.86 | 42.86 |
| MMPI-2-RF externalizing (rBXD) | 29 | 0.09 (3.92) | -1.60 | 2.40 | -0.10 | 10.71 | 10.71 | 32.14 | 28.57 | 3.57 | 14.29 |
| MMPI-2-RF thought disorders (rTHD) | 29 | 0.86 (3.57) | -1.20 | 4.80 | 0.70 | 0.00 | 7.14 | 14.29 | 57.14 | 0.00 | 21.43 |
| **Fatigue** | | | | | | | | | | | |
| FSS total | 34 | 3.99 (1.81) | -0.14 | 6.71 | 4.49 | 0.00 | 0.00 | 2.94 | 2.94 | 5.88 | 88.24 |
| CIS-20-R total | 47 | 2.63 (0.81) | 1.14 | 4.52 | 2.40 | 0.00 | 0.00 | 0.00 | 0.00 | 2.13 | 97.87 |

*Note. Abbreviations: TAS-20: Toronto Alexithymia Scale-20; FEEL-E: Fragebogen zur Erhebung der Emotionsregulation bei Erwachsenen (Questionnaire for the survey of emotion regulation in adults); CISS: Coping Inventory for Stressful Situations; TO: Task Oriented; EO: Emotion Oriented; AO: Avoidance Oriented; DEX: Dysexecutive Questionnaire; BRIEF-A: Behaviour Rating Inventory of Executive Function- Adult Version; SCL-90: Symptom Checklist-90-R; BDI-II: Beck Depression Inventory-II; ABCL: Adult Behaviour Checklist; MMPI-2-RF: Minnesota Multiphasic Personality Inventory-2 Restructured Form; FSS: Fatigue Severity Scale; CIS-20-R: Checklist Individual Strength-20-Revised.*

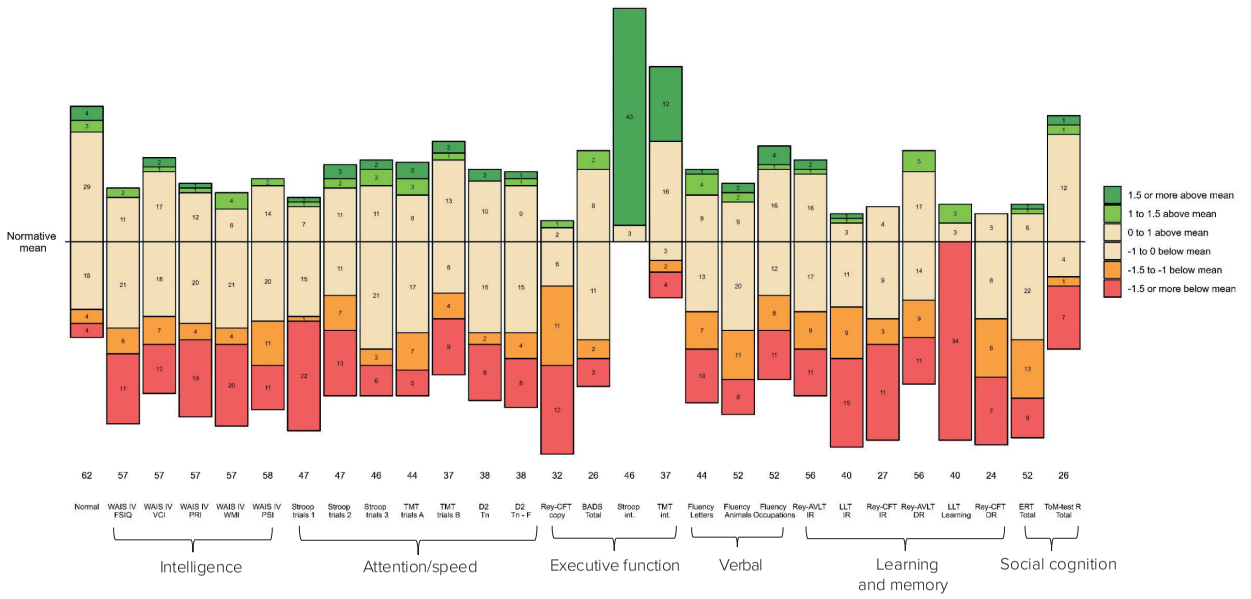



**Figure 1a.** Numbers of participants and z-scores on cognitive measurements compared to normative group.

*Note.* The horizontal line represents the normative mean based on the statistics described in the test manuals of the measures (normative controls). The numbers in the bars represent the number of participants in the corresponding range. The numbers below the bars reflect the size of the NF1 sample on that measure. Performance is visualized based on the selected cut-off points (and classifications): 0 to ±1 (average); ±1 to ±1.5 SD (below or above average); >±1.5 (= low or high). Orange and red colors indicate unfavorable compared to the normative mean. Green and dark green colors indicate favorable compared to normative mean.
*Abbreviations:* WAIS-IV-NL: Wechsler Adult Intelligence Scale-IV-NL; FSIQ: Full Scale Intelligence Quotient; VCI: Verbal Comprehension Index; PRI: Perceptual Reasoning Index; WMI: Working Memory Index; PSI: Processing Speed Index; TMT: Trail Making Test; D2: D2 Test of Attention; Tn: Total number; F: Faults; Rey CFT; Rey Complex Figure Test; BADS: Behavioural Assessment of the Dysexecutive Syndrome; Stroop: Stroop Color and Word Test; int.: interference; ALVT: Auditory Verbal Learning Task; IR: Immediate Recall; DR: Delayed Recall; LLT: Location Learning Test; ERT: Emotion Recognition Task; ToM-R: Theory of Mind Test Revised.

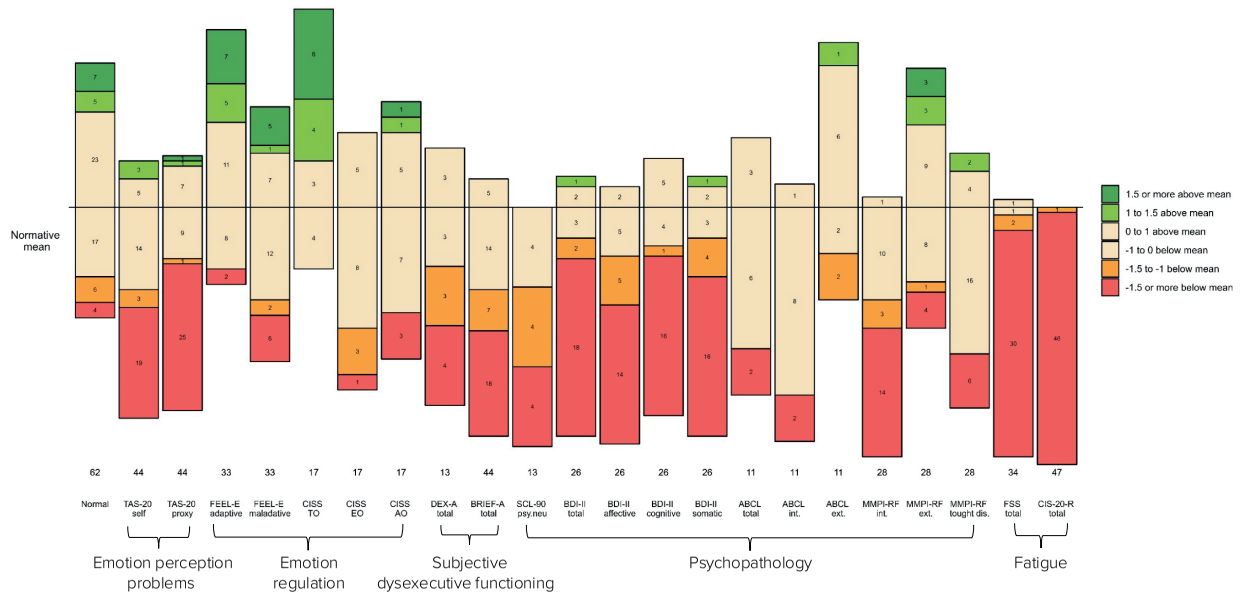



**Figure 1b.** Numbers of participants and z-scores on behavioral measurements compared to normative group.

*Note.* The horizontal line represents the normative mean based on the statistics described in the test manuals of the measures (normative controls). The numbers in the bars represent the number of participants in the corresponding range. The numbers below the bars reflect the size of the NF1 sample on that measure. Performance is visualized based on the selected cut-off points (and classifications): 0 to ±1 (average); ±1 to ±1.5 SD (below or above average); >±1.5 (= low or high). Orange and red colors indicate unfavorable compared to the normative mean. Green and dark green colors indicate favorable compared to normative mean.
*Abbreviations*: TAS-20: Toronto Alexithymia Scale-20; FEEL-E: Fragebogen zur Erhebung der Emotionsregulation bei Erwachsenen (Questionnaire for the survey of emotion regulation in adults); CISS: Coping Inventory for Stressful Situations; TC: Task oriented Coping; EC: Emotion oriented Coping; VC: Avoidance oriented coping; DEX: Dysexecutive Questionnaire; BRIEF-A: Behaviour Rating Inventory of Executive Function-Adult Version; SCL-90: Symptom Checklist-90-R; psy.neu: psychoneurotic; BDI-II: Beck Depression Inventory-II; ABCL: Adult Behaviour Checklist; int: internalizing; ext: externalizing; MMPI 2-RF: Minnesota Multiphasic Personality Inventory-2 Restructured Form; thought dis: thought disorders; FSS: Fatigue Severity Scale; CIS-20-R: Checklist Individual Strength-20-Revised.

z-scores lower than -1. In both the visual and auditory delayed recall conditions, the performance of the NF1 sample was overrepresented at the lower end of the normal distribution. In addition, the delayed recall performance of the NF1 sample was also underrepresented at the upper end of the normal distribution.

In terms of social cognition, the mean z-scores of the two measures were both below zero, but remained in the average range. However, the observed scores in the NF1 sample on both measures were overrepresented at the lower end. On the Emotion Recognition Task (ERT), 42.31% of the NF1 sample scored below average and low, compared to 12% of the normative group. Similarly, on the Theory of Mind Test, 30.77% of the NF1 sample scored low and 3.85% scored below average; most of them (26.92%) low, compared to 7% of the normative group. Again, the observed scores of the NF1 sample were underrepresented at the upper end of the normal distribution.

Regarding the perception of one's own emotions, the mean level of experienced problems (as inventoried by the Toronto Alexithymia Scale-20 self; TAS-20 self) was above average ($z$ = 1.13). Half of the entire NF1 sample (50%) had above average and high levels of problems compared to 16% in the normative group. Underrepresentation was also observed at the lower end of the normal distribution.

With respect to the regulation of emotions (the ability to deal with emotions as inventoried by the *Fragebogen zur Erhebung der Emotionsregulation bei Erwachsenen;* FEEL-E and the Coping Inventory for Stressful Situations; CISS), the two mean z-scores for adequate coping ranged from -1 to 0, while the mean z-scores for inadequate coping ranged from 0 to 1. Although all mean z-scores of emotion regulation in the NF1 sample were in the average ranges, inadequate emotion regulation was overrepresented at above average and at high levels and adequate emotion regulation was underrepresented at below average and at low levels in the NF1 group compared to the normative group.

In terms of subjective dysexecutive functioning, the mean z-scores indicated that the NF1 group experienced executive problems at above average to high levels. More than half of the NF1 sample reported dysexecutive functioning at above average to high levels (53.85% on the questionnaire Dysexecutive functioning (DEX) and 56.82 % on the Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A), compared to 16% of the normative group), with most at the high level.





Regarding psychopathology, the mean z-scores on the measures of internalizing pathology Complaints List (SCL-90), Beck Depression Inventory-Second Edition (BDI-II Total), MMPI-2-RF Emotional-Internalizing Dysfunction (MMPI-2-RF rEID) were all high ($z$ > 1.5). Specifically, on the SCL-90 30.77% of the observed Z-scores in the total NF1 sample were above 1.5; on the BDI-II Total 69.23%; and on the MMPI-2-RF Internalizing behaviors 42.86% of (all compared to 7% in the normative group). Mean z-scores for externalizing pathology (MMPI-2-RF rBXD) and thought disorders (MMPI-2-RF rTHD) were above zero, but at average levels. However, 14.29% of the entire NF1 sample reported symptoms of externalizing pathology at a high level, and 21.43% of them symptoms of thought disorders at a high level, compared to 7% of the normative group.

With respect to fatigue, the mean z-scores of the two measures (Fatigue Severity Scale; FSS and Checklist Individual Strength; CIS-20-R) ranged from 2.6 to 4. Almost the entire NF1 sample (88.2% and 97.9%, respectively) reported fatigue at high levels.

For cognition and behavior tested at the domain-level using bootstrapping, the observed mean z-scores of the NF1 study sample per domain did not fall all within the values of the population distribution per domain. As shown in **Figure 2**, the blue boxes in this normal distributions represent 95% of the population scores with a mean of 0. The bars reflect the observed NF1 study group mean z-score per domain. With at least 95% confidence, the probability that the NF1 sample means of all the other domains were part of the population distribution with a mean around 0 is less than < 5% ($p$ < .05). The mean z-scores of the NF1 study group differed significantly from the population on all cognitive and behavioral domains, except for the domain emotion regulation. Specifically, the mean domain performances on intelligence (FSIQ), attention/speed, verbal fluency, learning and memory (immediate and delayed), and social cognition were lower. Consequently, these domains may be considered to reflect cognitive weaknesses in the NF1 study group. In addition, the mean performance was higher in the executive function domain, driven by lower interference sensitivity, which may therefore be considered a relative strength. The mean observed z-scores of the domains emotion perception problems, subjective dysexecutive functioning, psychopathology, and fatigue were higher, indicating the presence of behavioral weaknesses in the NF1 sample. In contrast, the domain mean emotion regulation did not differ from the population mean.

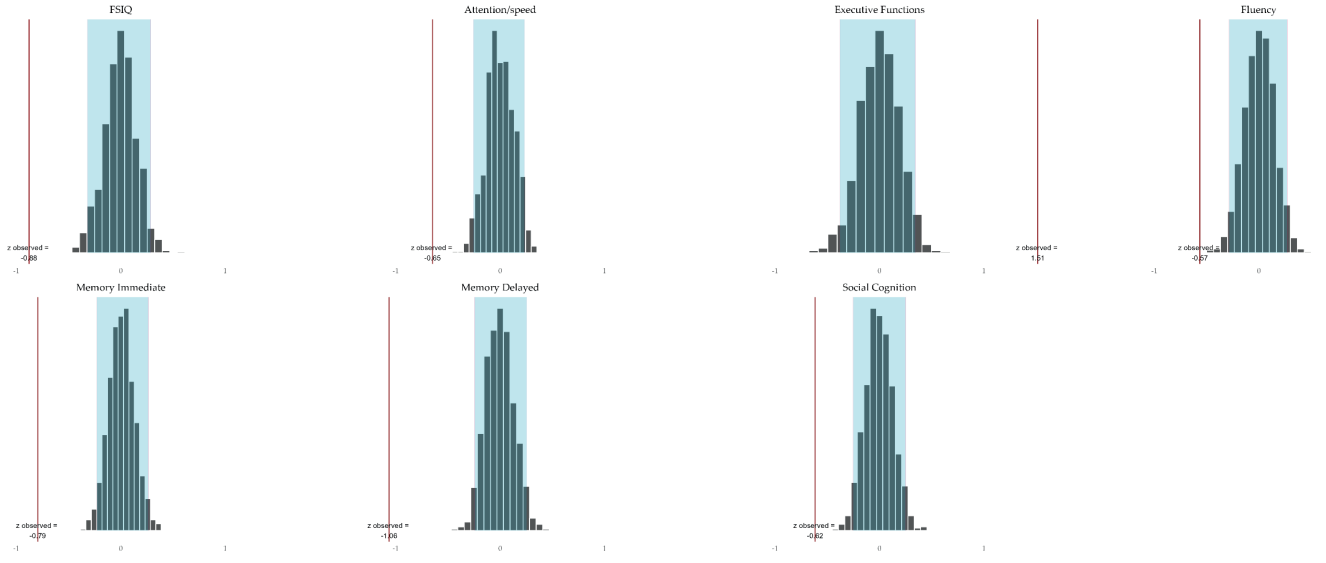



**Figure 2.** Bootstrapped simulated population domain distributions and mean observed domain z-scores of the NF1 study sample tested on 95% confidence level.

**Figure 2a Cognition.** The red bar to the left of the distribution indicates that the observed mean of the NF1 group was significantly lower than 0. A red bar to the right of the distribution indicates that the mean performance of the NF1 group was significantly higher than 0.

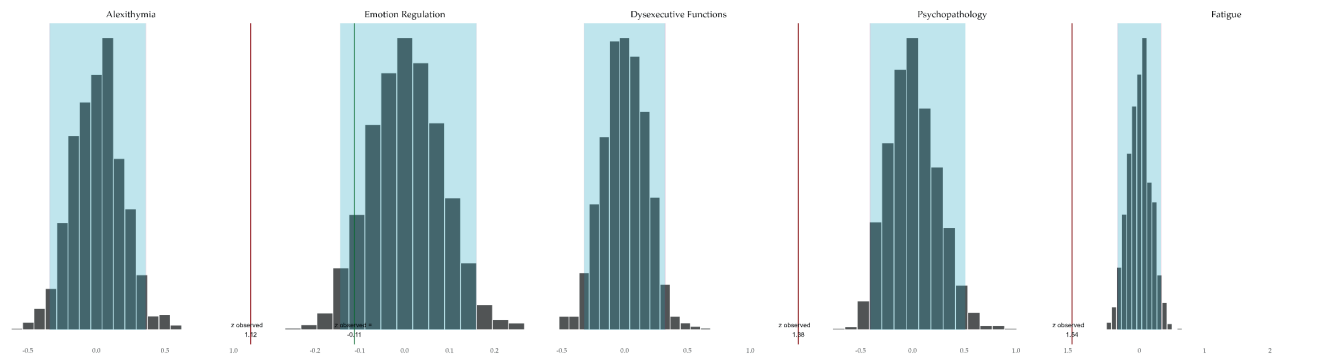



**Figure 2b. Behavior.** The red bar to the right of a distribution indicates that the observed mean of the NF1 group was significant higher than 0. The green bar in the distribution indicates that observed mean of the NF1 group was not significant different from 0.

## Discussion

This study describes the neuropsychological phenotype of adults with NF1.

In terms of cognitive functioning, performances of the NF1 group were lower than the normative means on the following measures: oral reading speed, visuospatial perception, visual learning, and visual memory (immediate recall). Behavioral functioning measures revealed higher levels of emotion perception problems, subjective dysexecutive functioning, internalizing psychopathology (anxiety, depression), and fatigue in the NF1 group. These findings are consistent with our first and second hypotheses.

In addition, the proportions of the NF1 group with lower levels of cognitive functioning and higher levels of behavioral problems were larger than in the normal population distributions. This is consistent with our third hypothesis. These larger proportions were true for almost all cognitive outcome measures (except the 2 measures of interference sensitivity), and for all behavioral outcome measures.

Fourth, the NF1 group appeared to have lower levels of intelligence, and cognitive dysfunctions in attention/speed, verbal fluency, learning and memory, and social cognition. Executive functioning (in terms of planning, organization, and inhibitory control) was not impaired in our sample, contrary to our expectations. In terms of behavior, the mean levels of emotion perception problems, experienced dysexecutive functioning, psychopathology, and fatigue were significantly higher in the NF1 group than in the general population. In contrast, the mean level of emotion regulation in the NF1 group did not differ from the population.

With respect to the domain of executive functioning, low interference sensitivity as we found in the adult NF1 group is consistent with the previous finding of low interference sensitivity in children with NF1 (Beaussart et al., 2018). However, interference sensitivity was measured by a task that depends in part on information processing speed. Therefore, the finding that the NF1 group was not affected by interference sensitivity, may be, at least in part, explained by their slower information processing speed (38% of the NF1 group had PSI scores below the cut-off point of 1 SD). As a consequence, low sensitivity to interference in both children and adults may seem to reflect a strength in executive functioning, but is primarily driven by slowness, which drives up the domain score. Therefore, the effect of interference sensitivity is difficult to be measured properly.





Memory function measures show that delayed recall performance was less impaired than immediate recall performance. Again referring to the slower speed, this finding may reflect that people in the NF1 study group need more time to process and consolidate information in both learning and memory conditions. Moreover, both learning and memory in the NF1 sample were likely affected by deficiencies in visual information processing, considering the fact that results on primary measures of visuospatial information processing were low. Impairments in visuospatial processing and visuospatial memory have been consistently found in both children and adults with NF1 (Descheemaeker et al., 2013). Congruent to this, performances on visual memory tasks were, in our sample, worse than those on auditory/verbal learning and memory tasks. This finding is also consistent with previous studies showing nonverbal learning problems in adults (Shilyansky et al., 2010) and (nonverbal) (working) memory problems in children (Torres Nupan et al., 2017).

Regarding the verbal fluency deficits in our study group, the literature is conflicting. Reduced verbal fluency has been found in adults with NF1 (Descheemaeker et al., 2013; Lorch et al., 1999; Pavol et al., 2006), while the opposite has also been reported (Schütze et al., 2018). Findings on verbal fluency in children with NF1 are also inconsistent. Speech/expressive language problems have previously been reported in (very young) children with NF1 (Rietman et al., 2017; Thompson et al., 2009), while other studies have found no significant differences in children with NF1 compared to a comparison group (Brei et al., 2014; Hyman et al., 2005). It should be noted that the results may vary to some extent due to the different definitions of “verbal fluency”, the different test instruments used, and/or the cut-off points chosen.

Impairments in social cognition as demonstrated in our study group are consistent with previous findings in children, who typically show difficulty with facial emotion recognition and theory of mind (Huijbregts et al., 2015; Lewis et al., 2016; Payne et al., 2016).

In terms of behavior, the fact that emotion regulation in our NF1 group did not differ significantly from the population mean is contrary to our expectations, as emotional problems have been found in previous studies with children with NF1 (Cipoletta et al., 2018; Domon-Archambault et al., 2018; Rietman et al., 2018a). This finding is also inconsistent with our clinical observations of difficulty with emotion regulation in individuals with NF1. A closer look at the different measures within the emotion regulation domain revealed that the proportions of maladaptive coping were higher and the proportions of adaptive coping in the NF1 group were lower than

those in the normative group. In particular, the study sample showed little active and task-oriented coping, with a concomitant tendency to experience emotions without being able to differentiate them properly. Thus, although significance levels were not reached for emotion regulation at the domain level, coping of these NF1 patients can be characterized as predominantly passive in nature, possibly contributing to the high levels of psychopathology that were found in this study sample.

While the recognition and expression of one's own emotions have yet to be studied in adults with NF1, alexithymia has been demonstrated repeatedly in other RASopathies, such as Noonan syndrome (Roelofs et al., 2015; Wingbermühle et al., 2022). Consequently, our results for the NF1 group regarding this trait are rather novel, yet not necessarily surprising.

Finally, levels of internalizing psychopathology (e.g., anxiety, depression) and fatigue appear to be remarkably high in the study sample, even when considering that medically unexplained fatigue was the reason for referral. Anxiety and depression in adults with NF1 have been consistently reported in the literature (Doser et al., 2020; Wang et al., 2012). High levels of experienced fatigue are consistent with the literature in children and adolescents (Vasallo et al., 2020). High levels of fatigue in adults with NF1 were not related to their somatic conditions, suggesting that fatigue may be induced and/or maintained by cognitive and psychological rather than physical conditions (Rosenberg et al., 2024).

Overall, cognitive and behavioral performance of the NF1 study group on many measures differed from the normative population. The proportions of the NF1 study group with lower than expected cognitive test scores and higher levels of behavioral problems were higher than in the normal population distribution. In addition, domain testing revealed impaired intelligence, attention/speed, memory, and social cognition. In addition, the levels of emotion perception problems, experienced executive dysfunction, internalizing psychopathology (e.g., anxiety, depression), and fatigue can be considered as significantly high compared to the expected/simulated population group mean. There were no behavioral strengths according to our measurements.

A notable limitation of the study is that all participants in the study were referred to the outpatient clinic of the Centre of Excellence for Neuropsychiatry by their medical specialist because of fatigue or other psychosocial symptoms that could not be sufficiently explained somatically. This may have entailed a selection bias. It is possible that the average level of cognitive performance may be lower and





the average level of behavioral dysfunction may be higher in this sample than in individuals with NF1 who experience lower levels of fatigue or psychosocial symptoms. Related to this, it is also relevant to note that only patients with NF1 with somatic disorders in the course of their genetic condition were referred, and there was no control group of patients without such somatic burdens or complaints. This weakness may limit the generalizability of the results to the NF1 population in general. However, is it is challenging to avoid a certain degree of selection bias in patient studies in the field of rare genetic disorders. Moreover, several characteristics of the NF1 sample (such as the FSIQ as established) are consistent with those of other studies and clinical observations. In addition, the study group was large for its kind, and demographic variables like gender and education level were equally distributed in this NF1 sample.

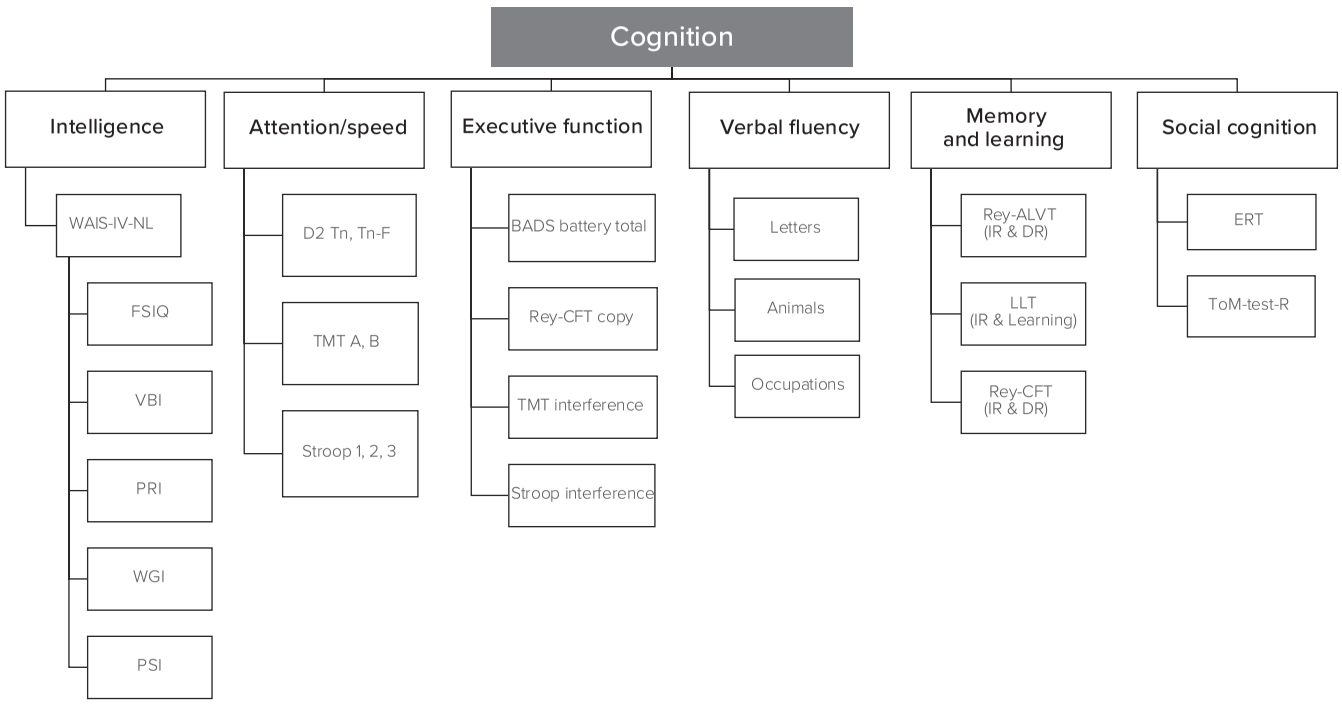
As a strength of this study can be mentioned that the neuropsychological profile of this NF1 group was comprehensively and extensively mapped, and appropriate analytical methods were deliberately selected. The selected cut-off points revealed both subtle (1 to 1.5 SD) and robust (more than 1.5 SD) deficits. Phenotyping the NF1 study sample at different levels of analysis revealed that the proportion of unfavorable performance is overrepresented and the proportion of favorable results is underrepresented. This could have been easily overlooked if only the mean scores of the instruments administered had been inspected. The distributions in the NF1 group as described indicate multiple cognitive and behavioral vulnerabilities. Furthermore, analysis at the function domain levels (conventionally at least 2 neuropsychological tests) also revealed dysfunction across multiple domains.

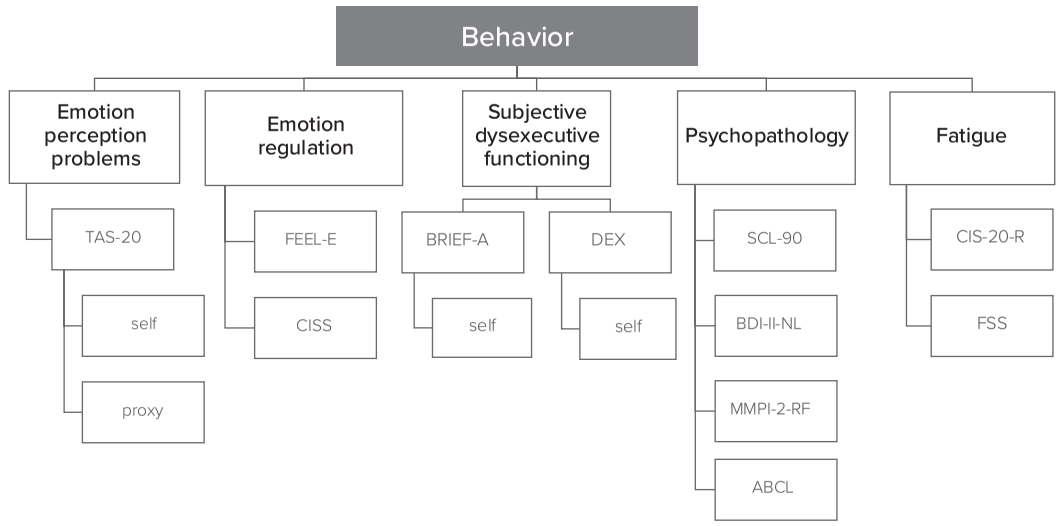
For future studies, it is important to include comparison groups in the neuropsychological phenotyping of NF1. Given that both genetic variability and symptom expression are highly variable in NF1, adults with NF1 without fatigue as well as IQ-matched adults with and without fatigue could be valuable control subjects. As part of the wide range of behavioral problems, our study group had very high levels of fatigue. To further address this issue, a future study could analyze the potential associations and interactions between fatigue and cognition and behavior, and determine whether the fatigue symptoms can be statistically explained by cognitive and behavioral dysfunction. Cognitive dysfunction and behavioral difficulties, such as inadequate coping, are likely to impair an individual's ability to engage effectively in occupational and daily activities and to meet (self-imposed and societal) expectations. In addition, deficits in social cognitive functioning, such as impaired perception and regulation of emotions and impaired mentalizing skills, have been linked to internalizing psychopathology, including mood disorders (Pride et al., 2013; 2014; Sloan et al., 2017). Symptoms of fatigue

(both physical and mental) in NF1 may be bidirectionally related to cognitive impairment and behavioral dysfunction (Rosenberg et al., 2021; Rosenberg et al., 2024). Addressing the interconnectedness of NF1 issues requires a comprehensive (research and clinical) approach that analyses the interplay between cognitive function and behavior, including coping mechanisms, and mental well-being (Caspi & Moffitt, 2018).

Our findings underscore the importance of individualized clinical neuropsychological assessment in individuals with NF1 who present with symptoms that cannot be adequately explained medically. It is also prudent to consider that cognitive deficits are not always immediately apparent or quantifiable in everyday life and may therefore go unnoticed. Due to the concomitant absence of externalizing psychopathology, cognitive and behavioral dysfunction of individuals with NF1 may not attract immediate clinical attention. However, in the absence of sufficient adaptive coping, the risk of psychopathology, and high levels of fatigue, clinicians should be alert to even (subtle) cognitive and behavioral symptoms (e.g., a history of learning problems, lower verbal participation in oral conversation, withdrawal or delayed follow-up of treatment or appointments, and perceiving own NF1 symptoms or burden as predominantly physical with less attention for the mental aspects) and refer for clinical neuropsychological assessment. Based on individual assessment, personalized treatment options can be provided. For example, evidence-based dialectical behavior therapy (DBT) tailored to adults with NF1 in the Netherlands (Van Leeuwen et al., 2024), tailored psychoeducation (for individual patients and their proxies), cognitive compensation strategies, and evidence-based treatment of anxiety and depression can be offered, along with interventions aimed at optimizing and adapting the environment to the capabilities of the individual with NF1.

In summary, this study comprehensively inventoried and tested cognition and behavior in a large group of adults with NF1 across a broad age range, in accordance with the gold standard for individualized clinical neuropsychological assessment. In line with brain imaging research, that has not yet shown robust correlations between specific brain morphologies and dysfunction in NF1, we found dysfunction in adults across multiple domains.




**Supplementary Figure 1.** Overview of cognitive and behavioral domains and instruments administered.

*Abbreviations:* WAIS-IV-NL: Wechsler Adult Intelligence Scale-IV-NL; FSIQ: full scale intelligence quotient; VBI: verbal comprehension index; PRI: perceptual reasoning index; WGI: working memory index; PSI: processing speed index; D2: D2 Test of Attention; TMT: Trail Making Test; Stroop: Stroop Color and Word Test trials 1,2, and 3; Rey-CFT; Rey-Osterrieth Complex Figure Test; BADS: Behavioural Assessment of the Dysexecutive Syndrome; Rey-ALVT: Rey Auditory Verbal Learning Test; IR: Immediate Recall; DR: Delayed Recall; LLT: Location Learning Test; ERT: Emotion Recognition Task; ToM-test-R: Theory-of-Mind test Revised. TAS-20: Toronto Alexithymia Scale-20; FEEL-E: Fragebogen zur Erhebung der Emotionsregulation bei Erwachsenen (Questionnaire for the survey of emotion regulation in adults); CISS: Coping Inventory for Stressful Situations; BRIEF-A: Behaviour Rating Inventory of Executive Function- Adult Version; DEX: Dysexecutive Questionnaire; SCL-90: Symptom Checklist-90-R; BDI-II: Beck Depression Inventory-II; MMPI 2-RF: Minnesota Multiphasic Personality Inventory-2 Restructured Form; ABCL: Adult Behaviour Checklist; FSS: Fatigue Severity Scale; CIS-20-R: Checklist Individual Strength-20-Revised.

**Supplementary Table 1.** Overview of neuropsychological instruments, abbreviations, and references.

| Neuropsychological instrument | Abbreviation | Reference |
|---|---|---|
| Amsterdamse Korte Termijn Geheugen Test *(Dutch short-term memory test)* | AKTG | Schmand, B., De Sterke, S., & Lindeboom, J. (1998). *AKTG : Amsterdamse korte termijn geheugen test.* Lisse: Swets Test Publishers.<br>Cut-off point: ≤84 |
| Test of Memory Malingering | TOMM | Tombaugh, T. N. (1996). *Test of Memory Malingering (TOMM).* New York: MHS.<br>Tombaugh, T. N. (2013). *Test of memory malingering TOMM; user's manual.* New York: MHS.<br>Cut-off points: trial 1 < 18; trial 2 < 45 |
| Visual Association Test – Extended | VAT-E | Meyer, S. R. A., & De Jonghe, J. F. M. (2019). *Visuele associatietest – Extended*: Handleiding. Amsterdam: Hogrefe Uitgevers BV.<br>Meyer, S. R. A., De Jonghe, J. F. M., Schmand, B., & Ponds, R. W. H. M. (2017). The Visual Association Test – Extended: A cross-sectional study of the performance validity measures. *The Clinical Neuropsychologist*, *31*(4), 798-813. https://doi.org/10.1080/13854046.2017.1280181<br>Cut-off points: ≤ 21 immediate recognition; ≤ 20 delayed recognition; ≤ 21 consistency; ≥ 7 free recall combined with ≤ 9 multiple choice |
| Wechsler Adult Intelligence Scale IV-NL | WAIS-IV-NL | Wechsler, D. (2012). *Wechsler Adult Intelligence Scale – Fourth Edition, Nederlandstalige Bewerking* (WAIS-IV-NL): Technische handleiding *(WAIS-IV Dutch version: Technical manual).* Amsterdam: Pearson. |
| Rey Auditory Verbal Learning Test (*Dutch translation:* 15-Woorden Test) | AVLT | Rey, A. (1964). *Rey auditory verbal learning test (RAVLT).* L'Examen clinique en psychologie *[Clinical tests in psychology].* Paris: Presses Universitaires de France (PUF).<br>Bouma, A., Mulder, J., Lindeboom, J. & Schmand, B. (2012). Handboek Neuropsychologische Diagnostiek (tweede herziene druk) *[Handbook neuropsychological assessment].* Amsterdam: Pearson. |
| Rey-Osterrieth Complex Figure Test | Rey CFT | Lezak, M. D., Howieson, D. B., Bigler, E. D., & Tranel, D. (2012). *Neuropsychological Assessment (5th ed).* New York: Oxford University Press.<br>Bouma, A., Mulder, J., Lindeboom, J., & Schmand, B. (2012). *Handboek Neuropsychologische Diagnostiek (tweede herziene druk).* Amsterdam: Pearson Assessment and Information B.V. |
| Location Learning Test | LLT | Kessels, R. P. C., Bucks, R. S., Willison, J. R., & Byrne, L. M. T. (2012). *Location Learning Test Herziene Uitgave – Handleiding [LLT Manual].* Amsterdam: Hogrefe. |
| Verbal Fluency | Fluency | Luteijn, F., & Barelds, D. P. F. (2004). Groninger Intelligentie Test 2 Handleiding. Amsterdam: Harcourt Assessment B.V.<br>Schmand, B., Houx, P., & De Koning, I. (2012). *Normen voor Psychologische Tests voor gebruik in de Klinische Neuropsychologie.* Sectie Neuropsychologie, Nederlands Instituut voor Psychologen (NIP). |
| Behavioural Assessment of the Dysexecutive Syndrome | BADS | Wilson, B. A., Alderman, N., Burgess, P.W., Emslie, H., & Evans, J. J. (1996). *BADS: Behavioural Assessment of the Dysexecutive Syndrome.* London: Pearson.<br>Krabbendam, L., & Kalff, A. C. (1997). *BADS-NL. Handleiding [BADS-NL Manual].* Lisse: Swets & Zeitlinger. |
| Behavior Rating Inventory of Executive Function, Adult | BRIEF-A | Gioia, G., Isquith, P. K., Guy, S. C., & Kenworthy, L. (2004). *Behavior Rating Inventory of Executive Function (BRIEF*): *Professional manual.* Lutz, FL: Psychological Assessment Resources. [Dutch translation: Scholte, E., & Noens, I. (2011). *Vragenlijst over executieve functies bij volwassenen (BRIEF-A). Handleiding*]. Amsterdam: Hogrefe. |
| Dysexecutive Questionnaire | DEX | Krabbendam, L., & Kalff, A. C. (1997). BADS Behavioural Assessment of the Dysexecutive Syndrome Handleiding. Lisse: Swets & Zeitlinger. |
| d2 Test of Attention | d2 | Brickenkamp, R., & Oosterveld, P. (2014). *d2 Aandachts- en concentratietest. Handleiding [Test of Attention. Manual*]. Amsterdam: Hogrefe. |
| Stroop Color and Word Test | Stroop | Bouma, A., Mulder, J., Lindeboom, J., & Schmand, B. (2012). *Handboek Neuropsychologische Diagnostiek (tweede herziene druk).* Amsterdam: Pearson Assessment and Information B.V.<br>Schmand, B., Houx, P., & De Koning, I. (2012). *Normen voor Psychologische Tests voor gebruik in de Klinische Neuropsychologie.* Sectie Neuropsychologie, Nederlands Instituut voor Psychologen (NIP). |
| Trail Making Test | TMT | Lezak, M. D., Howieson, D. B., Bigler, E. D., & Tranel. D. (2012). *Neuropsychological Assessment (5th ed.).* New York: Oxford University Press.<br>Schmand, B., Houx, P., & De Koning, I. (2012). *Normen voor Psychologische Tests voor gebruik in de Klinische Neuropsychologie.* Sectie Neuropsychologie, Nederlands Instituut voor Psychologen (NIP). |
| Emotion Recognition Task | ERT | Kessels, R. P. C., Montagne, B., Hendriks, A. W., Perrett, D. I., & De Haan, E. H. F. (2014). Assessment of perception of morphed facial expressions using the Emotion Recognition Task (ERT): Normative data from healthy participants aged 8-75. *Journal of Neuropsychology,8*(1), 75-93. https://doi.org/10.1111/jnp.12009 |
| Theory-of-Mind test Revised | ToM-test-R | Steerneman, P., & Meesters, C. (2009), *ToM test-R: Handleiding.* Antwerpen/Apeldoorn: Garant. |
| Toronto Alexithymia Scale-20 | TAS-20 | Kooiman, C. G., Spinhoven, P., & Trijsburg, R. W. (2002). The assessment of alexithymia: A critical review of the literature and a psychometric study of the Toronto Alexithymia Scale-20. *Journal of Psychosomatic Research, 53*(6), 1083-1090. https://doi.org/10.1016/S0022-3999(02)00348-3 |
| Coping Inventory for Stressful Situations | CISS | Endler, N. S., & Parker, J. D. A. (1999). *Coping Inventory for Stressful Situations (CISS*): Manual. MHS: Toronto. [Dutch translation: De Ridder, D. T. D., & Van Heck, G. L. (2004). *CISS-NL*. Handleiding]. Amsterdam: Pearson. |
| Questionnaire for the survey of emotion regulation in adults | FEEL-E | Grob, A., & Horowitz, D. (2014). *FEEL-E. Fragebogen zur Erhebung der Emotionsregulation bei Erwachsenen.* Bern: Verlag Hans Huber. [Dutch translation: Punt, D. J. (2014). *Vragenlijst over emotieregulatie bij volwassenen. FEEL-E.*] Amsterdam: Hogrefe. |
| Adult Behavior Checklist | ABCL | Achenbach, T. M. & Rescorla, L. A. (2003). *Manual for the ASEBA Adult Forms & Profiles.* Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families. |

**Supplementary Table 1.** Continued.

| Neuropsychological instrument | Abbreviation | Reference |
|---|---|---|
| Checklist Individual Strength-20-Revised | CIS-20-R | Vercoulen, J. H. M. M., Alberts, M., & Bleijenberg, G. (1999). Kort instrumenteel: de Checklist Individual Strength (CIS). *Gedragstherapie, 32*(2), 131-136.<br>Vercoulen, J. H. M. M. , Swanink, C. M. A, Fennis, J. F. M., Galama, J. M. D., van der Meer, J. W. M., & Bleijenberg, G. (1994). Dimensional assessment of chronic fatigue syndrome. *Journal of Pychosomatic Research, 38*(5), 383-392. https://doi.org/10.1016/0022-3999(94)90099-X |
| Fatigue Severity Scale | FSS | Krupp, L. B., LaRocca, N. G., Muir-Nash, J., & Steinberg A. D. (1989). The Fatigue Severity Scale: application to patients with multiple sclerosis and systemic lupus erythematosus. *Archives of Neurology, 46*(10), 1121-1123.<br>Dutch translation: Rietberg, M. B., van Wegen, E. E. H., & Kwakkel, G. (2010). Measuring fatigue in patients with multiple sclerosis: reproducibility, responsiveness and concurrent validity of three Dutch self-report questionnaires. *Disability and rehabilitation, 32*(22), 1870-1876. https://doi.org/10.3109/09638281003734458<br>Retrieved from: https://meetinstrumentenzorg.nl/instrumenten/fatigue-severity-scale/ [2022, November 14]. |
| Minnesota Multiphasic Personality Inventory-2 Restructured Form | MMPI-2-RF | Ben-Porath, Y. S., & Tellegen, A. (2008). *MMPI-2-RF manual for administration, scoring, and interpretation.* Minneapolis, MN: University of Minnesota Press.<br>Van Der Heijden, P., Derksen, J., Egger, J., Rossi, G., Laheij, M., & Bögels, T. (2013). *MMPI-2-RF. Minnesota Multiphasic Personality Inventory-2 Restructured Form. Handleiding voor Afname, scoring en interpretatie [Manual for administration, scoring and interpretation: Dutch-Flemish translation].* Nijmegen: PEN Tests Publisher. |
| Beck Depression Inventory-II | BDI-II-NL | Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for the Beck depression inventory-II.* San Antonio, TX: Psychological Corporation. Van Der Does, A. J. W. (2002). *BDI-II Dutch translation. Handleiding [BDI-II-NL Manual].* The Netherlands, Pearson.<br>Roelofs, J., van Breukelen, G., de Graaf, L. E., Beck, A. T., Arntz, A., & Huibers, M. J. H. (2013). Norms for the Deck Depression Inventory (BDI-II) in a large Dutch community sample. *Journal of Psychopathology and Behavioral Assessment*, *35*(1), 93–98. https://doi.org/10.1007/s10862-012-9309-2 |
| Symptom Checklist-90 Revised | SCL-90-R | Arrindell, W. A., & Ettema, J. H. M. (1986; 2003). *Handleiding bij een multidimensionele psychopathologie-indicator [SCL-90-R. Manual of a multi-dimensional psychopathology indicator].* Amsterdam: Pearson. |

# 3

## Treatment of emotion regulation problems in people with Neurofibromatosis type I

Van Leeuwen, J. P. A., Urganci, Y., Ossewaarde, L., Boumans, C. E., Van Den Bosch, L. M. C., & Egger, J. I. M. (2024). Treatment of emotion regulation problems in people with neurofibromatosis type 1. *Dutch Journal of Psychiatry, 66* (6), 331-335. https://pubmed.ncbi.nlm.nih.gov/39162159/

## Summary

People with the genetic disorder Neurofibromatosis type 1 (NF1) are usually seen in a medical setting where the diagnosis is made based on the presence of well-defined physical symptoms such as neurofibromas or pigmentary spots (so-called café-au-lait spots). In mental health services, except for a few highly specialized centres, the treatment of people with NF1 receives little attention, while the need for psychological treatment is increasingly identified, both in clinical practice and in the scientific literature. The current occasional referrals of people with NF1 to the mental health system are mainly focused on the diagnosis of psychological disorders where subsequent treatment, however, is mostly absent. Here we describe how two people with NF1, who were indicated for participation in Dialectical Behavior Therapy (DBT) skills training based on clinical neuro-psychological assessment, were able to develop their skills and how they themselves and their relatives experienced the treatment.



## Introduction

Neurofibromatosis type 1 (NF1), formerly Von Recklinghausen's Disease, is an autosomal dominant inherited disorder, occurring in one in 2,700 individuals, caused by a mutation in the so-called *NF1 tumor supressor* gene (Evans et al., 2010). NF1 is characterized by a wide variety of physical and psychological symptoms. Somatic manifestations are pigment abnormalities in the skin and eyes (café-au-lait spots, lish nodules), skeletal abnormalities and neurofibromas in the skin, nervous system and brain, with an increased risk of developing malignant tumours. The variation in suffering burden, as well as the variation in physical and psychological symptoms is great (Potter & Mendoza, 2019).

While people with NF1 are hardly ever referred to the mental health system, both in clinical practice and in the scientific literature, increasing attention is being drawn to their psychological functioning and the need for treatment and counselling in that area (Bottesi et al., 2020). Research shows that coping mechanisms of people with NF1 are predominantly passive, with little active and task-oriented coping, and that they have difficulty differentiating emotions. This lack of effective coping mechanisms may contribute to high levels of psychopathology. Frequently reported are high burden of suffering, prolonged anxiety and mood symptoms, reduced social functioning and lower quality of life (Doser et al., 2020; Fjermestad et al., 2018). These problems are associated with the unpredictable course of disease, risk of malignancy and associated uncertainty, concerns about heredity, stigma, reduced social activity, deficits in prosocial behavior and lower self-esteem (Bottesi et al., 2018; Copley-Merriman et al., 2020; Crawford et al., 2015). Also, it is a target population in which cognitive problems are observed such as lower than average total IQ, decreased attention and speed of information processing, memory problems and problems in social cognition as confirmed in our recent unpublished manuscript on cognition and behavior in adults with NF1 (Descheemaeker et al., 2013).

Since NF1 can have a great impact on daily life due to the complex interplay of physical, neurocognitive and psychological symptoms and is incurable, psychological treatment may be important to reduce the functional impact of the disorder (Potter & Mendoza, 2019). A useful starting point here is the phenomenon of emotion regulation which refers to the ability to influence emotions and is considered a transdiagnostic and dimensional construct (McRae et al., 2013). Based on a systematic review, it is shown that emotion regulation is involved in the development and maintenance of various forms of psychopathology (Sloan et al., 2017). Especially in patients with a high degree of comorbidity and complexity, as for example in people with NF1 where physical, neurocognitive and (psycho)pathological

symptoms interact with each other, problems with emotion regulation may play a burdensome role.

### Psychological treatment of patients with NF1

Dialectical behavior therapy (DBT) is an evidence-based treatment program for people with severe emotion regulation disorders (Linehan, 1993; 2015). Although originally focused on the treatment of suicidal and self-harming behaviors in severe personality disorders, DBT has also been shown to be effective with emotion regulation problems within other target groups and treatment settings; in particular, the DBT skills training (DBT-ST) has evolved into a widely applicable transdiagnostic intervention for emotion regulation problems (Swales, 2018; Valentine et al., 2015). To investigate whether DBT is an appropriate treatment for people with NF1, a feasibility study was conducted by van Leeuwen et. al. in which both patients in the present article participated. In it, a three-month DBT-ST was given, based on Soler's program, in four distinct skill areas, i.e., (a) mindfulness; (b) interpersonal efficacy; (c) frustration tolerance; and (d) emotion regulation skills. Successively, it focuses on:

- increasing environmental awareness and encouraging attentiveness and (self-) observation;
- practice pursuing one's own goals more strategically without irreparably damaging relationships or compromising self-respect;
- dealing with and not intensifying strong emotions and associated physiological processes for the benefit of an accepting attitude
- understanding the function of emotions and relationship to emotional vulnerability which reduces negative emotions and finally allowing resilience and positive emotions/experiences to increase.

For further discussion of goals and methods, see Linehan and Soler (Linehan, 2015; Soler et al., 2009).

Two of the seven participants in the first DBT-ST were interviewed and selected on the basis of life stage, representativeness for the target group and the presence of relatives in order to collect qualitative data on treatment experiences and effects. Involving relatives appears to be important in generalizing skills in one's environment as well as in perceived change by the environment (van Leeuwen et al., 2022). In this way an attempt is made to highlight results from different perspectives. Both participants were referred by the Outpatient Clinic for Hereditary and Congenital Disorders of the Erasmus MC in Rotterdam to the Centre of Excellence for Neuro-psychiatry of Vincent van Gogh. The results of the interviews are discussed in the present article.





## Case descriptions

Patient A is a 52-year-old woman, married and mother of a young adult son and two daughters (twins), all known to have NF1. The diagnosis of NF1 was made later in life based on clinical genetic testing following a plexiform neurofibroma in her son. Somatically, NF1 manifests itself mainly in the form of (increasing) neurofibromas on the skin, from which she experiences limited discomfort. Fatigue, on the other hand, plays a huge part in her life. In daily life, she performs administrative work at her and her husband's construction company and also takes care of the family and her mother. In 2018, to objectify persistent fatigue complaints, concentration problems, memory complaints and social-cognitive problems, she was referred for clinical neuropsychological assessment. This revealed an overall (low)average level of intelligence with a delayed rate of information processing and suboptimal executive and social-cognitive skills, as well as a mild imprinting disorder. With regard to symptom representation, personality traits and coping strategies, a low self-esteem with a high sense of responsibility emerged with internalizing problems being central. She experiences many anxiety and mood symptoms, and a high level of fatigue complaints and problems in recognizing and describing the emotional inner world. In addition, she has a very limited repertoire in dealing with stress. Based on the above findings, DBT treatment was indicated to learn to better recognize and verbalize signals from the body and emotions and to expand her stress management skills. In addition, the patient wished to be more assertive, to enter social situations more easily without losing herself and to be able to indicate her boundaries more.

Patient B is a 24-year-old woman who was admitted clinically to the Centre of Excellence for Neuropsychiatry for the purpose of diagnosis and indication. After inpatient treatment, she began living independently in an apartment; during treatment, she stayed at her parents' home on weekends, along with her three younger sisters. She was diagnosed with NF1 at a young age using café-au-lait spots. In addition, she struggled with NF1-related dysmorphias in her neck, which at the time of her admission she experienced a great deal of discomfort and was insecure about. She was referred because of increased fatigue symptoms, head and muscle pain, irritability, gloominess, negative thoughts and feelings of inferiority in a short period of time. Results of the clinical neuropsychological assessment indicated an overall low gifted to below average intelligence level, with suboptimal visual information processing and limited executive skills leading to overview and initiation problems, difficulty with planning and strategy handling. With respect to symptom representation, personality traits and coping strategies, a picture emerges of a young woman with anxiety and gloom symptoms, feelings

of hopelessness and suicidal ideations, all mediated by disabling pain and fatigue symptoms. Patient had low self-confidence and a tendency to withdraw from herself while she enjoys being in contact with others. Several psychological treatments aimed at anxiety and mood symptoms and her low self-confidence as well as drug treatment had insufficient results. On the basis of the above findings, DBT treatment was indicated with the goal of learning to cope with emotion regulation problems, expanding coping skills and engaging in difficult situations when stress rises, rather than withdrawing, giving up and ruminating.

## Discussion interviews

### Complaints and concerns due to Neurofibromatosis type I

Both patients worry about the course of NF1 when it comes to developing malignant neurofibromas. A: *You just hope that you don't get the worse symptoms. That it passes by your door, that it stays at brown spots and some bumps. The sword of Damocles, that always hangs over your head.* Both patients indicate that the external features, appropriate to NF1, cause less trouble than the disabling fatigue and reduced personal functioning. For Patient B in particular, fatigue symptoms bother her to such an extent that it interferes with all activities of daily living such as studying or working, going out with friends or attending therapies. Reduced interpersonal functioning is at the forefront for Patient A; especially her reticence and difficulty in social contact. She notices that as she gets older it becomes more difficult to connect with others and she is more likely to make negative interpretations of "social cues" (such as other people's facial expressions). Disregarding emotions in others also hinders her contact. Both indicate that they have found it difficult to accept that there is an incurable condition.

The different stage of life in which they both find themselves brings with it a different perspective on NF1. Whereas patient A struggles with intense feelings of guilt regarding the inheritance of NF1 and worries about the course of the condition in her children, patient B would like to be a real part of society by being able to work, go out with friends and not be hindered by disabling fatigue and anxiety symptoms.

### Taking control: perceived outcomes of DBT treatment

Both patients describe being able to view a situation better from a distance after treatment, creating space to see what is actually going on at the time and reducing fretting and being overwhelmed by emotions. This is particularly helpful when there are concerns about the course of the disease and hospital check-ups are pending and about the judgment of others regarding external features of NF1.





Observing and mindfully paying attention to thoughts is part of this. Also, both patients report an increased ability to describe emotions. Not only for themselves, but in particular they cite this as helpful in communication with others, in which they both experience difficulties, because by more easily expressing the emotional inner world, they can better describe what they need at that moment. For B, practicing mindfulness has helped by dwelling on what exactly is emotionally driven behavior (emotional mind) and what is rationally/cognitively driven (rational mind). She has learned how to arrive at a middle ground between the two (wise mind). This has facilitated moving into public spaces and social occasions by acting contrary to emotions when appropriate and checking facts. Doing a breathing exercise or withdrawing herself allows her to regulate her tension. Other changes she has noticed since treatment involve how she deals with her insecurities and greater acceptance of reality. For example, she says she cares less about what others will think and say of her, allowing her to enjoy the (outside) world more. B: *Yes, now I do feel a little better and more confident. Before, I really had to put on mascara before I went out and now I can really think "whatever!". I just am who I am. Yes, I've done a lot of things, in a short time.*

Both patients give as a side note about the DBT treatment that online meetings were perceived as less pleasant than the physical meetings, it gave less opportunity for "a chat" during the break. Both indicated that following the training online also demands more from the ability to concentrate. For Patient A, it was true that during the training the corona pandemic broke out so the last four meetings were completed online. Patient B took most of the training online because of the measures in place during that same corona pandemic. Both advocate for at least a blended treatment offer so that there are enough physical meetings to make it easier to connect with each other and to have more space to share experiences with each other in an accessible way, even before or after the meeting.

### Generalization to the environment: what do relatives see?

Interviews with loved ones (husband and daughter of A, sister of B) reveal many similarities mentioned in the changes experienced by loved ones. There is a noticeable increase in observing and describing emotions in both patients. This component of mindfulness skills seems to be very central. It is mentioned by several loved ones that there is more mutual (re) recognition because patients actually see what is happening and understand where the emotions come from, both in themselves and the environment (validation). Describing experienced emotions to those around them allows for mutual understanding and the possibility of support if desired.

Furthermore, changes were noted in the way patients handled their emotions. In particular, changes in the areas of emotion regulation and frustration tolerance were mentioned several times, with the earlier recognition of rising tensions and being able to regulate higher tension better, which, according to loved ones, had an effect on patients' moods and resulted in less mutual conflict. Interpersonal efficacy skills also reported an increase: goal setting and saying no were increasingly present. According to loved ones, this led to both patients being able to articulate themselves more clearly to those around them, having a clearer vision of what they actually wanted to do and less doubt about choices she made with the result that she felt better. Daughter of A: *At first she was a bit of a people pleaser, but now she also just says what she wants for herself. Then it becomes a lot clearer and you know what you have in common. Otherwise you're just guessing how she feels.*

## Considerations and conclusion

Whereas people with NF1 may lose some of the control over their own lives because of the uncertain course of the disease and the associated significant physical and (neuro)psychological problems, we believe that a treatment that focuses broadly on regulation of emotion and behavior, for example by training mindfulness, emotion regulation, frustration tolerance and interpersonal effectiveness, provides them with the skills to regain control over their own inner emotional world. Both patients and their loved ones describe the positive impact the DBT skills training has had on themselves and their system of loved ones. In particular, the increased skills in observing and describing and learning to differentiate emotions to themselves, as well as describing experienced emotions to others seems to have increased their ability to anticipate stressful situations and take more control. The ability to better express oneself to physicians, employers and loved ones may help one to be taken more seriously in the broad range of symptoms experienced. In the absence of severe externalizing psychopathology, cognitive and behavioral disorders of individuals with NF1 may not initially attract the clinical attention it needs. By focusing on an underlying transdiagnostic, dimensional construct such as emotion regulation, the underlying emotional dysregulation can be treated from a biosocial model rather than a variety of resulting symptoms. A wider range of treatment modalities might be indicated if aimed at treating emotional dysregulation. Follow-up research on a larger scale is necessary to make statements about the effectiveness of DBT in people with NF1 and to investigate which mechanisms of action contribute to change in perceived symptoms and possible increase in quality of life.





*Both patients gave permission for publication and provided comments on an earlier version of this article. Anonymized verbatims of the interviews are available for review from the first author.

# 4

## Perceived Criticism in relation to the Dialectical Behavior Therapy network training in a residential program: a pre-post study

Van Leeuwen, H., van den Bosch, W., Ossewaarde, L., & Egger, J. I.M (2022). Perceived criticism in relation to the Dialectical Behavior Therapy network training in a residential program: a pre-post study. *International journal of psychology and psychological therapy*, *22*(3), 267-276. https://www.ijpsy.com/volumen22/num3/620.html

## Abstract

Perceived Criticism (PC) is a transdiagnostic construct that captures the patients' perception of criticism. PC seems to be a reliable predictor of negative clinical outcomes concerning recurrence of symptoms or relapse in a broad range of stress-related psychiatric disorders and is thought to be related to underlying stress-related psychobiological vulnerabilities. Dialectical Behavior Therapy (DBT) is a treatment targeting these stress-related psychobiological vulnerabilities. In this pilot study we focus on the possible change in PC due to a (residential) DBT network training. This study follows a pre-post design where PC is recorded in 33 patients (mean age 25 years) and 61 relatives during 8 group sessions undergoing a DBT network training, as part of a residential DBT program. The degree of perceived criticism is systematically assessed using the Perceived Criticism Measure (PCM), a two item self-report questionnaire that assesses mutual (perceived) criticism from patients and network members. Overall scores of the perceived criticism measure decrease significantly for both patients and relatives after following the DBT network training. More specific, item scores of both patients and relatives concerning how critical they are towards the other and how critical they thought the other was of them also decreased significantly after following the DBT network training. Findings suggest that a DBT network training as part of a residential DBT program may be instrumental in decreasing levels of perceived criticism. We recommend further exploration of PC as a possible moderator in effect size studies in randomized controlled clinical trials on DBT and in more fundamental research on the putative mechanisms of behavioural change such as improved perspective taking, and the evaluation of social cues.



## Introduction

Perceived Criticism (PC) is a transdiagnostic construct that captures the individuals' perception of criticism. It reflects how critical a person believes a relative is towards them and is assessed by the Perceived Criticism Measure (PCM; Hooley and Teasdale, 1989). The PCM captures criticism and perceived criticism by two questions, respectively, "How critical are you towards your relative?" and "How critical do you think your relative is of you?". The PCM seems to be a reliable predictor of negative clinical outcomes concerning recurrence of symptoms or relapse in a broad range of stress-related psychiatric disorders (for an overview, see Masland & Hooley, 2015; Masland et al., 2019; Renshaw, 2007). Furthermore, not only clinical outcomes for patients are associated with PC. Research suggests that high levels of expressed emotions (EE), including elevated criticism in challenging interpersonal dynamics, are associated with greater burden for caregivers of patients as well (Baily & Grenver, 2015; Kirtley et al., 2019).

Little research has focused on the underlying mechanisms behind the predictive value of PC. Research suggests that PC is an independent construct (Masland et al., 2019) and that both psychopathology and demographic characteristics do not explain the predictive value of PC (Hooley and Teasdale, 1989; Masland and Hooley, 2015; Masland et al., 2019; Renshaw, 2007). Pulopulos et al. (2021) had the substantiated hypothesis that the predictive value of PC might be related to the level of functioning of the stress regulation system. More specifically, in this study, the psychophysiological differences in response to a social stress task in young women with high and low PC were investigated. They found that women with a high PC score anticipate more on social threats and interpretations and have less active coping when they are exposed to socially stressful events. This supports the assumption that PC is indeed associated with underlying stress-related psychobiological vulnerabilities that contribute to its association with negative clinical outcomes. So far, research mainly focusses on understanding the underlying mechanisms and the construct of PC. Although, Masland & Hooley (2015) recommended in their review that given the growing evidence that PC is a key transdiagnostic construct to understand clinical outcomes, future research should focus on altering PC in targeted interventions. Given the assumption of Pulopulos et al. (2021), a treatment targeting stress-related psychobiological vulnerabilities could be appropriate for altering PC.

Dialectical Behavior Therapy (DBT) is a treatment that focusses on psychobiological vulnerabilities. DBT is an empirically supported treatment program developed by Marsha Linehan for individuals with severe emotion dysregulation problems

(Linehan, 1993, 2015). The biosocial theory assumes that the disruption of the emotional regulation is the result of a complex and longitudinal transaction between someone with emotional vulnerabilities (the biological component, the stress system) and their (invalidating) environment (the social component). Examples of the biological component include trait impulsivity (Beauchaine et al., 2010; Beauchaine & Gatzke-Kopp, 2012; Beauchaine & McNulty, 2013; Caspi & Silva, 1995), trait anxiety (Gray & McNaughton, 2007) and emotional sensitivity (Forbes & Dahl, 2005). Chronic and pervasive emotion dysregulation lead to the disruption of a person's emotional life on both an individual (identity, behaviour, cognition) and interpersonal level (rejection, sensitivity, difficulties in belonging, cooperation, chronic loneliness and negative self-esteem) (Lis & Bohus, 2013).

As mentioned before, multiple papers suggest to give more attention to PC within clinical treatment (Kirtley et al, Pulopulos 2021, Masland & Hooley 2015). Until now, few studies have focused on altering perceived criticism by a targeted intervention. This current study is the first to pilot possible change in perceived criticism due to a (residential) DBT network training. It did so by including the DBT network training in an existing residential DBT program. The network training was given to patients and their relatives. To assess changes in interpersonal judgment, we measured perceived criticism with patients and their relatives before and after the network training. It was hypothesized that after following the DBT network training patients and their relatives would be less critical of each other.

## Method

### Participants

This study comprises 33 female patients aged 17-50 (M=25.3 years, SD=8.6) who all participated in a step-down DBT program at Jelgersma Center for Personality Disorders, a therapy program based on Linehans' protocol (Linehan, 1993, 2015) modified for a residential setting by van den Bosch et al. (2014). This program consisted of 3 months residential DBT plus 6 months of outpatient DBT.

All patients met the criteria for Borderline Personality Disorder according to the Dutch version of the Structured Clinical Interview for DSM-IV Axis II personality disorders (SCID-II; First et al., 1997; Weertman et al., 2000) and showed a severe level of borderline symptomatology (> 24 on the Borderline Severity Index; BPDSI; Arntz et al., 2003) with parasuicidal behaviour present in the last month preceding the start of residential DBT. Other inclusion criteria were adequate understanding of the Dutch language and acceptable travelling distance from the study center in Leiden, the Netherlands. Exclusion criteria are described in van den Bosch





et al. (2014) and included among others intellectual disabilities, major psychiatric disease, and previous DBT treatment.

The network training was considered as a part of the residential DBT program and took place within the first 3 months of the step-down DBT program. Participation in the network training was a free choice. It was permitted for patients to bring family members, partners, friends or other persons of importance to them to the DBT network training and there was no restriction to the number of invitees. There were 33 patients that followed the network training and brought one or two relatives with them, two of them followed it without their relatives. The network group consisted of 61 relatives: mothers (N=21), fathers (N=16), partners (N=11), sisters (N=6) and friends (N=7). All patients and network members were asked to sign a written informed consent about the use of the data for scientific purposes. Patients were informed about the residential program through an extensive script that was discussed during an appointment with a professional that was involved in the residential program. Patients were informed that that all information would be anonymously processed, and all participants gave informed consent and permission to make video recordings of therapy sessions.

### Measures

The Perceived Criticism Measure (PCM; Hooley & Teasdale, 1989) consists of two questions that are rated on a 10-point likert scale from not critical at all to extremely critical. The first question 'How critical is your relative of you' has been used as a valid indicator of overall criticism in families (Hooley & Miklowitrz, 2017; Renshaw, 2007). The second question is 'How critical are you on your relative'. Both patients and relatives self-rated their level of (perceived) criticism at start of the first DBT network session and after 16 weeks at the end of the last DBT network session. Although there is no recommended cut-off, higher scores reflect higher levels of criticism and a score above 6 raises concern about an increased relapse risk (Masland & Hooley, 215) and the measure appears to be most informative when relatives are persons whom patients live with (Renshaw, 2007).

### Intervention

The residential DBT treatment program was centered around the standard elements of DBT: a weekly skills training and individual therapy. This program was supplemented with daily mindfulness classes, daily meetings concerning living together as a group, weekly drama therapy, weekly group sessions on validation skills and chain analyses. The program lasted for 3 months during which a support staff was present during office hours to help the patients apply DBT skills (van den Bosch et al., 2014).

The DBT network training was based on the network training of Hoffman, Fruzzetti & Swenson (1999) and consisted of 8 sessions of two hours including a break (see table 1 for the content of the sessions). The DBT network training was led by experienced skills trainers from the DBT team who received supervision on a regular basis by a certified DBT clinician.

**Table 1.** Topic and goals of the DBT network training per session.

| DBT network meeting | Topic | Goals |
|---|---|---|
| 1 & 2 | Psycho-education: information about Borderline Personality Disorder, the DBT treatment program, emotion dysregulation, the biosocial theory, case management strategies. | Inform patients and relatives. |
| 3 | Mindfulness | Bring the emotional mind and rational mind into balance and come to a wise mind. |
| 4 | Interpersonal Effectiveness | Achieving desired changes, maintaining relations and maintaining self-respect in interpersonal conflicts. |
| 5 | Emotion Regulation | Understanding emotions, decrease emotional vulnerability and emotional suffering. |
| 6 | Distress Tolerance | Overcome crisis by accepting both yourself and the present situation in a non-evaluating and non-judgmental way. |
| 7 | All DBT skills discussed previous | |
| 8 | All DBT skills discussed previous | |

The structure of these sessions was identical starting with a mindfulness exercise, followed by an overview of the content of the current session, then a summarization of the theory of the previous session, a discussion of the homework assignments, short intermission, and lastly the introduction and practice of new theory. Participants were asked to prepare for a session by reading the corresponding chapter of the skills training manual. During each session an overview of the associated skills was presented, and homework assignments were discussed that corresponded with the module at hand. For instance, when interpersonal skills were subject, skills that were learned is how to describe a situation properly without judgements, express feelings, assert wishes, stay mindful, appear





confident, negotiate, be gentle etcetera. They learned how to use these skills to deal with everyday issues, and subsequently how to practice these by filling in homework sheets together. At the end of the last meeting the group discussed how to continue practicing the DBT skills.

### Procedure

All patients participated in an intensified adapted DBT program, which consisted of 3 months residential DBT plus 6 months of outpatient DBT (van den Bosch et al., 2014). Patients could choose who they wanted to participate with in the DBT network training. In clinical practice, this meant that mothers, fathers, partners, friends and siblings were invited in person by the patients to join the DBT network training with them. At the start and at the end of the last network-training session everyone was asked to fill in the PC scale.

Data collection took place from 2012-2014, when residential DBT was provided by the Jelgersma Centre. In the last part of this period, the study of the effectivity of residential DBT treatment took place (Sinnaeve et al., 2018) but the collection of data of the network training was not included in the study protocol. The scientific commission and the board of GGZ Rivierduinen agreed to support the execution of the data collection.

### Statistical analyses

Statistical analyses are performed with SPSS for windows version 22. The impact of the residential DBT network training is determined by paired sample t-tests. Scores of the perceived criticism measure before and after following the DBT network training were compared. All tests where two-tailed tests and alpha was set at 0.05. To determine the size of the effect, Cohen's d is calculated.

## Results

First, we examined the total score, which includes the two PC items together. The perceived criticism scores of both patients (PCM-P) and relatives (PCM-R) were significantly higher before the DBT network training than after the training with a large effect (table 2 and figure 1).

**Table 2.** Scores of the perceived criticism scale (PC) for patients and relatives.

| | Pre Training (T0) | Post Training (T1) | Outcomes | | | |
|---|---|---|---|---|---|---|
| | M (Sd) | M (Sd) | T | Df | P | Cohen's d |
| *Total scores PC scale* | | | | | | |
| PCM-P (N33) | 6.91 (1.84) | 5.01 (1.47) | 7.90 | 32 | <0.001 | 1.38 |
| PCM-R (N61) | 6.54 (1.40) | 4.89 (0.99) | 7.57 | 30 | <0.001 | 1.36 |

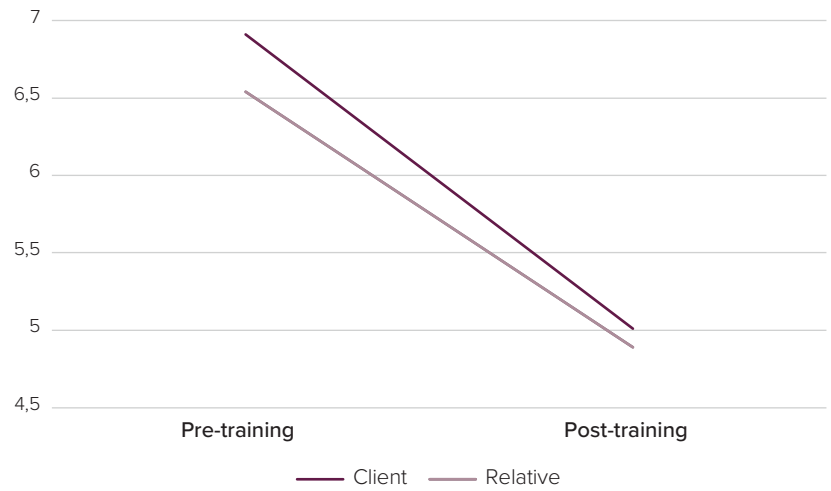



**Figure 1.** Pre and post scores of the perceived criticism scale (PC) for patients and relatives: overall.

Next, differences in PC scale scores were also examined per item. The scores of both patients and their relatives concerning how critical they think the other is towards *them* decreased significantly following the DBT network training, with a large effect (Table 3). Furthermore, the scores of both patients and their relatives concerning how critical they are towards *the other*, also decreased significantly after following the DBT network training, with a large effect (Table 3).





**Table 3.** Scores of the subitems of the perceived criticism measure (PCM) for patients and relatives

| | Pre Training (T0) | Post Training (T1) | Outcomes | | | |
|---|---|---|---|---|---|---|
| | M (Sd) | M (Sd) | T | Df | P | Cohen's d |
| *Item: 'How critical do you think your relative is towards you?'* | | | | | | |
| PCM-P (N33) | 7.48 (1.69) | 5.27 (1.49) | 7.16 | 32 | <0.001 | 1.25 |
| PCM-R (N61) | 6.91 (2.19) | 5.30 (1.60) | 6.21 | 30 | <0.001 | 1.12 |
| *Item: 'How critical do you think you are towards your relative?'* | | | | | | |
| PCM-P (N=33) | 6.34 (2.39) | 4.75 (1.92) | 5.76 | 32 | <0.001 | 1.00 |
| PCM-R (N=61) | 6.16 (1.43) | 4.48 (0.96) | 5.77 | 30 | <0.001 | 1.04 |

## Discussion

To the best of our knowledge, this is the first study to examine the possible change in perceived criticism due to a (residential) DBT network training. We found a significant decrease of perceived criticism both in patients and relatives after following the DBT network training. More specific, the levels of how critical they think the other is towards them and how critical they are towards the other decreased significantly. Given the large effect sizes, this may be considered a relevant finding, although the specific mechanisms underlying the indicated change remain unclarified. The findings also show that perceived criticism rates for both patients and relatives are higher than 6 before the DBT network training. Although there is no official cut-off score, Masland & Hooley (2015) described an increased relapse risk by PC scores above 6. After following the DBT network training PC-levels dropped which might be considered a more desirable condition with regard to possible negative clinical outcomes. While the results of this exploratory study seem to be in line with our initial hypothesis that DBT would be a useful for altering PC, any definitive conclusion would be preliminary.

From an explanatory perspective, first, emotion regulation capacity has to be mentioned. This transdiagnostic and dimensional construct is thought to play a key role in a broad range of mental illnesses (Sloan et al., 2017; Caspi & Moffitt, 2018; Ruggero et al., 2019; Mulay et al., 2019). If we assume that PC is associated with underlying stress-related psychobiological vulnerabilities than it makes sense that DBT could alter PC rates because the development of DBT is based on the biosocial theory that relates to stress-related psychobiological vulnerabilities

(Fruzetti et al., 2005; Sinnaeve et al., 2021). The latest Cochrane meta-analysis about the effects of psychological treatments for BPD confirm that DBT is especially effective in reducing inappropriate anger and non-suicidal self-injury (NSSI) as well as in improving general functioning (Storebø et al., 2020).

Another possible explanation for the predictive value of PC in treatment outcome, as mentioned by Masland and Hooley (2015), is because it measures how much criticism 'is getting through' to the individual (Hooley & Teasdale, 1989). It may be related to the amount of criticism there objectively is in the person's social environment but it may also be linked to the person's experience of what is meant as criticism and what leads to interpersonal disturbances. These disturbances have received significant attention in BPD research. Instability in relationships is one of the most profound symptoms in BPD (Gunderson, 2007; 2011). Individuals with BPD are likely to evaluate social cues in a negative way and to notice criticism or rejection where others would not (Domsalla et al., 2014). As a result, interpersonal problems develop. Since individuals with BPD are prone to feeling rejected or to experiencing criticism, they tend to avoid social relationships which ultimately result in feelings of abandonment or loneliness (Thome et al., 2016). Furthermore, it is known that family members of individuals with BPD themselves suffer, more than average, from affective and interpersonal problems like anger, affective instability, emptiness, intense unstable relationships and fear of abandonment (Gunderson et al., 2011). As a result they are more likely to form an invalidating environment and a negative spiral of emotions and reactions between relatives and patients ensues whereby disruption of interpersonal contact leads to increased reactivity to social stressors (Deckers et al., 2015) and to higher rates of perceived criticism. Given previous research it is likely that both relatives and network members may have benefitted from the DBT skills that they learned in the DBT network training.

Cognitive behavioural explanations for changes in PC would encompass changes in perspective taking, which is defined as the ability to see the world from both the own and the others' perspective (David et al., 2006). It is an important feature of social cognition and interpersonal communication that can be trained to help develop empathy and adequate reaction to others and consists of affective, cognitive and behavioural elements (Hendriks et al., 2016; Teding van Berkhout & Malouff, 2016). As to the latter two, it could be that a change in perspective taking is directly influenced by role playing and group activities during the DBT network training since patients and family members are asked to take each other's perspective and learn and train new behaviour and social skills during the various training sessions. These are forms of active learning (Van Ments, 1999) that are





considered to be highly effective and superior to passive learning when developing new skills (e.g., Holsbrink-Engels, 2001; Bell, 2001). Finally, Montgomery-Graham (2016) shows that DBT enhances perspective taking skills by making automatic or indirect thoughts, feelings and behaviour more explicit, for example through the process of chain analysis. The combination of more explicit mentalization with interpersonal skills learned in DBT can help patients to better influence control their behaviour instead of being led by impulsive, automatic responses.

While an important strength of this study is the fact that it has been conducted in a clinical setting and with a heterogeneous sample of patients representative for the population, there are several methodological and other limitations to this study that may hamper the generalization of its results and of which at least the following three need to be mentioned here. First and most importantly, because this pilot study on perceived criticism was conducted via convenience sampling, i.e., by integrating DBT network training in an existing residential DBT treatment program, we lacked the possibility of contrasting our findings with that of a control group, hence, there is no certainty whether the DBT network training or the residential DBT treatment causes specific altering in PC. Secondly, the PC scale is a two-item scale with straightforward content that has not been designed to yield refined differentiation between interpersonal contact in general or criticism in a broad sense. It has been proven, however, to be a valid indicator of this transdiagnostic construct (Hooley & Miklowitrz, 2017; Renshaw, 2007). A final point is that the results may have been influenced by the fact that the residential DBT program was a national program with well-trained and experienced staff and highly motivated participants with high illness burden. These circumstances might have had a limiting effect on the external validity if the results.

## Conclusion

Notwithstanding these limitations, the findings of the current pilot study point at the possible value of a (residential) DBT network training for the reduction of perceived criticism in both patients and their relatives. The underlying mechanisms causing change in PC remain unclarified. Multiple hypotheses are described in this paper and from the literature, there is growing evidence that perceived criticism is a key transdiagnostic construct to understand clinical outcomes. Involving PC more systematically in research on targeted treatments seems to be a logical step.

In future studies, particularly the underlying mechanisms that influence the change in perceived criticism should be investigated. The (added) value of the network training should be tested in a high-quality randomized controlled study (RCT) where patients enrolled in a standard DBT program randomly participate in the network training. An alternative for this RCT would be to use an interrupted time series design with a control group, given the fact that multiple DBT therapists in the Netherlands already give the network training. Measurements should take place throughout the whole study, preferably after every session, and have to contain instruments that capture change in BPD symptomatology, perspective taking and perceived criticism. This way, the relationship between DBT treatment, network training and perceived criticism can be further clarified.

# 5

## Reviewing the availability, efficacy and clinical utility of Telepsychology in Dialectical Behavior Therapy (Tele-DBT)

Van Leeuwen, H., Sinnaeve, R., Witteveen, U., Van Daele, T., Ossewaarde, L., Egger, J.I.M., & van den Bosch, L.M. (2021). Reviewing the availability, efficacy and clinical utility of Telepsychology in dialectical behavior therapy (Tele-DBT). *Borderline personality disorder and emotion dysregulation*, *8*, 1-15. https://doi.org/10.1186/s40479-021-00165-7

## Abstract

Telepsychology is increasingly being implemented in mental health care. We conducted a scoping review on the best available research evidence regarding availability, efficacy and clinical utility of telepsychology in DBT. The review was performed using PRISMA-ScR guidelines. Our aim was to help DBT-therapists make empirically supported decisions about the use of telepsychology during and after the current pandemic and to anticipate the changing digital needs of patients and clinicians. A search was conducted in PubMed, Embase, PsycARTICLES and Web of Science. Search terms for telepsychology were included and combined with search terms that relate to DBT. Our search and selection procedures resulted in 41 articles containing information on phone consultation, smartphone applications, internet delivered skills training, videoconferencing, virtual reality and computer- or video-assisted interventions in DBT. The majority of research about telepsychology in DBT has focused on the treatment mode of between-session contact. However, more trials using sophisticated empirical methodologies are needed. Quantitative data on the efficacy and utility of online and blended alternatives to standard (i.e., face-to-face) individual therapy, skills training and therapist consultation team were scarce. The studies that we found were designed to evaluate feasibility and usability. A permanent shift to videoconferencing or online training is therefore not warranted as long as face-to-face is an option. In all, there is an urgent need to compare standard DBT to online or blended DBT. Smartphone apps and virtual reality (VR) are experienced as an acceptable facilitator in access and implantation of DBT skills. In addition, we have to move forward on telepsychology applications by consulting our patients, younger peers and experts in adjacent fields if we want DBT to remain effective and relevant in the digital age.


## Background

Telepsychology[1], i.e., the provision of psychological services using telecommunication or digital technologies (e.g., internet, telephone applications and virtual reality), is on the rise (Andersson & Titov, 2014; Joint Task Force, 2013; Lannin & Scott, 2014; Shore et al., 2018; Smoktunowicz et al., 2020). COVID-19 accelerated this trend (van Daele et al., 2020). However, a scoping review about the efficacy and clinical utility of telepsychology in DBT is lacking. The aim of the current review is to help DBT-therapists make empirically supported decisions about the use of telepsychology during and after the current pandemic and to anticipate the changing digital needs of patients and clinicians.

Standard DBT is an empirically supported, cognitive behavioral treatment for adults and adolescents suffering from chronic suicidal and self-harming behavior, characteristic for borderline personality disorder (BPD) (Fernández-Álvarez & Fernández-Álvarez, 2021; McMain et al., 2009). DBT is a comprehensive program that consists of four primary modes of treatment delivery, to address the multiple needs of suicidal patients (Linehan, 1993; McMain et al., 2009). In individual therapy, patients figure out how they can take realistic steps to a life worth living and how to stay motivated. In skills training, the focus is on acquiring skills from trainers and peers. Consultations outside of office hours, preferably by the individual therapist, facilitate generalization of skills to situations where patients need them the most, e.g., during suicidal crises. Even though this mode is often called “phone consultation”, DBT-teams have used all kinds of technology to stay in touch with clients (Linehan, 2015). The therapist consultation team, lastly, helps individual therapists and skills trainers to deliver adherence treatment and remain motivated throughout the process (Linehan, 1993; McMain et al., 2009).

Although primarily designed for suicidal and self-harming behavior, DBT remains effective when tailored to fit the needs of other clinical populations, age groups, or treatment settings (Chapman, 2018; Swales, 2018). A significant part of this customizability relates to the underlying treatment rationale, Marsha Linehan’s biosocial theory. This theory explains maladaptive behavior, including suicidal behavior and non-suicidal self-injury (NSSI), as manifestations of pervasive emotion dysregulation or as ways of coping with it (McMain et al., 2009; Sinnaeve et al., 2018). Emotion regulation capacity is a transdiagnostic and dimensional construct, assumed to play a key role in a broad range of mental illnesses (Caspi

1 Standard terminology is lacking as yet (Mulay et al., 2019), reason why we use the term telepsychology to broadly refer to concepts such as e-health, telemedicine, telepsychiatry, digital health, teletherapy.

& Moffitt, 2018; Ruggero et al., 2019; Sinnaeve et al., 2018; Sloan et al., 2015). Especially the DBT skills training is evolving from a treatment mode for suicidal patients with BPD to a transdiagnostic intervention (McMain et al., 2009). Telepsychology is increasingly being used in DBT supervision and -training for professionals (Carmel et al., 2016; Dimeff et al., 2009; Dimeff et al., 2015; Dimeff et al., 2011; Kauth et al., 2017; McCay et al., 2017; Worrall & Fruzzetti, 2009) and in mental health care in general (De Witte et al., 2021; Nicholas et al., 2021). Arguments both in favor and against such an evolution can be made. On the one hand, evidence suggests that the efficacy of telepsychology is comparable to face-to-face care in diverse populations and settings (Barak et al., 2008; Hilty et al., 2013; Nelson & Sharp, 2016). On the other hand, studies about telepsychology have primarily focused on short-term effects (Berryhill et al., 2019; Berryhill et al., 2019; Bolton & Dorstyn, 2015). In addition, there is insufficient research to consider any telepsychology intervention as evidence-based for suicidal ideation, self-harm or BPD (Ilagan et al., 2020; Stefanopoulou et al., 2020). However, a comprehensive overview of research regarding the use of telepsychology in DBT is lacking.

We conducted a scoping review to fill this research gap (Tricco et al., 2018). Since we are interested in the use of telepsychology in DBT in all of its capacities and welcome the evolution toward dimensional theoretical constructs in psychiatry, we did not restrict ourselves to one specific diagnostic category. The overarching aim was to document the best available research evidence regarding the efficacy and clinical utility of telepsychology in DBT. In doing so, we used the definitions of the American Psychological Association (APA) (APA, 2002; APA Presidential Task Force on Evidence-Based Practice, 2006). *Treatment efficacy* referred to the scientific evaluation of whether a treatment works. *Clinical utility* comprised the applicability, feasibility, and usefulness of the intervention in specific situations, as well as the generalizability of an intervention whose efficacy had been established (APA, 2002; APA Task Force, 2006). To obtain a detailed overview, we reviewed all types of research evidence (i.e., clinical opinion, observation, consensus among recognized experts, systematized clinical observation, quasi experiments, randomized controlled trials) that could help answer our research questions. At the same time, we took the difference in methodological quality into account when interpreting the results (De Vet et al., 1997; Valentine & Thompson, 2013). Within our overarching aim, we had three specific research questions (RQ):

RQ1:What do we know about the efficacy and clinical utility of telepsychology in standard DBT, i.e., using telecom for between-session-contact, in support of skills generalization?





RQ2: To what extent is telepsychology equivalent or superior to face-to-face contact in other modes of DBT treatment, i.e., individual therapy, skills training, consultation team?

RQ3: Does the addition of telepsychology to standard DBT modes, -strategies, -procedures and skills increase the efficacy or clinical utility of DBT?

## Methods

### Criteria and identification of studies

A search was conducted in PubMed, Embase, PsycARTICLES and Web of Science (WoS) until the 9th of March 2021, following PRISMA-ScR guidelines (Tricco et al., 2018). Search terms for telepsychology were included and combined with search terms that relate to DBT. Search terms (additional file 1) and syntax (additional file 2) were modified as necessary for each database. Only 1) English, French, German and Dutch manuscripts from 2) peer-reviewed sources, that 3) provided quantitative or qualitative research evidence 4) on efficacy or clinical utility of 5) the use of digital technology 6) in DBT treatment or 7) implementation of telepsychology in DBT treatment were considered. To identify other potentially relevant studies we 1) crosschecked the reference lists and citing articles of identified studies, 2) checked the references of *The Oxford Handbook DBT* (Swales, 2018), and 3) screened the references of *Phone Coaching in Dialectical Behavior Therapy* (Linehan, 1993) (Figure 1).

### Selection of studies

All records from the database searches were imported in EndNote. This collection was electronically and manually deduplicated. The titles and abstracts were screened for eligibility by two review authors independently (HvL, RS). Records that clearly did not fulfill the criteria were excluded. The remaining references were made available in full text and assessed for eligibility by the same two review authors (HvL, RS) (additional file 3). Conflicting decisions were discussed until agreement was reached. If necessary, we consulted with two other authors (UW, LvdB).

For the randomized controlled trials (RCTs) and pre-post studies, detailed descriptions of design, participants, experimental and comparator interventions, measures, and statistical significance of changes in the primary outcome variables can be found in Table 1. If an effect was significant, we also reported Cohen's d or calculated it ourselves, following the formulas and procedures mentioned in Lakens et al. (2013). In the results section, we go over the main findings per research question and per technology.

# Results

## Sample of studies

The original database search yielded 804 reports. Cross-checking and screening *The Oxford Handbook DBT* and *Phone Coaching in Dialectical Behavior Therapy* resulted in 10 records. This sample of 814 records contained 196 duplicates. After screening titles and abstracts, 83 references were selected as potentially eligible, of which 41 clearly met the inclusion criteria (Figure 1). A detailed overview of the 83 full-text articles that we assessed, and the reason why specific articles were excluded, can be found in additional file 3.

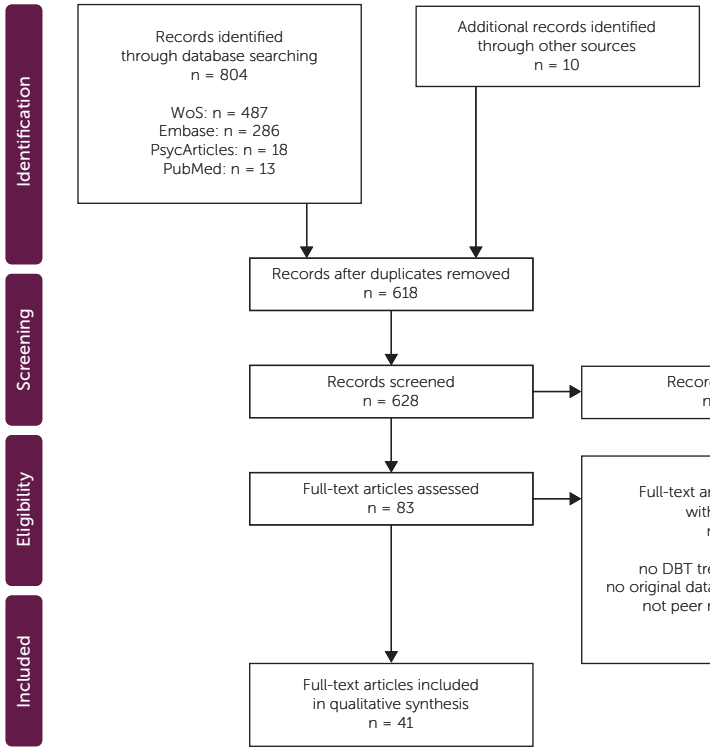



**Figure 1.** PRISMA Flow Diagram of literature search and selection.

## Study characteristics

In total, 41 studies were selected. The majority of the studies consist of observational data, secondary analyses, focus groups and surveys, patients' opinions and expert opinions. Eighteen out of 41 studies focused on the frequency, efficacy and utility





of phone consultation. Nine studies focused on the added value of smartphone applications. Nine studies focused on internet delivered skills training. Four studies focused on virtual reality in DBT. One study focused on a computer program and one study focused on learning a DBT skill by means of video. All studies were in the initial stage of clinical research (i.e., feasibility, acceptance, usability).

RCCS, Rovai Community Connection Scale; DBT-WCCL, Dialectical Behavior Therapy Ways of Coping Checklist; DERS, Difficulties in Emotion Regulation Scale; AAQ , Acceptance and Action Questionnaire; PHQ-9, Patient Health Questionnaire-9; OASIS, Overall Anxiety Severity and Impairment Scale; KIMS, Kentucky Inventory of Mindfulness Skills; OQ-'45, Outcome Questionnaire 45-item version; CSQ, The Client Satisfaction Questionnaire; GAD-7, General Anxiety Disorder-7; BDI, Beck Depression Inventory; BSI, Brief Symptom Inventory & GSI, Global Severity Index (mean of all BSI items); GAF, Global Assessment of Functioning via the SCID-I, Structured Clinical Interview for DSM-IV Axis I Disorders; n.s, not statistically significant; n.c; non calculable; SITBI, Self-Injurious Thoughts and Behaviors Interview; OASIS, Overall Anxiety Severity and Impairment Scale; PHQ-9, Patient Health Questionnaire-9; OAKQ, Opposite Action Knowledge Questionnaire; SSI, Scale for Suicide Ideators; AUDIT, Alcohol Use Disorders Identification Test; TLFB, Timeline Follow back;

[1] every time the DBT Coach was activated questions about emotional intensity (a) and urges to use substances (b) were assessed

[2] short questionnaire at the end of each day to rate their highest urge to use substances (a), how helpful the DBT Coach app (b) and the Opposite Action skill (c) were that day

[3] a 7-item self-report measure Behavioral Confidence Questionnaire

[4] therapists were asked to rate their patients 'skill use in general (a) and the use of the opposite action skill before and after using the DBT Coach application (b). In addition, they asked therapists to count the number of phone calls outside the sessions two weeks before and after the use of de DBT Coach application (c)

**Table 1.** Summary of the primary outcomes of randomised controlled trials (RCTs) and pre post studies using classical statistics.

| Study | Design | Participants | Technology | Experimental intervention | Comparator Interventions | Measures | Cohen's d | Test-scores & p-values |
|---|---|---|---|---|---|---|---|---|
| *Lopez (2020)* | Post-only | Adults diagnosed with depression, bipolar disorder or anxiety disorder.<br><br>N: 15 + 20<br><br>Age *M (SD):* 40 (16) | Videoconferencing | Two **weekly DBT skills training group online** via Video Teleconferencing (VTC) | Two weekly DBT skills training group face to face | *Efficacy*<br>RCCS<br><br>Utility<br>Satisfaction | | $t(24) = 3.7, p = .001$<br><br>$t(24) = 1.39, p = .19$ |
| *Lungu* (2015) | Pre-post | Adults with a wide range of psychopathology<br><br>N: 25<br><br>Age M (SD): 44 (15) | Internet delivered skills training | An 8 week **online trans-diagnostic DBT skills training** for Emotion Regulation (iDBT-ER) | None | *Efficacy*<br>DBT-WCCL<br>DERS<br>AAQ<br>PHQ-9<br>OASIS<br>KIMS<br>OQ-45<br><br>*Utility*<br>CSQ | $d = 1.11$<br>n.c.<br>n.c<br>$d = 0.69$<br>$d = 0.89$<br>$d = 0.02$<br>$d = 1.00$ | $F(1, 45.32) = 28.67, p <. 01$<br>$F(1, 42.73) = 30.53, p < .01$<br>$F(1, 23.64) = 21.98, p < .01$<br>$F(1, 24.35) = 22.20, p < .01$<br>$F(1, 44.30) = 9.05, p < .01$<br>$F(1, 22.49) = 18.38, p <. 01$<br>$F(1, 24.05) = 22.55, p <. 01$ |
| *Navarro-Haro (2019)* | Pre-post | Adults diagnosed with a Generalized Anxiety Disorder according to the MINI<br><br>N: 19<br><br>Age M (SD) : 44 (10) | Virtual Reality | Six one hour Mindfulness Based Intervention (MBI) group sessions plus six ten minutes additional **Virtual Reality** Mindfulness Skills Training (VR DBT) individual | None | *Efficacy*<br>GAD-7* | $d = 1.33$ | $\beta = -4.38, p < .001$ |
| *Rizvi* (2011) | Pre-post | Adults diagnosed with BPD and had a comorbidity with substance abuse disorders who had been in DBT treatment for at least 2 months, and their therapists.<br><br>N: 22<br><br>Age M (SD) : 34 (10) | Mobile (web) Application | 10 to 14 days access to **DBT coach application** for smartphones, to enhance generalization of the emotion regulation skill of opposite action in an interactive way, as an add-on for patients who were participating in a standard DBT program | None | *Efficacy*<br>DBT Coach Data[1]<br>(a) emotional intensity<br>(b) urges to use substances<br><br>Daily assessments for patients[2]<br>(a) urge to use substances<br>(b) how helpful is the DBT Coach app<br>(c) how helpful is the Opposite Action skill | a) $d = -1.32$<br>b) $d = -0.90$<br><br>a) $d = -0.48$ | a) $t(21) = -6.17, p < .001$<br>b) $t(21) = -4.22, p < .001$<br><br>a) $t(21) = -2.26, p = .035$<br>b) $t(21) = -1.14, p = .269$<br>c) $t(21) = .67, p = .508$ |

**Table 1.** Continued.

| Study | Design | Participants | Technology | Experimental intervention | Comparator Interventions | Measures | Cohen's d | Test-scores & p-values |
|---|---|---|---|---|---|---|---|---|
| *Rizvi* (2011) | | | | | | Confidence in executing opposite action[3] | *d* = 0.59 | *t*(21) = 2.93, *p* = .008 |
| | | | | | | BDI | *d* = 0.55 | *t*(21) = 2.69, *p* = .014 |
| | | | | | | BSI | *d* = 0.43 | *t*(21) = 2.49, *p* = .021 |
| | | | | | | "Therapist Questionnaire"[4]<br>(a) patients skill use in general<br>(b) the use of the opposite action skill before and after using the DBT Coach application<br>(c) number of phone calls outside the sessions | b) *d* = - 0.84 | a) *t*(21) = -1.06, *p* = .30<br>b) *t*(21) = -2.79, *p* = .01<br>c) *t*(21) = 1.15, *p* = .26 |
| *Rizvi* (2016) | Pre-post | Adults diagnosed with BPD and had a recent history of repeated nonsuicidal self-injury (NSSI)<br>N: 16<br>Age *M* (*SD*) : 28 (8) | Mobile (web) Application | **DBT coach application** for smartphones, a mobile web app to enhance generalization of mindfulness, emotion regulation, interpersonal effectiveness and distress tolerance skills in an interactive way, as an add-on for patients who were participating in a standard DBT program | None | *Efficacy*<br>GAF<br>GSI<br>BSI<br>DERS<br>SITB<br>DBT-WCCL | | n.s.<br>"<br>"<br>"<br>" |
| *Salamin (2020)* | Pre-post | Adults diagnosed with BPD who 1) were participating in a standard DBT program in the period of interest (i.e., 8 weeks before confinement and 8 weeks during confinement) and 2) filled out the online diary cards.<br>N: 7<br>Age *M (SD)*: 35 (12) | Telephone consultation and videoconferencing | 6 weeks of **individual therapy and DBT skills training by means of telephone consultation or videoconferencing.** Skills training was limited to 45 minutes (instead of two hours) per week and was provided individually. Adaptions were necessary to continue standard DBT during lockdown. | None | *Efficacy*<br>#Suic. behaviour/ week<br>#NSSI/ week<br>#Alcohol/ week<br>#Binge-eating/ week<br>Suic. ideation/ day<br>Fear/ day<br>Shame/ day<br>Tension/ day<br>Distress/ day | <br><br>n.c.<br>n.c.<br><br>*d* = -0.42<br>*d* = -0.34<br>*d* = -0.01<br>*d* = -0.17 | <br>n.s.<br>n.s.<br>F(1, 63.1) = 3.1, p = .08<br>F(1, 63.5) = 4.3, p = .04<br>β = − 0.00, p = .964<br>β = − 0.59, p < .001<br>β = − 0.48, p < .001<br>β = − 0.35, p = .029<br>β = − 4.57, p = .030 |

**Table 1.** Continued.

| Study | Design | Participants | Technology | Experimental intervention | Comparator Interventions | Measures | Cohen's d | Test-scores & p-values |
|---|---|---|---|---|---|---|---|---|
| *Schroeder* (2018) | Pre-post | Adults diagnosed with depression (52%), General Anxiety Disorder (48%), Borderline Personality Disorder (40%), PTSD (27%), Bipolar Disorder (14%)<br>N Tot : 73<br>Age *M*: 37 | Mobile (web) Application | **28 days of semi-personalized text messages** in the morning to motivate people to use **"Pocket Skills",** a mobile web app containing written information, videos, and a conversational agent (avatar of M. Linehan) offering information on the basics of DBT, DBT skills and a DBT diary card. | None | *Efficacy*<br>OASIS<br>PHQ-9<br>DBT-WCCL | <br>n.c.<br>n.c.<br>n.c. | <br>$\beta$ = -0.66, $p$ < .001<br>$\beta$ = -0.79, $p$ <.001<br>$\beta$ = -0.06, $p$ <.001 |
| *Waltz (2009)* | RCT Cross-over | Adults diagnosed with BPD according to SCID II, naïve to DBT<br>N: 15 + 15<br>Age *M* (*SD*): 33 (9) | Video | **Video** of Marsha Linehan teaching the 'opposite action' skill step by step from the emotion regulation module of DBT. | Episode from a serie called *The Desert Speaks* on the culinary, medicinal and scientific uses of pepper plants. | *Efficacy*<br>OAKQ | $d$ = 0.8 | $F$ = 18.74, $p$ <.001 |
| *Wilks (2018)* Wilks (2017) | RCT Cross-over | Adults diagnosed with BPD that show suicidal behaviour and heavy episodic drinking.<br>N: 29 + 30<br>Age *M* (*SD*): 38 (10) | Internet delivered skills training | **Internet-delivered DBT skills training** (8 sessions, consisting of mindfulness, reducing problematic drinking, emotion regulation and distress tolerance) and daily emails and/or text messaging for motivation. | Waiting list | *Efficacy*<br>SSI<br>AUDIT<br>TLFB<br>DERS | <br><br><br>n.c.<br> | <br>$\beta$ = − 1.08, $p$ = 0.22<br>$\beta$ = − 2.05, $p$ = 0.09<br>$\beta$ = 0.81, $p$ = 0.02<br>$\beta$ = − 4.57, $p$ = 0.18 |

## Efficacy and clinical utility of telecom for between-session-contact, in support of skills generalization (RQ1).

### *Telephone*

Looking first at the treatment efficacy, we did not find any RCTs or pre-post studies about the added value of phone consultation in DBT. However, there are articles that contain data on phone consultation frequency and associations with treatment outcome. **Chalker** et al. (2015) investigated the association between phone calls, satisfaction (patients and therapists), and treatment outcome (patients) in a standard DBT program with adults diagnosed with BPD. More frequent between-session contact was significantly associated with client satisfaction, therapist satisfaction, treatment retention and decrease in psychosocial problems. There was no association between violation of personal limits regarding phone calls and any of the outcome measures. **Oliveira and Rizvi** (2018) studied the frequency of phone calls and text messaging in a sample of patients with BPD who were participating in six months of standard DBT. Results showed that therapists received an average of 2.55 phone calls a month. **Limbrunner** et al. (2011) investigated DBT phone consultation to reduce eating disorder-related urges in DBT for eating disordered adults. Results indicated that the average number of calls ranged between 0 to 4 calls per day. The duration of the phone consultation range between 1 to 30 minutes, with an average of 6 minutes.

The other studies focus on the clinical utility of phone consultation. **Linehan** formulated most of her expert opinions regarding phone consultation in the DBT treatment manual (1993). In later articles (Linehan 1993, Linehan 2011) she highlighted aspects of this mode of treatment and substantiates the assumption that

DBT reduces the contingency of between-session contact and suicidal behavior. Linehan emphasizes the importance of *timing*, i.e., calling before self-destructive behavior takes place, and *content*, i.e., focused on skills in a 'matter of fact' tone. She also asserts that the individual therapist is best placed to provide phone consultation, since it is the only person who can assuage relationship cracks between sessions, knows the patients' learning history and current skills, and can discuss the chain of events that led up to the consultation. At the same time, Linehan accentuates the necessity of teaching the patient skillful ways of asking for help (i.e., "making the therapist want to talk to them on the phone"), because it can be life saving for chronic suicidal patients. This requires firm but flexible use of personal limits that may vary by patient, time and context.

In response to the first RCT of **Linehan** et al. (1991), on the effectiveness of DBT, R.E. Hoffman wrote 'a letter to the editor' (1993) where several comments and questions about the trial were posed, including the comment that for the treatment as usual (TAU) condition, telephone consultation 24/7 is not feasible. Linehan and Heard acknowledged that the availability of therapists probably had been greater in DBT compared to TAU. However, the actual amount of telephone calls per month did not differ. Linehan and Heard also pointed out that there was no correlation between the number of phone calls and the number of parasuicide episodes in DBT, in contrast to TAU, where such a correlation was found.

Implementation studies and expert opinions provide some additional insight in the clinical utility of telephone consultation in DBT. **Chugani and Landes** (2016) conducted a survey amongst clinicians to investigate the implementation of DBT in College Counseling Centers. A frequently reported barrier to implement the standard DBT program was the unwillingness of individual therapists to offer phone consultation. **Flynn** et al. (2020) reported similar findings in a survey exploring challenges experienced by clinical sites of implementation of DBT in community settings. Common issues concerned therapists' reluctance, lack of management support and issues regarding clinical responsibility. **Landes** et al. (2016; 2017) made a step-by-step inventory of the implementation process of DBT in the Veterans Health Administration (VHA) healthcare system. Barriers in the implementation of DBT in a routine setting, rated as 'unable to overcome', were all related to phone consultation. In **Landes** et al. (2021), the authors identify four specific challenges and solutions with regard to phone coaching: 1) 'tools' such as work telephone, laptop that gives access to the electronical medical records of patients, organizational policies and procedures, 2) compensation for after-hours phone coaching, 3) willingness of clinicians to provide phone coaching and 4) consistent program and leadership support.





**Manning** (2011), **Koons** (2011) and **Ben-Porath** (2004; 2005; 2011; 2015), describe how to carry out phone consultations. They emphasize the importance of explaining in detail the essence and the works of phone consultation to the patient, resulting in an agreement. When carefully introduced at forehand, patients will be more aware of the contingencies of problem behavior. Based on clinical experience, myths are confronted that exist about the expected disastrous impact of phone consultation on the therapists' life and professional career (among others: being called each night, burnout, inadvertently reinforcing maladaptive behavior and thus enhancing suicide risk, risk of being sued). At the same time, common errors (among others: failure to orient patients, errors concerning contingency management, using phone consultation for other needs than skill generalization, contact recovery or encouragement, setting limits when they are not crossed) and the need of support, validation and problem solving in the therapist consultation team are discussed. Finally, **Steinberg** et al. (2011) emphasizes the importance of making informed decisions concerning parental involvement in phone consultation, therefore they wrote a decision-tree to assist in determining when parental involvement is necessary with adolescents.

### *Videoconferencing*

**Chu** et al. (2015) describe two case studies on the DBT school refusal (DBT-SR) program. In this program, DBT strategies were used to target emotional and behavioural dysregulation (including internalizing problems like anxiety and depression) in youth that refuse to go to school. DBT for adolescents (DBT-A) (Miller et al., 2007) served as the foundation for DBT-SR. Chu et al. added Web-Based Coaching (WBC), via video-conferencing, to the traditional option of phone consultation. This way, both youth and parents could be present and the therapist could directly observe and coach interactions among multiple family members. WBC sessions lasted 5 to 30 minutes and had a flexible format. The frequency depended on the number of school days the youth had missed the previous week. Results of two case studies show that WBC seemed to provide unique value that improved generalizability of skill acquisition and a sense of support. Both youth, parents and therapists commented that WBC helped increase morning structure, provided real-time assessment and encouragement/support, and helped youth and parents practice skills at critical times.

## Efficacy and clinical utility of telepsychology in other modes of treatment, i.e., individual therapy, skills training, consultation team (RQ2).

### *Internet*

We found two controlled trials about the efficacy of internet-delivered DBT skills training. **Lungu** (2015) developed and evaluated the effectiveness of a computerized, transdiagnostic DBT skills training for Emotion Regulation (iDBT-ER) for adults with a wide range of psychopathology. This online intervention consisted of eight one-hour weekly sessions: the first two sessions focused on mindfulness skills, followed by six sessions on emotion regulation skills. Every session followed the same structure: an overview of session material, mindfulness practice, homework review, teaching new skills (using videos), practicing new skills (variety of online assignments), assigning new homework and anticipating potential obstacles. Results of this pilot were compared to a matched historical control group who received face-to-face DBT skills training (DBT-ST). Participants of the iDBT-ER reported progress in all of the primary outcomes, namely emotion dysregulation, psychopathology (anxiety, depression), general distress, DBT skills practice and mindfulness skills practice. Compared to the historical control group, pre-post effect sizes were similar for skills practice. Pre-post effect sizes were lower for iDBT-ER concerning anxiety, depression and general distress. Compared to DBT-ST, iDBT-ER reported a strong and significant increase in self-reported mindfulness (See Table 1).

**Wilks** et al. (2017; 2018; 2020) performed an RCT to evaluate the feasibility, acceptability and efficacy of an eight-session internet delivered DBT skills training intervention (iDBT-ST), for suicidal adults who engage in heavy episodic drinking. Each session lasted approximately 30–50 minutes and included 2–3 new DBT skills. Each skill was introduced via a short video. Finally, participants engaged in interactive and guided practice. At the end of each session, participants selected a homework exercise. Participants received DBT worksheets and were encouraged via daily emails and/or text messaging. One third of all participants completed the training. No clinical differences were found between drop-outs and completers of iDBT-ST (See Table 1). Results showed that technical problems appeared to pose barriers to treatment feasibility and completion. However, over the four-month study period, an immediate and significant reduction in suicidal ideation, alcohol use, alcohol quantity and frequency and emotion regulation compared to the waiting list controls was found, with large effect sizes for suicidal ideation and alcohol consumption.





### *Videoconferencing*

**Salamin** et al. (2020) compared the diary card data of seven patients suffering from borderline personality disorder during two periods: eight weeks prior to confinement (i.e., set of measures to slow down the spread of COVID-19) and during eight weeks of confinement. From the 16th of March 2020 to the 26th of April 2020, individual therapy, DBT skills training and consultation team meetings were only possible by means of phone consultation or videoconferencing. Moreover, DBT skills training was limited to 45 minutes (instead of two hours) per week and was provided individually. Using a multilevel approach, they found a significant decrease in self-reported binge-eating, fear, shame/ guilt and tension even when they switched to videoconferencing. At the same time, problem behaviours including suicidal behaviour, NSSI, anger outbursts, and experiences including sadness, anger, happiness, emptiness and suicidal ideation did not change significantly in this period of time. Self-reported distress increased significantly (See Table 1).

**Lopez** et al. (2020) performed a pilot study comparing group cohesion between patients who participated in a DBT skills training group via Video Teleconferencing (VTC) and an in-person DBT group. The primary diagnosis of the patients was depression but patients with bipolar and anxiety disorders were also included. Results show that the relationship with the facilitator and the feeling of their learning capacity did not differ between the two groups. There was a significant difference on the relation to member interaction and group cohesion between the two groups (Table 1). The VTC group found it harder to connect with each other in the virtual environment. Compared to the in-person DBT group, the VTC group had a significant better attendance although they reported that attending the group via telehealth would not have been their first choice. Treatment via VTC was preferable to no treatment at all.

Concerning the clinical utility, one survey study and one expert opinion was found. **Lakeman** and **Crighton** (2020) conducted a survey amongst clinicians to explore the impact of the COVID-19 measures on various DBT programmes for patients with BPD and obstacles to engaging with patients and colleagues via online platforms. Results show that the primary obstacles to providing DBT via online platforms were service and clinician centred obstacles. Few clinicians expressed confidence in being able to adapt to online DBT. Clinicians had no experience of using online platforms and some did not have access to internet or privacy in their home environment. The authors concluded that clinicians need to be supported through education, supervision and coaching in the use of telehealth interventions.

**O'Hayer** (2021) highlighted challenges and opportunities of comprehensive DBT for BPD via the online video conferencing platform ZOOM. Challenges in the skills training were that patients tended to get distracted, feel ashamed or disconnect. Opportunities included using the chat function to communicate with participants, spontaneous 'virtual tours' during the break and the ability to choose a screen name. Challenges for the individual treatment were less engagement and increased concerns about the therapist being distracted. Overall, patients reported that they felt less connected.

### *Video*

**Waltz** et al. (2009) performed an RCT to evaluate the feasibility of a psychoeducational video to learn adults with BPD naïve to DBT a novel DBT skill. In the experimental condition participants viewed the experimental video first and watched the control video after a week (designed to control time, attention and repeated testing). In the control group the order was reversed. Follow up was one week later. In the experimental video Marsha Linehan taught 'opposite action', part of the emotion regulation module of DBT (Linehan, 1993). Twenty percent of the participants dropped out. All remaining participants used the opposite action skill one or more times in the week after watching the experimental video. At follow-up, a significant reduction in painful emotions was reported as well as an increase in knowledge, increase in expectations of a positive outcome, and high satisfaction after watching the video of opposite action (Table 1).

## Efficacy and clinical utility of adding telepsychology to standard DBT modes, -strategies, -procedures (RQ3).

### *Mobile (web) Application*

Four trials provided data on the efficacy and clinical utility of DBT mobile applications. **Rodante** et al. (2020) investigated the acceptability and preliminary effectiveness of an interactive mobile-health application in eighteen adults who participated in DBT at least a month and showed suicidal behaviours or NSSI. The app, named CALMA, provided DBT skills and evidence-based tools to prevent suicide. There were four modalities: "out of crisis", "I need help", "problem-solving" and "emergency". The emergency modality provides users with their emergency contacts and the possibility to share their location with others. It is automatically activated if the app detects that distress does not decrease after three attempts to use skills. Bayesian analysis[2] showed a high probability of decreased suicidal

2 Because of the difference between 'classical' null-hypothesis significance testing and Bayesian procedures, we decided to cite the primary outcomes of Rodante et al. in the text instead of Table 1





ideation (p = .966), suicidal plan (p = .849), suicidal gesture (p = .760), thoughts about NSSI (p = .909) and NSSI (p = .826) in the group where CALMA was added to DBT. The authors reported a high probability of a greater decrease in suicidal ideation and NSSI in DBT + CALMA, compared to DBT only. However, all interval of the comparisons included zero. The app also showed good acceptability by users.

**Rizvi** et al. (2011) explored the feasibility of a DBT Coach smartphone app for the emotion regulation skill 'opposite action'. Adults diagnosed with BPD and a comorbidity with substance abuse disorders, already in standard DBT treatment, received a smartphone with the app for 10-14 days, which they could use whenever needed. The app consisted of instructions on how to apply the opposite action skill, and mindfulness. Each app usage started and ended with a rating on emotional intensity and urges to use drugs on a 0-10 Likert scale. The app was on average used 15 times over the course of 13 days. Participants reported that the use of the app strengthened their knowledge and self-efficacy in execution of the skill. The intensity of the emotions and the urge to abuse substances decreased significantly after usage and finally a decrease in depression, psychological distress and in overall substance use during the trial was found (See Table 1). An extended version of the DBT Coach was evaluated by **Rizvi**, Hughes and Thomas (2016). The app was used by adults diagnosed with BPD and had a recent history of NSSI. The app was used as an add on to 6 months of standard DBT. The app included skills from mindfulness, emotion regulation, interpersonal effectiveness and distress tolerance. Results showed a reduction in distress and in urges of self-harm directly after using the app. Frequency of use did not correlate with treatment outcomes, except for the frequency of NSSI episodes, where higher use led to fewer episodes (See Table 1). Over 90% of the participants reported that the app was easy to understand and to use, and that they would use the app if available outside the trial.

**Schroeder** et al. (2018) developed "Pocket Skills", a mobile web app that uses texts, videos and images of Marsha Linehan to teach DBT-skills (i.e., basics, mindfulness, emotion regulation, distress tolerance and addiction). A conversational agent promotes engagement to the app and use of the skills. Pocket Skills also gives access to a DBT diary card day by day. Participants were adults diagnosed with depression, Generalized Anxiety Disorder (GAD), BPD, Post Traumatic Stress Disorder (PTSD) or bipolar disorder. Schroeder et al. conducted a 4-week field study. Participants were randomized in two groups. The experimental group received semi-personalized text messages each morning like '*One of your mindfulness goals is to reduce pain, tension and stress! Keep practicing*

*mindfulness skills!*'. The other group received non-personalized text messages. Depression, anxiety and dysfunctional coping decreased, and the use of DBT skills increased (Table 1). Participants who received daily semi-personalised messages practiced more skills, which resulted in faster improvements. However, we found no information about the randomization process and the number of participants in each group. The app was rated 'very usable'. Exit-survey data confirmed that Pocket Skills helped patients to stay engaged in DBT and practice their skills.

Four articles contained descriptions of clinical utility by opinions and qualitative data on DBT-applications for smartphones and tablets. **Austin** et al. (2020) evaluated a smartphone application that was developed to support DBT. Participants who were receiving DBT used the app. Overall, there was a positive perception of the app's efficacy and usability. **Helweg-Joergensen** et al. (2019) developed a smartphone application as an adjunct to DBT to fill in DBT diary cards, called mDiary. Adults who were enrolled in active DBT treatment used the app for at least four weeks. The diary card data could be consulted by therapists online. The authors concluded that the mDiary App was an acceptable and relevant innovation for both patients and therapists, although patients experienced a better usability than therapists. **Cristol** (2018) describes the perspective of one BPD patient in DBT on how using technology in DBT can be validating and helpful in discovering typical responses to common stressors. This patient tried several mobile applications and found 'Daylio' most useful. The usage of this app helped this patient to minimize stigma as using a smartphone is a common habit, in contrast to filling our diary cards using paper and pencil. **Washburn** and **Parrish** (2013) described their experience with the DBT Self-Help mobile application, that gives access to key DBT skill sets such as mindfulness, distress tolerance, emotional regulation and interpersonal effectiveness. They recommended the application for patients already enrolled in a DBT program.

### *Virtual Reality*

Looking first at the treatment efficacy, **Navarro-Haro** et al. (2019) evaluated the virtual reality Dialectical Behavior Therapy (VR DBT) mindfulness skills training in a pre-post study with patients with a GAD. Patients were randomly assigned to a Mindfulness-Based Intervention (MBI) with or without 10 minutes of VR DBT Mindfulness skills training. The MBI consisted of seven modules, once a week. Following the first six sessions of the MBI, half of the participants also took part in six individual ten-minute sessions of VR DBT mindfulness skills training. During the VR DBT mindfulness skills sessions, a participant made use of a headset, float down a 3D computer-generated river while listening to one of three mindfulness





skills training audio tracks. The audio tracks were 'observing sound', 'observing visuals' and 'wise mind'. Both groups showed a significant decrease in GAD symptoms (see Table 1). The MBI plus VR DBT group retained significantly more participants than the MBI group alone. Additional pre-post improvements showed that the MBI plus VR DBT group improved in the non-judging facet of mindfulness, the interference subscale of the Emotion Regulation Scale and the state of relaxation after all the VR DBT sessions.

There are three studies concerning the clinical utility of virtual reality. First, **Navarro-Haro** et al. (2016) investigated the clinical utility of virtual reality (VR) by using immersive VR to facilitate mindfulness skills training in DBT, as described above. They wrote a case study of a 32-year-old woman diagnosed with BPD and substance use disorder who received standard DBT. Key measurements were administered before and after each VR DBT mindfulness skills training session and results showed that urges to commit suicide, self-harm, quit therapy, use substances and negative emotions measured by the diary card were all reduced after each VR mindfulness session.

**Gomez** et al. (2017) used the VR DBT mindfulness skills training in a case study of a 21-year-old male with severe skin burn covering one third of his body. The primary assessment consisted of measurements of post-traumatic stress disorder, mindfulness acceptance and positive and negative emotions before and after each VR DBT skills training. Results show that the patient accepted the VR DBT and wanted to continue using mindfulness. There was a small reduction in PTSD symptoms after four VR DBT sessions and the reduction in negative emotions was most pronounced after the first VR DBT session but decreased even more the second time and stayed near zero the third and fourth time. Positive emotions were very high after the VR DBT sessions. The same virtual reality enhanced DBT mindfulness skills training was used by **Flores** et al. (2018). They describe a case study investigating the feasibility of the virtual reality enhanced DBT (VR DBT) mindfulness skills training for two patients with spinal cord injury. The primary assessment consisted of measurements of depression, anxiety and positive and negative emotions before and after each VR DBT skills training. Results showed that patients not only accepted VR as part of their treatment, but also liked using it. Both patients showed a reduction in ratings of depression, nervousness/anxiety and reported being less emotionally upset after the VR DBT skills training. Patient 1 showed also a reduction of negative emotions, where the negative emotions of patient 2 increased directly after the VR DBT mindfulness skills session.

### *Computer program*

**Görg** et al. (2016) examined the acceptance and feasibility of the computer program MORPHEUS, as a part of a Dialectical Behavior Therapy Post Traumatic Stress Disorder (DBT-PTSD) residential treatment, that allows computer-assisted in sensu exposure and exercise in self-management during the treatment of PTSD. MORPHEUS can be used to record, and listen to the recordings of, in sensu exposure sessions. Meanwhile playing the recorded sessions patients monitor their level of distress and state dissociation. If the level of state dissociation is too high, MORPHEUS offers one of the 15 diverse skills in order to regulate themselves. Patients received a 12-week multicomponent residential treatment based on the principles of DBT. All participants were diagnosed with PTSD and used MORPHEUS as often as it was required in the standard DBT-PTSD protocol, that is, at least 2 to 5 times a week. Results show that patients found the skills helpful to block dissociation and wanted to use the program again in therapy and would recommend this program to a friend. Meanwhile, patients rather used their DBT skills during exposure instead of using the digital skills in MORPHEUS.

## Discussion

We conducted a scoping review to help DBT-therapists make empirically supported decisions about the use of telepsychology during and after the current pandemic and to anticipate the changing digital needs of patients and clinicians.

Our first focus was the efficacy and clinical utility of telepsychology in standard DBT, i.e., using telecom for between-session-contact, in support of skills generalization. The literature provides us with valuable information about using telephone and videoconferencing to support this mode of treatment. Despite the fact that telephone was the first technology that was used to provide between-session coaching, quantitative information on efficacy and utility of phone coaching by the individual therapist remains limited. We found data about frequency of out of session contact (Chalker et al., 2015; Limbrunner et al., 2011; Oliveira & Rizvi, 2018), percentages for which calls are made in telephone consultation (Limbrunner et al., 2011; Oliveira & Rizvi, 2018), associations between out of session contact and decrease in drop out and greater change of psychological symptoms (Chalker et al., 2015). However, an RCT about the added value of out of office availability is missing. This is striking, given the function telephone consultation has, the fact that this treatment mode is a key barrier for the implementation of DBT (Chugani & Landes, 2016; Flynn et al., 2020; Landes et al., 2016; Landes et al., 2017; Landes et al., 2021) and that experts describe how out of office availability places a substantial strain on DBT teams. A RCT in suicidal BPD patients that compares 24/7 access to between-session coaching provided by the individual therapist versus another service/ application versus no between-session coaching is delicate. However, a trial performed by Nadort et al. (2009), about the added value of telephone availability in schema focused therapy (SFT) for BPD, suggests that it is feasible. An alternative would be to build on previous work of Oliviera and Rizvi (2018) and collect more fine-grained data on the between-sessions contact in ongoing and future DBT –trials. As there is a strong increase of research into DBT (Storebø et al., 2020), a meta-analysis on the subject could be within reach.

Our second focus was to identify research about telepsychology in DBT modes of treatment that are usually provided face-to face (i.e., individual therapy, skills training or consultation team). Quantitative studies on individual therapy or DBT skills training by means of videoconferencing (i.e., synchronous communication with trainers and peers) or blending face-to-face individual therapy with interactive online modules (i.e., asynchronous communication with trainers) are scarce, and still in an early phase of clinical research: evaluating feasibility, acceptance and usability. We did not find RCTs that tested the hypothesis that online or blended DBT is superior or at least equally effective as standard, face-to-face DBT. At the same time, we observe a steady increase of online or blended care in clinical practice, with the coronavirus pandemic as a catalyst (De Witte et al., 2021; Fernández-Álvarez & Fernández-Álvarez,2021; Nicholas et al., 2021). In the absence of sufficient evidence, we think it is advisable to return to face-to-face contact as soon as possible and to remain aware of selection bias, confirmation bias and technology optimism. Cautioning against bias is not the same as stating that online or blended DBT is not efficacious or useless. Despite the concerns and challenges that were reported (i.e., technical issues, difficulties to achieve connectedness and group cohesion (Lakeman & Crighton, 2020; O'Hayer & Virginia, 2021; Virginie et al., 2021), we found no reports of serious adverse events or loss of learning capacity in teams that switched to videoconferencing-platforms during the pandemic (Lopez et al., 2020; O'Hayer & Virginia, 2021; Virginie et al., 2021). Treatment via videoconferencing was preferable to no treatment at all (Virginie et al., 2021). In addition, the results of pre-post studies about acquiring DBT-skills by means of internet-delivered modules (Lungu, 2015; O'Hayer & Virginia, 2021; Wilks et al., 2017; Wilks et al., 2018;) and the psychoeducational video (Waltz et al., 2009) are promising. The next step is to test the efficacy of online or blended DBT in trials with more sophisticated methodologies, and to understand what works for whom, why and in what circumstances. Recent RCTs that were performed in the adjacent field of telepsychology in DBT-trainings and -supervision for clinicians can be a source of inspiration (Carmel et al., 2016; Dimeff et al., 2009; Dimeff et al., 2011; Dimeff et al., 2015; Kauth et al., 2017; McCay et al., 2017; Worrall & Fruzzetti, 2009).

The third and last focus was to review the efficacy or clinical utility of adding telepsychology to standard DBT modes, -strategies, -procedures and skills. We did not find a trial that investigated the added value of standard DBT + telepsychology in comparison to standard DBT. However, smartphone apps are experienced as an acceptable facilitator in access and implantation of DBT skills and led to decrease of a broad range of psychopathology (Austin et al., 2020; Helweg-Joergensen et al., 2019; Rizvi et al., 2011; Rizvi et al., 2016; Rodante et al., 2020; Schroeder et al., 2018; ). One patient described how usage of an application could help to minimalize stigma, as the use of a smartphone is experienced as a common habit (Wilks, 2020). The advantages of a mobile application is that daily personal (text) messages can be added to support using the app. Individuals who received such daily semi-personalised messages practice more skills than those who do not, which results in faster improvement (Schroeder et al., 2018). Future applications could extend current functionalities, for example by creating tailored and gamified content, easily accessible at the right place and time (Karekla et al., 2019). It is also worth investigating to what extent advanced mobile applications could be a assistive technology for DBT therapists, especially in the implementation of out of office availability. Furthermore, we could add the use of wearables to passively monitor patients' state and become even more effective in orienting patients to DBT skills when they need them the most (Debard et al., 2020; Sinnaeve et al., 2021). In line with the positive experiences of using mobile applications, the preliminary results of using VR to facilitate mindfulness skills training are positive (Navarro-Haro et al., 2016; Navarro-Haro et al., 2019; Gomez et al., 2017; Flores et al., 2018). The usage of VR helped preventing drop-out in GAD patients (Navarro-Haro et al., 2019) and two case studies showed that patients liked using VR (Flores et al., 2018; Gomez et al., 2017).

In our introduction, we stated that is important to anticipate the needs of future patients and clinicians (Andersson et al., 2016; Baumeister et al., 2020; Ebert et al., 2015; Sinnaeve et al., 2021; van Leeuwen et al., 2021). In performing our scoping review we could not help but wonder whether we aren't always a couple of steps behind of our youngest patients. For example, we know from clinical practice that patients in DBT skills training groups stay in touch via mobile apps and social media, to share information and to support each other. There are podcasts, youtubers and influencers that discuss DBT-skills. These phenomena may have a larger impact on acquisition and generalization of DBT skills than we think (for better or for worse). At the same time, we know that people build identities and friendships online, and that conflicts, ostracism, bullying and abuse are increasingly taking place in virtual environments. Maybe it is time to add worksheets about 'digital technology skills' in the next DBT skills manual? The point here is that,





more than ever, we think that it is wise to consult with our patients, younger peers and experts in adjacent fields if we want to remain accessible, effective and relevant in a digital age.

## Conclusion

A shift towards videoconferencing and online trainings is justifiable if it is the only way to get an evidence-based treatment like DBT to patients that need it. However, current research evidence does not support a permanent shift towards online or blended DBT. It is pivotal and timely to increase efforts to investigate the efficacy of online/ blended DBT, compared to standard face-to-face DBT. In addition, we need to gain insight into the benefits of out-of-office availability (e.g., 'phone consultation) as a standard module of DBT for suicidal patients. Lastly, other technologies should continue to be explored, as smartphone applications, virtual reality, social media platforms, podcasts, semi-automated online communication and more, all hold promise for assessment, skill acquisition and generalization. We need to move forward on this, to improve both the range and effectiveness of existing approaches, to address the high demand for professional support and to anticipate the needs of clinicians and patients with emotion regulation disorders.

# 6

## Feasibility, Acceptability and Initial Experiences with Dialectical Behavior Therapy Skills Training for Adults with Neurofibromatosis Type I

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## Abstract

Neurofibromatosis type 1 (NF1) is a genetic neurodevelopmental disorder that manifests with diverse physical symptoms, often accompanied by psychological challenges severely affecting quality of life. As yet, no therapeutic strategies have been reported that address the NF1-specific complex interplay of physical and psychological symptoms in a context of emotion regulation problems. For the latter, Dialectical Behavior Therapy (DBT) has been described earlier as a successful treatment option in various forms of psychopathology. The present study therefore aims to investigate the feasibility of application of DBT in patients with NF1. Seven NF1 patients underwent a three-month Dialectical Behavior Therapy Skills training for emotion regulation. Feasibility, acceptability, and initial experiences were evaluated using the Acceptance and Action Questionnaire II (AAQ-II), Positive and Negative Affect Scale (PANAS), and the questionnaire for adult emotion regulation (FEEL-E). Process evaluation revealed robust participant motivation despite recruitment challenges. Intervention delivery was successful, with all modules completed seamlessly, high attendance, and participant satisfaction. While improvements in emotion regulation were noted, initial experiences indicated limited impact on objectification of acceptance, positive and negative affect, and emotion regulation, with varying individual changes. The study suggests positive and potential preventive effects of DBT skills training on affective symptoms, particularly amid the COVID-19 pandemic. Varied results between participants underscore the need for tailored interventions. Considering NF1's diverse symptom profiles, temporal alignment and skill generalization within real-life contexts are crucial, warranting the integration of individual therapy into future DBT NF1 programs.

## Background

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder caused by mutations in the NF1 tumor suppressor gene that encodes components or regulators of the Ras/Mitogen-activated protein kinase pathway (Gutmann et al., 2017). It affects one in 2,500-3,000 individuals worldwide (Williams et al., 2009). This genetic disorder leads to a highly variable physical complaint pattern like cutaneous and subcutaneous neurofibromas that will lead to an increased susceptibility to various benign and malignant tumors, pigmentary lesions (café-au-lait macules, lish nodules), skeletal abnormalities and brain tumors (Gutemann et al., 2017). The latter research mainly focusses on mapping and understanding the psychological problems and cognitive phenotype of people with NF1 and demonstrates, a broad range of (neuro)psychological problems such as a slightly lower than average full-scale IQ, deficits in visuospatial processing, visuospatial learning, attention, (nonverbal) working memory, planning and executive functioning (Descheemaeker et al., 2013; Hyman et al., 2005; Lehtonen et al., 2015., Wang et al., 2019). Additionally, several studies have shown that patients with NF1 suffer from a range of psychological symptoms (Doser et al., 2020; Wang et al., 2012). In mental healthcare, the treatment of people with NF1 is still a niche, while the need for psychological treatment in this group is increasingly manifested (Botessi 2019; Dheensa, 2009; Domon-Archambault, 2018). The current study focusses on the treatment of psychological problems in people with NF1.

Neurogenetic disorders such as NF1 have an immense impact on quality of life and psychological functioning (Domon-Archambault et al., 2018; Doser et al., 2020; Foji et al., 2021). Because of the variety of signs and symptoms in NF1, some individuals have little disease burden or are even unaware of their condition for a long time, while others suffer severely from it (Potter, 2019). As to NF1, symptoms can change throughout life (Jett & Friedman, 2010). Due to the unpredictability in the course of the disease and the variety of physical problems, it makes sense that patients with NF1 suffer from accompanying psychological problems.

The psychological phenomena that were described in NF1 research so far concern a high burden of illness, emotional distress, reduced social functioning, and lower quality of life, affecting individuals with NF1 in all ages as well as impacting their parents (Bicudo 2016; Cipoletta, 2017; Coutinho, 2017; Dheensa 2009; Domon-Archambault, 2018; Doser, 2020; Fjermstad, 201; Foji, 2021; Hummelvoll, 2012; Krab, 2009; Rietman, 2017; Rosnau 2016; Vermeulen et al., 2021). In adults with NF1, significantly more symptoms of anxiety and depression have been reported compared to the population norm, even more than in other patient groups with

life-threatening diseases such as cancer patients (Doser, 2020; Wang et al., 2012; Zale et al., 2018). These mood and anxiety problems may be related to the unpredictable course of NF1, the predisposition to developing malignancies, uncertainty in life, concerns of passing NF1 on to offspring, stigma, decreased social activity, deficits in prosocial behavior, a lower self-esteem, and loneliness (Botessi, 2019; Copley-Merriman, 2021; Crawford 215; Foji 2021; Hummellvoll, 2012; Pride 2013; Rietman et al., 2018; Rosnau 2016; Wang et al., 2012; Zale et al., 2018).

Based on the aforementioned studies and on our clinical observations, NF1 patients can suffer from a wide range of symptoms. Since NF1 is not a curable condition, treatment of psychological functioning seems important in order to manage the functional impact of NF1 (Potter, 2019; Rosenberg et al., submitted). Treatment may focus on underlying mechanisms of psychopathology, in specific emotion regulation problems. Emotion regulation is called a transdiagnostic and dimensional construct, assumed to play a key role in a broad range of mental illnesses as mentioned above (Caspi & Moffit, 2018; Mulay et al., 2019; Ruggero et al., 2019; Sloan et al., 2017). The latter review of Sloan and colleagues indicates that emotion regulation is a process that has been implicated in the development and maintenance of various forms of psychopathology. This could be particularly relevant for patients with high rates of diagnostic comorbidity and (psychological) complexity for instance in people with NF1 where physical, neurocognitive and psychological symptoms are in transaction with each other. This study aims to describe a treatment program using the Skills Training of Dialectical Behavior Therapy (DBT) focussing on emotion regulation as underlying mechanisms of psychopathology.

DBT is an empirically supported treatment program developed by Marsha Linehan for individuals with severe emotion dysregulation problems (Linehan, 1993, 2015). Although primarily designed for suicidal and self-harming behavior, DBT remains effective when tailored to fit the needs of other clinical populations, age groups, or treatment settings (Sinnaeve et al., 2018; Swales, 2018). In particular the DBT skills training (DBT-ST) is evolving to a transdiagnostic intervention for emotion regulation problems (Swales, 2018; Valentine et al., 2015).

To investigate if DBT, as a treatment option for underlying emotion regulation mechanisms, is a suitable treatment for people with NF1, this study assesses feasibility and acceptability of a three months DBT skills group training and explores the initial experiences from the patient's perspective. The primary objective was to determine whether participants could complete the DBT skills





training with consistent attendance. Secondary aims were to explore changes in emotional experiences from first DBT skills training session to 3 months post-intervention.

## Method

### Participants

Seven patients with NF-1 participated in this study, divided into two groups of four and three participants. The descriptive characteristics of all seven participants are presented in Table 1. Participants were recruited from the Centre of Excellence for Neuropsychiatry of the Vincent van Gogh Institute after undergoing clinical neuropsychological assessment.

Inclusion criteria included a confirmed clinical diagnosis of NF-1, a minimum age of 16, and sufficient verbal abilities estimated during neuropsychological assessment. Participants also had to have emotion regulation problems to participate in the DBT skills training. None of the patients had a history of emotion regulation psychotherapy, and the treatment history varied among the seven participants.

Participation was voluntary and written informed consent was obtained from all participants. The study was performed in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the Vincent van Gogh Institute of Psychiatry.

### Measures

#### *Feasibility and acceptability*

The feasibility and acceptability of the study were assessed via a structured exploration of each process of the intervention (Reelick, et al., 2011). The process evaluation was structured into three components: 1) the success rate of recruitment and quality of the study population, 2) the quality of the execution of the complex intervention, and 3) the process of acquisition of the evaluation data.

#### *Initial Experiences*

The Dutch version of the Acceptance and Action Questionnaire II (AAQ-II) was used to measure acceptance, as part of psychological flexibility, and the opposite process, experiential avoidance and was assessed prior to each DBT session (Jacobs et al., 2008). The AAQ was developed by Hayes et al. (2004). The AAQ-II consists of ten items that can be scored on a Likert scale from 1 (never true) to 7 (always true). A higher score on the AAQ-II equals a higher acceptance, a lower score on the AAQ-II equals a higher experiential avoidance. The internal consistency reliability of the Dutch version of the AAQ-II is good with a Cronbach's α of .87.

**Table 1.** Participant characteristics (N=7).

| Participants (P) | P1 | P2 | P3 | P4 | P5 | P6 | P7 |
|---|---|---|---|---|---|---|---|
| **Age (years)** | 59 | 39 | 52 | 34 | 34 | 62 | 18 |
| **Sex** | Male | Male | Female | Female | Female | Female | Female |
| **Level of education*** | 4 | 5 | 6 | 5 | 5 | 6 | 5 |
| **Marital status** | Single | Single | Married | Single | Single | Married | Single |
| **WAIS-IV** | | | | | | | |
| **- VBI** | 86 – 97 | 89 – 101 | 97 – 109 | 88 – 99 | 78 – 89 | 107 – 118 | 95 – 107 |
| **- PRI** | 66 – 81 | 82 – 97 | 82 – 97 | 87 – 102 | 65 – 80 | 94 – 109 | 98 – 113 |
| **- WGI** | 60 – 75 | 74 – 89 | 85 – 100 | 82 – 97 | 66 – 81 | 77 – 92 | 97 – 112 |
| **- VSI** | 83 – 103 | 74 – 93 | 74 – 93 | 78 – 97 | 81 – 100 | 78 – 97 | 88 – 107 |
| **Total IQ** | 72 – 82 | 78 – 89 | 85 – 95 | 83 – 93 | 70 – 80 | 92 – 102 | 98 – 108 |
| **History of psychological treatments**** | 2 (0) (depression) | 1 (0) (systemic problems) | 1 (0) (anxiety) | 7 (0) (depression, anxiety & sleeping disorders) | 2 (0) (depression, anxiety & trauma) | 1 (0) (systemic problems, specific with daughter) | 2 (0) (depression, anxiety & trauma) |

*Note:* * Level of education by Verhage
** Number of psychological treatments (number of treatment focusing on emotion regulation problems)

The Dutch version of the Positive and Negative Affect Scale (PANAS) was used to observe the positive and negative affect prior to each DBT session (Peeters, Ponds, & Vermeeren., 1996). Initial, the PANAS was developed by Watson, Clark and Tellegen (1988). Participants were asked how they felt right now and ratings were averaged to generate positive and negative affect scores. The PANAS consists of ten positive and ten negative affect items that can be scored on a Likert scale from 1 (very slightly or not at all) to 5 (extremely). The positive affect (PA) refers to the degree to which a person is enthusiastic, active and alert. High PA scores are characterized by a state of energy, concentration and pleasure. Low PA scores are characterized by sadness and fatigue. The negative affect (NA) refers to the degree to which a person experiences unpleasant feelings. High NA is characterized by aggressive states of mind such as anger, contempt, disgust, guilt, fear and nervousness, while low NA is characterized by calmness and serenity (Watson, Clark, & Tellegen., 1996). The internal validity of the Dutch version of the PANAS is good with a Cronbach's α of the PA.79 and the NA .83.

To measure emotion regulation, a questionnaire for adult emotion regulation was used (FEEL-E; Grob & Horowitz, 2014) at the start of the first, last and follow up DBT session. The FEEL-E consists of 72 items that can be scored on a Likert scale form 1 (almost never) to 5 (almost always). The FEEL-E assesses adaptive (problem-oriented action, acceptance, cognitive problem solving, re-evaluation, positive mood and forgetting) and maladaptive (withdrawal, self-devaluation, giving up, rumination, negative thinking and allocating blame) emotion regulation strategies for anger, anxiety and sadness. The psychometric properties of the FEEL-E are good (Grob & Horowitz, 2014).

## Intervention

The three months format of the DBT skills training (DBT-ST) from Soler et al. (2009) was used and is described session by session in the Dutch handbook of DBT skills (Linehan, 2015). It is a program adapted from the standard version (Linehan, 1993a, 1993b), applying one of the four modes of DBT treatment: the skills training. DBT-ST included all the original skills in mindfulness, interpersonal effectiveness, emotional regulation and distress tolerance. Mindfulness skills focus on developing attentional control, learning how to have a nonjudgmental awareness and sense of true self by observing and describing sensations, thoughts and events and participating in the moment. The skills are meant to bring the 'emotional mind' and 'rational mind' into balance, and this way to come to 'wise mind'. The interpersonal effectiveness skills contain strategies for interpersonal problem solving and

assertion; asking what someone needs, to say no and to be able to deal with interpersonal conflicts. The effectiveness is about achieving desired changes, maintaining relations, and maintaining self-respect. Goals of emotion regulation skills are understanding emotions by identify, label and describe them, decreasing the emotional vulnerability to negative emotions, increase the occurrence of positive emotions and decreasing emotional suffering. The skills for tolerating distress concern the ability to accept both yourself and the present situation in a non-evaluating and non-judgmental way.

The structure of the training sessions is identical: starting with a mindfulness exercise followed by a discussion of the homework assignments, a short intermission, then an overview of the content of the current session and lastly the introduction and practice of new theory. Participants were asked to prepare for a session by reading the corresponding chapter of the skills training manual and made homework between the sessions.

## Procedure

After completing clinical neuropsychological assessment at the Centre of Excellence for Neuropsychiatry of the Vincent van Gogh Institute, people with NF1 who had emotion regulation problems were informed about the DBT skills training. Initially, 15 patients were interested in participating in the training. Eight patients were eligible for inclusion but did not (yet) participate because they could not combine the training with current work (3) or study obligations (2) or because they just started another psychological therapy that focused on emotion regulation problems (3).

Before starting with the DBT skills training each patient had one or two appointments (face to face or online) of pre-treatment with a certified DBT therapist, to talk about their problem behavior, to explain the DBT skills training and to gain commitment for personal goals patients wanted to work on. The DBT skills training had a duration of thirteen sessions and was given by two trainers of which at least one certified DBT therapist. The first group (P1, P2, P3, P4) started with a weekly face to face skills training located in the center of the Netherlands, so we could reach as much patients as possible given the national nature of the treatment. However, in the middle of the training, after session 9, COVID-19 occurred. Because of the physical distancing and quarantine measures, necessary to slow down the spread of COVID-19, the DBT skills training was given online via ZOOM until the end of the treatment, including the follow up meeting. The second group (P5, P6, P7) was also during the COVID pandemic, so this training was given entirely online via ZOOM from the first orienting appointment until the follow up meeting.





Participants filled in the AAQ-II and PANAS just before all the DBT skills training sessions. At the first, last and follow-up session, they also filled in the FEEL-E.

## Statistical analyses

**Visual analysis** is most commonly used to analyse data in single case designs for visual inspection to determine whether data patterns differed over time as an indication of an effect of the intervention (Morley, 2017). The visual analyses facilitate a detailed inspection of individual changes over time. As recommended by Morley (2017), we added statistical analysis to detect whether visual observed change is statistically significant and to detect smaller effects and remove potential observer bias in visual analyses. SPSS version 28 for Windows was used for statistical analyses.

Next, **reliable change indices (RCI)** will be calculated to determine the clinical significance of the changes of individual participants on measures before and after treatment. It is a statistical computation for identifying whether the observed change can be contributed to the clinical intervention or is probably due to measurement error (de Souza Costa & de Paula, 2015). RCIs were calculated for the initial experiences concerning the PANAS, AAQ-II and FEEL-E (see supplementary table 1 for standard deviations and Cronbach's α of the outcome measures), using the formula of Jacobson and Truax (1991):

$$RCI = \frac{X_2 - X_1}{SE_{diff}}$$

$$SE_{diff} = \sqrt{2 * SD^2 * (1 - r_{12})}$$

*$X_1$ = subject's pre-test score*
*$X_2$ = subject's post-test score*
*$SE_{diff}$ = standard error of difference between the two test scores*
*SD = standard deviation of the test score of norm group*
*$r_{12}$ = Cronbach's α of the measure*

When RCI is equal or greater than 1.96, it is likely that the difference between the pretest and post test scores reflect more than the fluctuations of an imprecise measuring instrument (Jacobson & Truax, 1991). Values equal or greater than 1.96 are representative of a reliable change at 95% confidence level (de Souza Costa & de Paula, 2015). Reliable changes indices were calculated for all study participants. For treatment efficacy, participants' first and last DBT session scores were used as pre-test and post-test scores, respectively. For follow-up efficacy,

participants' first and follow up DBT session scores were used as pre-test and post-test scores, respectively.

Finally, **Clinically Significant Change criteria** (CSC; Jacobson et al., 1984; Jacobson & Truax, 1991) will be calculated. The CSC shows whether the change of an individual is large enough to be regarded as clinically meaningful. The cut off for the CSC is set in such a way that scores after treatment should fall outside the range of the abnormal scores. This is defined as the extreme end of the dysfunctional distribution (> 2 standard deviations in the direction of the 'normal' reference group). CSC is calculated as mean baseline – 2x SD of the dysfunctional group. Standard deviations of the dysfunctional group were derived from test manuals. The CSC will be computed for patients who make a reliable change (improvement / deterioration).

## Results

### Feasibility and acceptability

In Table 2, detailed information regarding the process evaluation is displayed. In terms of recruitment and selection, the initial interest in participating in the training was expressed by 15 patients, out of which 8 patients were eligible and enrolled. However, the recruitment goal of including 12 patients was not achieved. Some barriers to participation included work or study commitments, as well as the initiation of alternative therapies. Despite these challenges, the eligible participants who chose to participate demonstrated a high level of motivation. Regarding the delivery of the intervention, all four modules of the Dialectical Behavior Therapy (DBT) skills training were successfully completed without any issues. Participants found the content to be comprehensible, as evidenced by their completion of assigned homework and positive feedback. Initial reservations about group training were overcome through individual appointments with certified DBT therapists, which increased participants' willingness to engage in the group training. The COVID-19 pandemic had an impact on the recruitment and delivery of the intervention, as patient visits were temporarily halted due to physical distancing and quarantine measures.

With respect to adherence to the intervention, all participants completed the sessions and adhered to the intervention components. Homework was completed by all participants, although some required additional explanation or support. Participants displayed a strong motivation to participate in the training program and reported high satisfaction with the delivery. The use of mindfulness exercises and other strategies was reported as beneficial for enhancing emotion regulation skills.





The evaluation data indicated that all outcome measures were assessed during each session, providing a comprehensive evaluation of the participants' progress. The dataset was complete, with no missing data or participants excluded from analysis. While statistically significant improvements were observed in certain outcome measures, it should be noted that we do not know if the tests are sensitive enough to detect substantial differences over a short period of time.

Overall, the findings suggest that despite recruitment challenges, the participants demonstrated high motivation, adherence, and satisfaction with the intervention. The successful delivery of the DBT skills training resulted in perceived benefits and improvements in emotion regulation skills. However, some outcome measures may have limitations in detecting significant changes.

### Initial Experiences

#### *Visual analysis*

All seven participants completed the DBT skills training and filled in the questionnaires each session. Figure 1 shows visualization of the total AAQ scores, total Positive Affect (PA) and Negative Affect (NA) scores for the intervention phase (pre-intervention and post intervention).

For participant 1, visual inspection and mean scores suggest an increase of acceptance and positive affect during the intervention until session 9, then the scores decrease to the starting level. The overall change in acceptance and positive affect from start to last session is close to zero. Negative affect stays the same over time.

For participant 2, visual inspection and mean scores suggest a small increase of acceptance and negative affect during the intervention, and a decrease of positive affect.

For participant 3, visual inspection and mean scores suggest an increase of acceptance and a decrease of negative affect during the intervention until session 9, then the acceptance scores decrease and negative affect scores increase to the starting level. The overall change in acceptance and negative affect from start to last session is close to zero. Positive affect increases at first until the one last session and then decreases in the last session to the starting level.

For participant 4, visual inspection and mean scores suggest a small increase of acceptance while positive and negative affect stay more or less the same.

**Table 2.** Results of the process analysis for the Dialectical Behavior Therapy Skills Training (DBT-ST) according to process evaluation components, related process measures, and process variables.

| Process components | Findings |
|---|---|
| Study population | 1. Recruitment and selection rate |
| | 1a. *Number of eligible persons in screened population*<br><br>There was no general screened population. Participants were recruited from the Centre of Excellence for Neuropsychiatry of the Vincent van Gogh Institute after undergoing clinical neuropsychological assessment. |
| | 1b. *Number of participants from the sample of eligible persons*<br><br>After completing clinical neuropsychological assessment at the Centre of Excellence for Neuropsychiatry of the Vincent van Gogh Institute, people with NF-1 who had objective or subjective emotion regulation problems were informed about the DBT skills training. Initially, 15 patients were interested in participating in the training. Eight patients were eligible for inclusion but did not (yet) participate because they could not combine the training with current work (3) or study obligations (2) or because they started another psychological therapy that focused on emotion regulation problems (3). The training was provided in two treatment groups (respectively n=4 and n=3) which started consecutively. |
| | 1c. *Number of participants versus aimed number*<br><br>The aim was to include 12 patients. The recruitment objective was not reached. |
| | 2. Barriers and facilitators in recruitment and selection |
| | 2a. *Difference in baseline characteristics between nonparticipating and participating eligible persons*<br><br>No information was available regarding the differences between participating and nonparticipating eligible patients. |
| | 2b. *Motivation of nonparticipating and participating eligible persons*<br><br>A subset of patients who initially expressed interest in the training program faced challenges in committing the necessary time due to their concurrent work or study commitments. Additionally, some individuals embarked on alternative psychological therapies based on recommendations provided in their clinical neuropsychological assessments. However, the eligible participants who chose to partake in the program displayed a remarkable level of motivation. They travelled from various regions across the country to attend the training sessions.<br><br>Initially, there were reservations among participants regarding the concept of group training. Nonetheless, after one or two individual appointments with a certified Dialectical Behavior Therapy (DBT) therapist for pre-treatment, all participants exhibited a willingness to engage in the group training. |
| | 2c. *Experience with recruitment and selection*<br><br>We exclusively enrolled patients diagnosed with Neurofibromatosis type 1 (NF-1) who were referred to the Centre of Excellence for Neuropsychiatry at the Vincent van Gogh Institute. However, the number of NF-1 patients referred during the data collection period was lower than anticipated. This could potentially be attributed to the occurrence of the COVID-19 pandemic during the data collection phase, which resulted in the implementation of physical distancing and quarantine measures to mitigate the spread of the virus. Consequently, appointments were postponed or cancelled, leading to a temporary halt in patient visits. |
| | 3. Number of participants completing follow-up versus number started |
| | All participants completed the measures at pre- and post-test. These were filled in before every DBT skills training in the presence of the DBT therapist. |
| | 4. Barriers and facilitators for follow-up |
| | There were no dropouts. All participants in the treatment group completed the training and wanted to improve their emotion regulation skills. Patients in both groups valued the importance of this study in order to increase the treatment options for patients with NF1 and were driven to contribute. |
| Complex intervention | 1. Quality of delivery of the interventional components |
| | 1a. *The part of each component and the complete intervention delivered by instructors*<br><br>All four modules, namely mindfulness, frustration tolerance, emotion regulation, and interpersonal effectiveness, were successfully completed without any issues. The content was comprehensible to the participants, and their understanding of the theory and exercises was evident through the completion of assigned homework and feedback received. The presented material was adapted flexibly to accommodate the group's or individual participants' level of comprehension. |
| | 1b. *Satisfaction with delivery*<br><br>All DBT modules appeared to be feasible. The structure of the skills training program was followed, commencing with a mindfulness exercise, followed by a discussion of homework, a break, a presentation of new theory along with corresponding exercises, and concluding with a review of the homework. Throughout the skills training and during the break, ample opportunity was provided for participants to exchange their experiences, which occurred frequently. These discussions encompassed both the skills training itself and the experiences related to living with NF1. |
| | 2. Barriers and facilitators for delivery of interventional components |
| | 2a. *Reasons for diverging from, or applying (planned) components*<br><br>No modifications or adjustments were made in the delivery of the skills training program. Despite a diversity in intellectual capacities, it was successfully feasible to adhere to all components of the program. |

**Table 2.** Continued.

| Process components | Findings |
|---|---|
| | 3. Adherence to interventional components |
| | 3a. *Number of sessions followed*<br><br>All participants followed all sessions. |
| | 3b. *Intervention components (partly) followed*<br><br>The participants received all four DBT modules. |
| | 3c. *Compliance to individual recommendations*<br><br>Individual recommendations were followed up. |
| | 3d. *Homework adherence*<br><br>All participants completed their homework; however, some required additional explanation or support. Actively encouraging participants to seek assistance from the DBT trainers was also emphasized, and assistance was provided whenever necessary. If participants were unable to complete their homework, during the homework review session, a collaborative approach was employed to identify the obstacles encountered. This facilitated the participants in addressing those challenges and resuming their homework the following week, ensuring progress and accountability. |
| | 4. Barriers and facilitators for adherence to interventional components |
| | *4a. Motivation for (lack of) attendance and compliance*<br><br>The participants demonstrated a strong motivation to participate in the training program. They recognized the significance of the training and exhibited a positive attitude towards the sessions, indicating a sense of enjoyment and satisfaction. |
| | 5. Experience of participants and instructors with interventional components |
| | 5a. *Perceived benefit*<br><br>During the follow-up meeting, all participants expressed that they benefited from the skills training program. In particular, the mindfulness exercises were highlighted as helpful, as participants found structured application of these exercises facilitated better observation and articulation of their own emotions. Participants reported improved ability to recognize and differentiate emotions, enabling them to effectively communicate them to others, resulting in fewer and less intense conflicts. The use of opposite action and problem-solving strategies, emphasized in the emotion regulation module, was frequently mentioned as valuable. Participants also found drawing, visualization, and the use of metaphors to be helpful in enhancing their understanding and application of new theories.<br><br>In the first group, two participants expressed disappointment that a face-to-face follow-up session could not be arranged due to COVID-19. They felt that the group was not fully concluded and suggested that additional in-person sessions alongside the online sessions would have been preferable. |
| | 5b. *Strong and weak aspects of the interventional components (structure and content), and the total intervention*<br><br>Strong aspects of the training concerned its (small) group based format, in which patients learned from each other's experiences, increased their awareness of emotional difficulties, and were able to practice learned strategies. Besides the small sample size, a weak aspect of the training may be the lack of an individual DBT coaching session to enhance generalisation of DBT skills in daily life. |
| Evaluation data | 1. Outcome measures: Coverage of interventional components |
| | The level of acceptance and experiential avoidance, as well as positive and negative affect, were assessed during each session, effectively capturing the impact of all DBT modules in the outcomes. To gain insight into the (shift in) emotion regulation skills, a coping inventory was administered at the beginning, end, and follow-up meeting of the training program. This allowed for a comprehensive evaluation of participants' emotion regulation abilities throughout the course of the program. |
| | 2. Completeness of data collection |
| | *2a. Number and characteristics of missing data*<br><br>The dataset was entirely complete, as all participants fully completed the questionnaires. |
| | 3. Barriers and facilitators for data collection |
| | 3a. *Feasibility of outcome measures.*<br><br>The questionnaires were completed immediately prior to the session of the DBT skills training. In cases where the training took place in a physical location, the questionnaires were administered on paper and promptly returned directly to the DBT trainers. Conversely, during online sessions, participants completed the questionnaires on their computers and subsequently submitted them electronically to the trainers. |
| | 3b. *Reasons why data were missing.*<br><br>No data was missing. |
| | 3c. *Reasons why participants were excluded from analysis.*<br><br>There were no participants excluded from the analyses. |
| | 4. Comparison of qualitative and quantitative effectiveness data.<br><br>The quantifiable data reflected the perceived benefits reported by two patients and their relatives. These outcomes were generally positive, with small but statistically significant improvements observed in certain primary and secondary outcome measures. However, it should be noted that some tests included in the current battery might not be sensitive enough to detect substantial differences over a short period of time. |

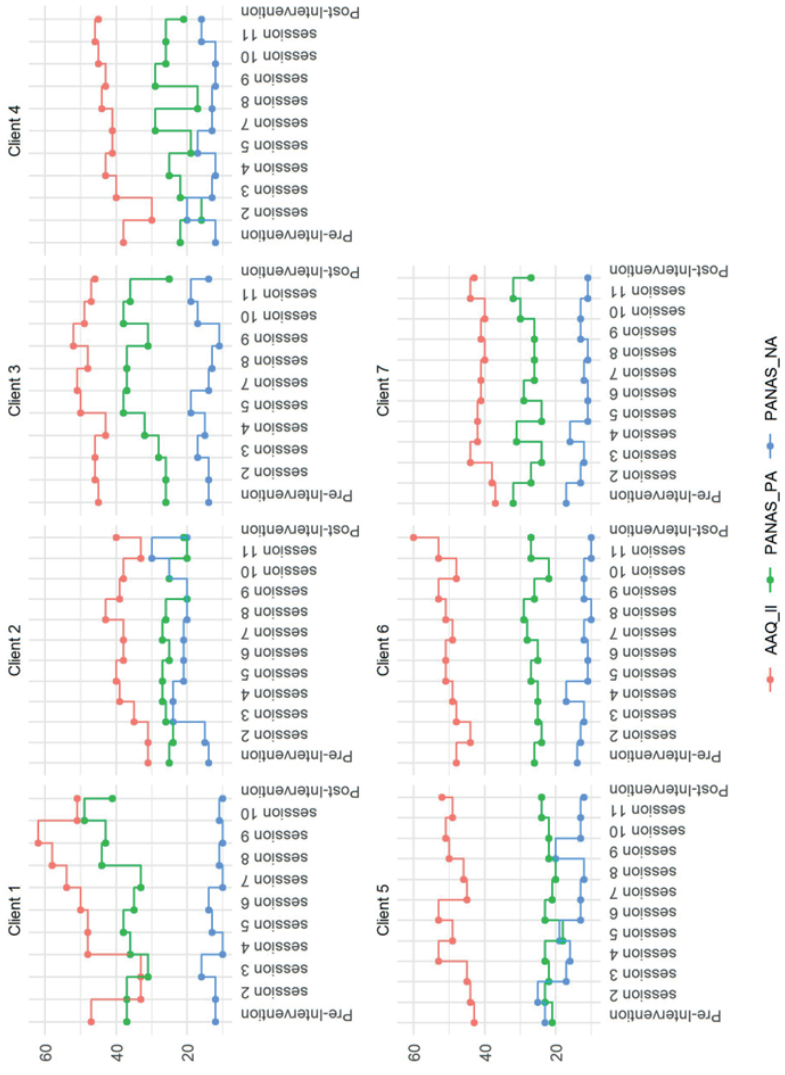


**Figure 1.** Visualization per participant of the total AAQ scores, total Positive Affect (PA) and Negative Affect (NA) scores for the intervention phase (pre-intervention and post intervention).





For participant 5, visual inspection and mean scores suggest an increase of acceptance and a decrease of negative affect while positive affect stay more or less the same.

For participant 6, visual inspection and mean scores suggest an increase of acceptance and a decrease of negative affect while positive affect stay more or less the same.

For participant 7, visual inspection and mean scores suggest an increase of acceptance and a decrease of positive and negative affect.

Table 3 shows the pre-post and follow-up scores, RCI and CSC of the total AAQ-II scores, Positive Affect (PA) and Negative Affect (NA) scores and total FEEL-E adaptive and maladaptive strategy scores.

### *Acceptance and experiential avoidance (AAQ-II)*

One of seven participants (P6) showed a reliable but not clinically significant change in acceptance from first to last DBT session. Two of seven participants (P5 and P6) showed a reliable but not clinically significant change in acceptance from first to the last three months follow-up session.

### *Positive and negative affect (PANAS)*

None of seven participants showed a reliable and clinically significant change in positive affect from first to last DBT session. One of seven participants (P4) showed a reliable but not clinically significant change in positive affect from first to follow-up session. One of seven participants (P5) showed a reliable and clinically significant change in negative affect from first to last DBT session. Two of seven participants (P2 and P5) showed a reliable but not clinically significant change in negative affect from first to the last three months follow-up session.

### *Emotion regulation (FEEL-E)*

Two of seven participants (P6 and P7) showed a reliable but not clinically significant change in adaptive strategies from first to last DBT session. Two of seven participants (P1 and P6) showed a reliable but not clinically significant change in adaptive strategies from first to the last three months follow-up session.

Two of seven participants (P5 and P6) showed a reliable but not clinically significant change in maladaptive strategies from first to last DBT session. One of seven participants (P1) showed a reliable and clinically significant change in maladaptive strategies from first to last DBT session. Two of seven participants (P5 and P6)

**Table 3.** Outcome measures pre-post treatment measurements

| Participant | P1 | P2 | P3 | P4 | P5 | P6 | P7 |
|---|---|---|---|---|---|---|---|
| | | | | *Primary outcome measures* | | | |
| Measure | | | | **AAQ-II** (SD=9.3, α=.87) | | | |
| Pre-intervention | 47 | 31 | 45 | 38 | 43 | 48 | 37 |
| Post intervention | 51 | 40 | 46 | 45 | 52 | 60 | 43 |
| Follow-up intervention | 41 | 36 | 51 | 43 | 53 | 63 | 45 |
| RCI[1] | .84 | 1.90 | .21 | 1.48 | 1.90 | 2.53* | 1.27 |
| RCI[2] | -1.27 | 1.05 | 1.27 | 1.05 | 2.11* | 3.16* | 1.69 |
| Measure | | | | **PANAS Positive Affect** (SD=6.3, α=.79) | | | |
| Pre-intervention | 37 | 25 | 26 | 22 | 21 | 26 | 32 |
| Post intervention | 41 | 21 | 25 | 21 | 24 | 27 | 27 |
| Follow-up intervention | 40 | 21 | 33 | 34 | 27 | 28 | 32 |
| RCI[1] | .98 | -.98 | -.24 | -.24 | .73 | .24 | -1.22 |
| RCI[2] | .73 | -.98 | 1.71 | 2.94(**) | 1.47 | .49 | .00 |
| Measure | | | | **PANAS Negative Affect** (SD=6.4, α=.83) | | | |
| Pre-intervention | 12 | 14 | 14 | 12 | 23 | 14 | 17 |
| Post intervention | 10 | 20 | 14 | 16 | 12 | 10 | 11 |
| Follow-up intervention | 15 | 26 | 12 | 13 | 12 | 9 | 10 |
| RCI[1] | -.54 | 1.61 | .00 | 1.07 | -2.95(**) | -1.07 | -1.61 |
| RCI[2] | .80 | 3.22(**) | -.54 | .27 | -2.95(**) | -1.34 | -1.88 |
| | | | | *Secondary outcome measures* | | | |
| Measure | | | | **Feel-E Total adaptive strategies** (SD=16.6/17.0, α=.92) | | | |
| Pre-intervention | 128 | 96 | 126 | 116 | 122 | 119 | 110 |
| Post intervention | 141 | 88 | 122 | 122 | 122 | 135 | 124 |
| Follow-up intervention | 145 | 84 | 127 | 128 | 119 | 128 | 125 |
| RCI[1] | 1.91 | -1.18 | -.59 | .90 | .00 | 2.35* | 2.11* |
| RCI[2] | 2.50* | -1.76 | .15 | 1.81 | -.45 | 1.32 | 2.26* |
| Measure | | | | **Feel-E Total maladaptive strategies** (SD=16.7/17.0, α=.90) | | | |
| Pre-intervention | 103 | 99 | 91 | 107 | 97 | 105 | 101 |
| Post intervention | 131 | 110 | 90 | 113 | 67 | 70 | 108 |
| Follow-up intervention | 144 | 119 | 86 | 110 | 80 | 77 | 102 |
| RCI[1] | 3.68(**) | 1.45 | -.13 | .80 | -4.02* | -4.60* | .94 |
| RCI[2] | 5.39(**) | 2.63(**) | -.66 | .40 | -2.28* | -3.68* | .13 |

*Note*: [1] Reliable Change Index treatment efficacy
[2] Reliable Change Index Follow-up
* RCI Significant reliable change
(**) CSC Clinical significant change





showed a reliable but not clinically significant change in maladaptive strategies from first to the last three months follow-up session. Two of seven participants (P1 and P2) showed a reliable and clinically significant change in maladaptive strategies from first to the last three months follow-up session.

## Discussion

Currently there is no evidence-based treatment program for patients with NF1. To the best of our knowledge, this is the first study that investigated the feasibility, acceptability and initial experiences of a DBT skills training on seven patients with NF1. The training appeared feasible, and promising results were found with regard to enhancement of acceptance, negative affect and emotion regulation strategies, although the overall effectiveness of the training could not be quantified, due to the small sample size.

The process evaluation of the Dialectical Behavior Therapy (DBT) skills training disclosed that, despite not attaining the recruitment goal and potentially influenced by the presence of COVID-19, enrolled participants exhibited notable levels of motivation. The delivery of the intervention was successful, all four modules (mindfulness, interpersonal effectiveness, emotional regulation and distress tolerance) were completed without problems, and participants found the content comprehensible. Attendance at the intervention was high; all participants completed the sessions and consistently engaged with the assigned homework. The evaluation of participants reflected improvements in emotion regulation skills, although some outcome measures may have limitations in detecting quantitative significant changes over a short period of time. Overall, the participants displayed satisfaction with the training. The results seem unaffected by demographic factors such as gender, employment status, intelligence level, or prior experience with other psychological treatments.

Based on the initial experiences of participants, the impact of Dialectical Behavior Therapy (DBT) skills training on acceptance, positive affect, negative affect, and emotion regulation among the seven participants in this study was found to be limited. Finding limited improvement on the measurements, may reflect an increased awareness of emotion regulation difficulties. Awareness of one's emotion regulation problems can be considered as an initial step towards behavioural change. Within the first group, the observed changes in acceptance, positive affect, and negative affect exhibited considerable variation among the four participants. While some individuals displayed fluctuations or reversals in their scores, others demonstrated more consistent patterns of change. These score

fluctuations are predominantly observed in the first group and could possibly be linked to the onset of the subsequent COVID-19 pandemic following the 9th session of the Dialectical Behavior Therapy (DBT) skills training. Research conducted by Tsamakis et al. (2021) suggests that the COVID-19 pandemic has had a significant adverse impact on mental health, resulting in increased rates of anxiety, depression, insomnia, and stress. Certain vulnerable populations, including those with pre-existing mental health conditions, appear to be at a higher risk of experiencing negative psychological outcomes (Nam et al., 2020). Sánchez-Garcia et al. (2021) found that individuals with genetic conditions reported higher levels of anxiety and depression compared to those without genetic conditions during the COVID-19 pandemic. These symptoms were associated with heightened concerns about health and fear of exposure to the virus. These findings suggest that individuals with genetic conditions may be more susceptible to the psychological effects of the pandemic and could benefit from targeted interventions to support their mental well-being. It can be argued that participating in the Dialectical Behavior Therapy (DBT) skills training in this case may have had a preventive effect on the escalation of anxiety and mood symptoms. The second group received the intervention entirely online due to COVID-19 measures that restricted physical gatherings during that period. It is important to note that this online format was implemented after the initial wave of the COVID-19 pandemic had subsided, potentially resulting in different impacts compared to the first group, which underwent training during the pandemic. Within the second group, all three participants experienced improvements in acceptance during the intervention. Additionally, two participants exhibited a decrease in negative affect, while positive affect remained relatively stable. However, one participant reported a decrease in both positive and negative affect. Overall, these findings contribute to our understanding of individual responses to the intervention, highlighting diverse patterns of change in acceptance and affective states among participants.

In reflecting upon the outcomes in the context of the symptom profile of individuals with Neurofibromatosis Type 1 (NF1), it is noteworthy that symptoms and complaints associated with NF1 can exhibit variations across the lifespan (Jett & Friedman, 2010). Given the incurable nature of NF1, both medical and psychological interventions primarily address symptomatic relief. The heterogeneous nature of signs and symptoms further complicates the disease experience, with some individuals experiencing minimal burden or even remaining unaware of their condition, while others endure significant suffering (Potter & Mendoza, 2019). The temporal alignment of Dialectical Behavior Therapy (DBT) skills training assumes significance, implying that the capacity to accept or regulate emotions might hold greater importance during specific life stages for individuals with NF1, such as





when neurofibromas or tumours manifest or when severe fatigue becomes predominant. Additionally, the significance of skill generalization within one's immediate environment is underscored, especially during critical moments. Hence, it is suggested, for future Dialectical Behavior Therapy (DBT) skills training, to incorporate individual therapy into the program, aligning with the standard DBT protocol. The role of individual therapy within DBT is envisaged as instrumental in facilitating skill development, addressing challenges in skill generalization, and reinforcing sustained changes. Consequently, it is recommended for future research to integrate individual therapy into DBT programs to enhance the generalization of acquired skills within real-life contexts.

An important strength of this study lies in addressing the absence of treatment options for individuals with NF1. This pilot study aimed to assess the feasibility, acceptability, and initial experiences of a DBT skills training. The utilization of an N=1 design was chosen to emphasize the understanding of individual variability, with the potential to aid in pattern identification and the acquisition of valuable data across multiple N=1 studies.

However, several limitations need acknowledgment. The design's drawbacks include limited generalizability and statistical power. The study's small sample size and varied treatment histories among participants may have influenced the results. Preliminary findings, reliant on self-report questionnaires, raise questions about the optimal measurement for objectifying change. Furthermore, certain tests within the current battery may have inadequately detected substantial differences between pre- and post-test evaluations. Employing alternative methods, such as objective measurements or performance-based assessments aligned with participants' goals, may be necessary for a more comprehensive and accurate assessment of progress. Despite these limitations, the results suggest that further research is needed to investigate the underlying factors influencing current outcomes and to evaluate the long-term effects of the intervention. It may also be beneficial to explore alternative or complementary interventions for individuals with NF-1 and emotion regulation problems.

In conclusion, this pilot study explores the feasibility and initial outcomes of a Dialectical Behavior Therapy (DBT) skills training for individuals with Neuro-fibromatosis Type 1 (NF1). Promising results were observed, including enhanced acceptance and improved emotion regulation. Despite challenges, such as a small sample size and diverse treatment histories, the study underscores the importance of individualized approaches in this population. The findings suggest the need for further research to understand underlying factors influencing outcomes and to

assess the intervention's long-term effects. The study highlights the potential of DBT skills training for individuals with NF1, underscoring the significance of tailored interventions in addressing emotion regulation difficulties.

# 7

## Summary and Discussion

The overall aim of this thesis is to increase understanding of the cognitive and psychological challenges faced by adults with Neurofibromatosis type 1 (NF1), as well as to investigate the applicability of a skills training programme based on Dialectical Behaviour Therapy (DBT) as a transdiagnostic intervention for this target group. Although NF1 is primarily known as a genetic disorder that affects the skin and nervous system, the psychosocial problems of this group like mood disorders, fatigue and emotion regulation problems, receive insufficient attention in mainstream care. Referral to mental health care usually only occurs when there are clear psychological complaints, following a predominantly categorical diagnostic approach, and without appropriate follow-up treatment. This practice fails to address the complexity of NF1. This thesis investigated the cognitive and behavioural functions of people with NF1 and examined the extent to which DBT, as an integrated transdiagnostic approach focused on emotion regulation and psychosocial functioning, can meet the specific needs of people with NF1. DBT offers a skills training that helps individuals develop skills in mindfulness, emotion regulation, interpersonal effectiveness and distress tolerance. Its dialectical foundation, emphasizing a balance between acceptance skills and change skills, allows DBT to help individuals to change behaviour and accept the reality at the same time. DBT addresses both individual and systemic factors, including the influence of social networks in maintaining or shaping behavior. As such, a treatment approach that broadly targets emotional and behavioral regulation may help people with NF1 regain a sense of control over their internal emotional experiences and improve their overall psychological functioning.

The first chapter of this thesis begins with a systematic and detailed assessment of cognitive functioning, behavior, and psychopathology in individuals with NF1. This is followed by an exploration of the applicability of DBT through in-depth interviews with two patients who underwent DBT skills training, as well as their significant others. The subsequent chapter addresses the importance of involving relatives in treatment. Next, a systematic review outlines current telepsychology applications in the context of DBT. The thesis concludes with a feasibility study in which the feasibility and potential therapeutic value of (blended) DBT skills training were evaluated, aiming to contribute to more accessible and tailored psychological care for adults with NF1.

## Summary and main findings

A detailed description of cognition, behaviour and psychopathology in a group of 62 adult patients with NF1 is provided in **chapter 2**. Results demonstrated lower intelligence levels and specific cognitive dysfunctions, including deficits in attention and speed of information processing, verbal fluency, learning and memory, and social cognition. Contrary to expectations, executive functioning related to planning, organization, and inhibitory control was not impaired. More specifically, the results revealed that the cognitive performance of the NF1 group was significantly lower than normative means in oral reading speed, visuospatial perception, visual learning, and immediate visual memory. Assessment of behaviour and psychopathology indicated higher levels of emotion perception difficulties, subjective dysexecutive functioning, internalizing psychopathology (anxiety and depression), and fatigue compared to the general population. A closer look at the emotion regulation measures revealed that the proportions of maladaptive coping were higher and the proportions of adaptive coping in the NF1 group were lower than those in the normative group. Specifically, the NF1 group exhibited limited use of active and emotion-oriented coping strategies, coupled with a tendency to experience emotions without adequately differentiating them. Although domain-level significance was not reached for emotion regulation, the coping style of individuals with NF1 can be characterized as predominantly passive. A larger proportion of the NF1 group showed lower-than-expected cognitive test scores and elevated behavioural problems compared to what is typically seen in the general population. These findings indicate high vulnerability in adults with NF1 and underscore the need for individualized neuropsychological assessment and tailored interventions

Subsequently, in **chapter 3**, the psychological challenges faced by two individuals with NF1, as well as experiences with an online Dialectical Behavior Therapy skills training, were extensively documented through an in-depth interviews conducted not only with the patients but also with their significant others. Both participants faced substantial problems associated with NF1, including concerns and persistent worrying about disease progression, debilitating fatigue, and impaired functioning. Social difficulties and emotional struggles were particularly pronounced, with one patient experiencing issues in social interactions and the other patient struggling with fatigue that disrupted daily activities. Following the DBT skills training, both patients noted improvements in their ability to observe and manage emotions. They described an improvement in taking distance from their situations, which reduced rumination and emotional overwhelm, particularly when facing concerns about disease progression or social judgment. The mindfulness skills taught in





DBT enabled them to reflect on thoughts and emotions more effectively. Improved ability to verbalize emotions also facilitated better communication with others, helping them express their needs more clearly. One of the two patients specifically benefited from the concept of “wise mind,” an exercise aimed to balance emotional and rational thought processes. She applied skills such as opposite action and fact-checking, which helped her navigate social situations and public spaces with greater confidence. Both patients reported increased acceptance of reality and decreased concern about others’ opinions, allowing them to engage more fully in life. For example, one patient expressed a newfound confidence in her appearance and a reduced need for external validation. Despite these positive outcomes, both patients found online DBT sessions less effective than in-person meetings, citing reduced opportunities for informal social interactions during breaks and greater difficulty concentrating. They advocated for a blended treatment model that includes sufficient in-person sessions to foster connection and facilitate the exchange of experiences. Family members reported positive changes in the patients, including enhanced emotional regulation, increased assertiveness, and reduced interpersonal conflicts. These improvements contributed to clearer communication, better decision-making, and strengthened relationships.

Looking at the importance of involving significant others in treatment; **chapter 4** explores a contextual factor that may influence treatment and could possibly improve its outcome. This pre-post study examined 33 patients and 61 relatives who participated in a DBT network training. Specifically, it investigated changes in perceived criticism (namely, how critical individuals felt towards their relatives and how critical they believed their relatives were towards them), through a training approach that actively involved both patients and their significant others. The emphasis here was on training emotion regulation skills for both clients and significant others. Results show a significant decrease in perceived criticism (PC) levels among both patients and their relatives following the DBT network training. Specifically, participants reported lower perceptions of how critical others were toward them and how critical they were toward others. The large effect sizes suggest these changes are clinically meaningful, though the underlying mechanisms remain unclear. Prior to the training, PC scores for both groups exceeded 6, a threshold associated with increased relapse risk. Post-training, PC levels dropped to a range that may indicate a more favourable condition for reducing negative clinical outcomes.

During the investigation of DBT as a possible psychological treatment for people with NF1, covid-19 occurred. **Chapter 5** presents a systematic review of telepsychology applications within DBT. The first focus was on telepsychology’s

role in between-session coaching, such as phone and video support, which aids skill generalization. While phone coaching is integral to DBT, limited quantitative data and a lack of randomized controlled trials (RCTs) hinder a definitive evaluation of its effectiveness. Nevertheless, existing studies suggest that between-session contact reduces dropout rates and enhances psychological outcomes. Future research should focus on collecting detailed data and conducting RCTs to gain insights in the advantages of out of office availability (such as telephone coaching). The second focus was to identify research about telepsychology in DBT modes of treatment that are usually provided face-to-face (i.e., individual therapy, skills training or consultation team). Evidence on videoconferencing and blended approaches is primarily centred on feasibility and acceptance, with no RCTs yet demonstrating equivalence to face-to-face DBT. Preliminary studies indicate that videoconferencing and online modules are preferable to no treatment at all and support skill acquisition, but further rigorous trials are needed to assess their efficacy and applicability. Third, the review assesses integrating telepsychology into standard DBT strategies and tools. Mobile applications emerge as promising, with features like personalized daily messages shown to encourage skill use and accelerate progress. Additionally, innovations such as gamification, wearable technology for passive monitoring, and virtual reality mindfulness training offer potential to enhance DBT delivery. Virtual reality studies suggest benefits in skill acquisition and reduced dropout rates for certain patient populations. The findings underscore telepsychology's growing role in DBT while highlighting the need for robust research to establish its efficacy and optimize its integration into clinical practice.

In the penultimate chapter, **Chapter 6**, the feasibility of the DBT skills training for individuals with NF1 was evaluated through a single case pilot study with 7 NF1 patients. The study indicates that DBT skills training was feasible for people with NF1, with all participants completing the intervention, attending sessions consistently, and engaging with homework assignments. Despite the small sample size and recruitment challenges, likely influenced by the COVID-19 pandemic, participants exhibited high levels of motivation throughout the intervention. The delivery of the training was implemented successfully, and its content, encompassing modules on mindfulness, interpersonal effectiveness, emotion regulation, and distress tolerance, was perceived as clear and accessible. Participant evaluations reflected high overall satisfaction with the intervention. Importantly, these outcomes appeared to be independent of demographic variables such as gender, employment status, cognitive ability, or prior psychological treatment. Although improvements in emotion regulation were observed, initial findings suggest a limited impact on variables such as the objectification of acceptance and both positive and negative affect, with notable variability in individual responses.





## General discussion

Cognitive and behavioral functioning in adults with NF1 significantly deviates from the normative population, with a notably higher prevalence of impairments. These findings point to increased vulnerability in this group and underscore the need for individualized assessment and intervention. Given the chronic nature of NF1 and its broad psychosocial impact, a treatment approach that integrates behavioral therapeutic principles and a systemic perspective is recommended. DBT emerges as a suitable intervention for individuals with NF1, due to its dual focus on acceptance and change, and its adaptability to individuals with diverse cognitive profiles. A treatment approach that broadly targets the regulation of emotion and behavior, such as mindfulness, emotion regulation, frustration tolerance, and interpersonal effectiveness, may support individuals in regaining a sense of control over their internal emotional world.

To further interpret the findings and to guide future research and clinical practice for individuals with NF1, some important reflection points will be addressed. First, emotion regulation will be considered as a relevant contextual factor in treatment. By focusing on a transdiagnostic and dimensional construct such as emotion regulation, emotional dysregulation can be addressed at its core, rather than focusing solely on the diverse symptoms that may result from it. Second, this transdiagnostic perspective will be further elaborated through reflection on categorical versus dimensional frameworks. Third, the underlying mechanisms of social functioning difficulties will be explored, with particular attention to the distinction between social cognition and social behavior, as this may help refine both assessment and intervention. Finally, attention will be given to the modernization of care and the potential role of telepsychology in developing accessible and flexible treatment formats tailored to the needs of adults with NF1. Together, these reflection points aim to deepen our understanding of the clinical implications of the findings and help shape future directions in care and research.

### Emotion regulation in context as target for intervention

Treatment in people with NF1 has not previously focused on emotion regulation problems as an underlying transdiagnostic construct associated with symptom-specific complaints, such as anxiety or depression. Although Chapter 2 did not reveal statistically significant deficits in emotion regulation at the domain level, further analysis showed that individuals with NF1, compared to normative data, made less use of adaptive coping strategies and more frequent use of maladaptive forms of coping, such as emotion suppression and withdrawal. Particularly low levels of active and emotion-focused coping were observed, alongside a tendency

to experience undifferentiated emotional states. When adaptive strategies were used, task-oriented coping, reflecting a problem-solving approach, was most common. However, this strategy may be less effective when applied to stressors rooted in a chronic and unchangeable genetic condition, potentially leading to increased frustration and emotional distress. While emotion regulation capacities in individuals with NF1 appear to be largely preserved, the limited use of adaptive coping is concerning in light of the considerable emotional demands. The chronic and unpredictable nature of the disorder, combined with cognitive vulnerabilities and fatigue often associated with NF1, increases the risk of overexertion and exceeding personal boundaries. Furthermore, individuals with NF1 often strive to participate fully in society and experience greater physical and social strain related to work compared to the general population (Fjermestad, 2018). Therefore, enhancing coping skills may serve as an important protective factor for mental health across multiple domains and help to mitigate the overall psychological impact of living with NF1.  Psychological interventions for individuals with neurofibromatosis type 1 (NF1) are rarely described in literature, although psychological complaints such as anxiety and mood disturbances are commonly acknowledged and often addressed symptomatically. A notable exception is the study by Martin et al. (2021), which evaluated the effectiveness of Acceptance and Commitment Therapy (ACT) in treating chronic pain in adolescents and adults with NF1. The ACT intervention significantly reduced pain interference in daily functioning, and improvements in pain acceptance and inflexibility mediated these outcomes. However, no improvements were observed in pain intensity, pain anxiety, or depressive symptoms. This suggests that while ACT may alleviate specific functional impairments, its transdiagnostic impact on emotion regulation remains limited.

The limited use of adapting coping strategies suggests a skills deficit among individuals with NF1, underscoring the potential utility of interventions that train emotion regulation skills. While emotion regulation skills training programs such as the VERS (Vaardigheidstraining Emotie Regulatie Stoornis) training may appear relevant, they are often exclusively *change-oriented* (Freije et al., 2002). This focus bears the risk of overlooking broader deficits in emotion recognition and interpersonal effectiveness as identified in Chapter 2. Moreover, a strictly skills-based approach may inadvertently reinforce a narrative of inadequacy, especially in a population that already struggles with self, and other, invalidating messages.

Dialectical Behavior Therapy (DBT) offers a more balanced and responsive framework, grounded in the biosocial model, which seems well-suited to individuals with NF1. The biological vulnerabilities characteristic of NF1 include cognitive impairments





and physical manifestations, such as café-au-lait spots, sometimes visible and potentially life-threatening neurofibromas, atypical freckling, and bone deformities, which make individuals particularly vulnerable to societal stigma (Fournier et al., 2023). Specifically, these visible traits often elicit negative reactions, ranging from social exclusion to discrimination (Konradi, 2021). Invalidating environments, whether through inadequate accommodation of challenges or overprotective behavior, limit opportunities to develop essential coping skills, thereby exacerbating emotional dysregulation.

The dialectical principle of DBT, pointing at the prospective balance, i.e., synthesis, between acceptance and change, aligns with the needs of this population by both validating their lived experience and supporting the development of more effective coping strategies. Moreover, the inclusion of the patients' environment as an active component in DBT, as highlighted in chapter 4, offers additional value. The importance of involving relatives and significant others in psychological treatment is reflected in the capacity for mutual validation and the ability to challenge judgmental or invalidating beliefs. This process is facilitated by informing the environment about the individual's emotional vulnerability and by actively working together on the acquisition of new skills. Reducing an invalidating environment, as described above, is strongly recommended and can be effectively achieved through active involvement of the relatives in the therapeutic process. By shifting environmental responses and enhancing social support, DBT not only targets individual coping mechanisms but also creates a context more conducive to sustainable therapeutic change.

### Transdiagnostic thinking: one approach for many challenges?

Current diagnostic systems, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM; American Psychiatric Association, 2022), are based on fixed categories. However, such systems have limited practical value when it comes to predicting how a mental health condition will develop over time or which treatment will work best (Conway et al., 2019). These two challenges, i.e., how we *classify mental health problems* and how we *understand their causes*, are closely connected. To improve how we define and group different psychological difficulties, we first need a clearer picture of what leads to these problems and how they develop. This knowledge is also essential for designing better treatments. By combining new scientific insights into both diagnosis and causes, we can speed up progress in understanding and treating mental illness (Latzman et al., 2020; Waszczuk et al., 2020).

When relying solely on traditional categorical classification systems to assess psychological functioning, there is a risk that individuals may not meet the full criteria for a formal classification or that a classification does not explain the problems someone is dealing with. When looking at the clinical profile of individuals with NF1, we often observe a wide range of behavioural and emotional difficulties. This raises the question whether traditional diagnostic classifications are always appropriate or sufficient for this group. In many cases, individuals may not meet the full criteria for a specific diagnosis or may receive a primary diagnosis such as depression or an anxiety disorder. However, these symptoms might actually be secondary outcomes of more complex, underlying problems such as challenges in social relationships, persistent and disabling fatigue, or a negative view of the self. In such cases, categorical diagnoses fail to capture the full range of clinically relevant experiences, thereby limiting the potential for appropriate and effective treatment planning.

Dimensional frameworks such as the Hierarchical Taxonomy of Psychopathology (HiTOP) and the Research Domain Criteria (RDoC) offer promising alternatives by moving beyond binary classification thresholds to emphasize transdiagnostic dimensions and underlying mechanisms (Kotov et al., 2017; Insel et al., 2010). In the context of neurodevelopmental disorders (NDDs) and NF1 specifically, these models allow for a more nuanced assessment of psychological functioning. For example, rather than asking whether an individual qualifies for a classification of a personality disorder, a dimensional model prompts clinicians to examine personality functioning, including self-related capacities (identity, self-direction) and interpersonal functioning (empathy, intimacy), as proposed in emerging models of personality pathology (Zimmerman et al., 2012; Sinnaeve et al., 2021). Similarly, rather than only diagnosing discrete disorders such as depression or anxiety, clinicians are encouraged to consider the broader behavioral spectra, such as internalizing or externalizing dimensions, and to interpret these patterns within the individual's developmental, biological, and psychosocial context. This approach is particularly valuable in populations with genetic and neurodevelopmental vulnerability, where psychological symptoms often emerge in interaction with longstanding biological and environmental risk factors. It enables clinicians and researchers to better understand and address the complexity of patient presentations that are otherwise underserved by rigid diagnostic categories.

This manuscript underscores the importance of adopting a transdiagnostic, but also multidisciplinary approach to the care of individuals with neurofibromatosis type 1. People with NF1 are predominantly treated within hospital settings, often with a focus on their medical symptoms. However, relatively mild phenotypic





presentations and subtle cognitive deficits may indicate underlying neurodevelopmental and genetic pathology, necessitating a broader perspective in their care (Bos-Roubos et al., 2020). Physicians should integrate neuropsychological and genetic assessments alongside medical evaluations to provide a comprehensive understanding of patients' challenges. Clinical neuropsychological assessments in particular can clarify cognitive and behavioral difficulties and guide tailored treatment options that address the full complexity of the condition.

### Interpersonal effectiveness: problems in social behaviour or social cognition?

A specific example of the limitations of categorical classification systems in the context of neurofibromatosis type 1 concern the social difficulties observed in individuals with NF1. Much of the current research focuses on determining whether these individuals meet the diagnostic criteria for autism spectrum disorder (ASD) and/or attention-deficit/hyperactivity disorder (ADHD). Clinical descriptions often highlight an increased prevalence of autism spectrum disorder (10-40%) and attention-deficit/hyperactivity disorder (38-67%) (Eijk et al. 2018; Morris et al. 2016; Hyman et al. 2005; Koth et al. 2000; Lidzba et al. 2012; Mautner et al. 2002). However, this diagnostic approach may overlook the core issue, which lies in understanding the precise nature of the social functioning difficulties themselves. Rather than focusing solely on whether a categorical diagnosis can be established, the discussion might be more constructively oriented toward identifying the specific social-cognitive and behavioural processes that underlie these difficulties. A useful distinction can be drawn between social cognition and social behaviour. Social cognition refers to the mental processes that allow individuals to interpret, predict, and respond appropriately to others' behaviour (Frith & Frith, 2007), while social behaviour encompasses the observable actions in social contexts and is shaped by both individual traits and environmental influences (Eisenberg et al., 2006).

In the current manuscript in chapter 2, findings suggest that Theory of Mind (ToM), a central component of social cognition, is not globally impaired in individuals with NF1. This would imply that the core difficulty may not lie in understanding others' mental states per se, but rather in the expression of social behaviour, which is influenced by a combination of individual vulnerabilities and contextual demands. This interpretation is consistent with recent findings by Remaud et al. (2024), who reported that while children with NF1 show weaknesses in social information processing and moral reasoning, their performance on standard ToM tasks did not significantly differ from that of healthy controls. In adults, similar patterns were observed. Specifically, patients demonstrated reduced performance in attributing

first-order false beliefs, suggesting a subtle difficulty in recognizing that others can hold beliefs that differ from reality. However, no significant differences were found in more complex ToM tasks, such as second-order false belief attribution or the identification of social missteps (Remaud et al., 2024).

The findings in chapter 2 revealed notable levels of alexithymia in the NF1 population that was examined. This emotional unawareness may severely hamper the ability to connect with others, as emotional expression and recognition are crucial for reciprocal social interaction. Furthermore, we could hypothesize that high anxiety rates may play a contributing role, since we know that negative reactions to physical manifestation of NF1 - ranging from social exclusion to discrimination- can play a role (Konradi, 2021). This might lead to the fear of making mistakes, not meeting others' expectations or being different than others. This suggests that social difficulties in NF1 are not per se the result of cognitive deficits in understanding others but reflect a broader profile of emotional vulnerability and behavioural inhibition.

Recent research highlights the importance of clearly identifying and understanding the specific skills that make up perspective taking for example as described by Hendriks et al. (2016) in the context of Relational Frame Theory (RFT). RFT is a behavioral theory that focuses on how people learn to relate things in their environment through subtle cues, even when those relations are not obvious. Furthermore, Eikelboom et al. (2025) introduced the HITS model of social cognition, which breaks down social skills into separate parts like emotion recognition, perspective taking, and empathy. This model helps guide future research by encouraging a focus on how these skills work, rather than just classifying problems. It offers a more useful way to understand social difficulties.

A broader conceptualisation of emotional vulnerability and behavioural inhibition in people with NF1 aligns with findings from related rasopathies, where social-emotional development is also affected (Foy et al., 2022, Pierpont et al., 2018). In particular, individuals with Noonan syndrome often display similar alexithymia features, and targeted interventions such as the SENS programme have been designed to address socio-emotional development in this population (Roelofs et al., 2019). Such parallels underscore the need for intervention models that go beyond cognitive understanding and focus on enhancing emotional awareness, self-expression, and contextually appropriate social behaviour.





## Blended care in the Digital Age: opportunities for Telepsychology

The use of telepsychology, which involves providing psychological services through technology like the internet, phone apps, and virtual reality, has become increasingly common (Andersson & Titov, 2014; Geraldo et al., 2024, van Daele et al., 2020). Blended therapy, which combines face-to-face and online care, has several benefits, including cost savings and improved effectiveness. However, the assumptions about its benefits still need solid evidence (van Daele & Assche, 2019). It remains highly questionable whether there is sufficient scientific evidence to support large-scale implementation of online interventions. This aligns with the findings presented in chapter 6, in which it is recommended within the context of DBT treatment to return to face-to-face sessions as soon as this becomes feasible.

Research shows that online interventions are most studied for anxiety and mood disorders, often showing better outcomes compared to waitlist controls. There's also evidence supporting its effectiveness for conditions like PTSD, sleep disorders, eating disorders, pain disorders, and substance abuse, with less evidence for OCD, tinnitus, psychosis, and pathological gambling. Most studies on telepsychology focus on short-term effects (Ebert et al., 2018; Nelson & Sharp, 2016; Berryhill et al., 2019; Berryhill et al., 2015; Bolton & Dorstyn, 2015).

Given the increasing use of telepsychology and the challenges posed by the covid-19 pandemic recent years, investigating the efficacy and feasibility of delivering DBT remotely became important as described in chapter 6. Understanding the available evidence on tele-DBT not only provided insights into its potential benefits but also informed the development of guidelines and strategies for delivering effective therapy while ensuring accessibility and continuity of care for individuals.

Ensuring accessible care for individuals with NF1 on a national scale could be achieved through blended care approaches delivered from specialized centres of expertise. These platforms, which combine in-person sessions with online resources, provide the flexibility to maintain consistent and broad-reaching care while adapting to individual needs. Additionally, the integration of mobile technology offers promising opportunities to further enhance care. The research findings as described in chapter 6 underscore the utility of videoconferencing as a treatment option, particularly when in-person sessions are not feasible. However, interviews with patients described in chapter 5 emphasized the importance of blended treatment formats that include sufficient face-to-face interaction. In-person sessions foster connection, create a sense of community, and provide opportunities for informal sharing of experiences before and after group meetings.

This combination of digital and in-person care ensures a balanced approach that leverages the strengths of both modalities.

## Limitations and strengths

The present research has several notable limitations and strengths that should be considered when interpreting its findings. Important to take into account is the selection bias of the sample, as all participants were referred to the outpatient clinic for fatigue or psychosocial symptoms that could not be somatically explained. This likely skewed the sample toward individuals with higher behavioral dysfunction and higher fatigue levels compared to the broader NF1 population. Additionally, only NF1 patients with (somatic) burdens were included, and the absence of a control group of patients without such burdens limits the generalizability of the results to the wider NF1 population. However, a major strength of the study is the comprehensive and detailed mapping of the individual neuropsychological profile of the NF1 group. By using carefully selected analytical methods, the study identified both subtle and robust deficits, revealing vulnerabilities across multiple cognitive and behavioral domains that could have been overlooked if only mean scores were considered.

The study's small sample size, particularly in the pilot study on the DBT skills training, constrained the statistical power and generalizability of the findings. Variability in participants' treatment histories may also have influenced the outcomes. Nevertheless, for a rare genetic disorder, the study included a relatively large and demographically balanced sample, enhancing the reliability of the findings and ensuring a representative depiction of the NF1 population. Additionally, while reliance on self-report questionnaires and the limited sensitivity of certain measures to detect pre- and post-intervention differences may have constrained the evaluation of treatment effects, the use of a single case design in the pilot study on the DBT skills training emphasizes individual variability and offers valuable data for pattern recognition and future research.

Another limitation is the absence of control groups in certain sub-studies, such as those on perceived criticism and the DBT network training, hindering the possibility to determine whether observed changes were attributable to the interventions or other factors. Additionally, the external validity of the DBT network training findings may be limited, as it was conducted in a national residential standard DBT program with highly trained staff and motivated participants who experienced significant illness burdens, circumstances that may not reflect typical treatment settings. The perceived criticism (PC) scale used in the study also had limitations, as its





straightforward, two-item structure lacked the granularity to differentiate nuanced interpersonal interactions or broader constructs of criticism, potentially over-simplifying a complex phenomenon. A strength on the other hand is the integration of telepsychology evidence, reflecting the study's forward-looking approach in adapting interventions to the digital age. Findings on mobile applications, virtual reality, and gamification demonstrated promising directions for enhancing DBT delivery.

## Future research

Future research on (neuro)psychological phenotyping and treatment for individuals with NF1 should adopt a multifaceted approach to address current gaps and improve the understanding and management of this complex condition. A key priority is the inclusion of carefully selected comparison groups in neuropsychological studies. Given the variability in genetic expression and symptom presentation in NF1, including adults with NF1 who do not experience fatigue, as well as IQ-matched control groups with and without fatigue, would provide valuable insights. This approach would allow for a more precise analysis of the relationships between fatigue, cognitive function, and behavioral dysfunction.

The current research identified high levels of fatigue as a prominent characteristic in individuals with NF1. Future studies should investigate the potential bidirectional relationships between fatigue, cognitive impairment, and behavioral dysfunction. Fatigue may act as both a predictor and an outcome of deficits in coping, social cognitive functioning, and internalizing psychopathology, such as mood and anxiety disorders. A comprehensive understanding of these interactions would help clarify how these factors collectively impact daily functioning, occupational engagement, and the ability to meet societal expectations. Additionally, there is a need for a broader focus on the interplay between cognitive function, coping mechanisms, and mental well-being in NF1. Behavioral difficulties, such as inadequate coping strategies, likely exacerbate psychological distress and fatigue. Deficits in social cognitive functioning are similarly linked to internalizing psychopathology. Addressing these interconnections through research could inform tailored interventions that target the underlying mechanisms driving these challenges in line with the Research Domain Criteria (RDoC) framework, which emphasizes dimensional, transdiagnostic constructs across multiple levels of functioning analysis (Cuthbert & Insel, 2013; Insel et al., 2010).

In terms of treatment, future research should explore personalized and adaptive approaches. Alongside DBT skills training, individual DBT coaching could enhance

the generalization of skills and better address individual needs. Techniques such as daily diary cards, used in standard DBT, could be incorporated to analyse specific behaviors and the application of skills in real-world contexts. This personalized feedback loop would provide a deeper understanding of individual progress and refine interventions for greater efficacy.

Given the niche nature of NF1 and its inherent variability, research at the N=1 level remains appropriate with use of the single-case experimental design (SCED). However, traditional methods relying on general questionnaires may fail to capture the nuances of this population. Instead, adopting innovative methodologies like Idiographic System Modeling (ISM) offers a promising alternative (Schiepek, 1986; Schiepek et al., 2016; van den Bergh et al., 2022). ISM is a bottom-up case formulation method that creates a personalized conceptual map of a patient's situation, which is then used to co-create individualized questionnaires. These questionnaires balance positive and negative items (e.g., "Today I felt self-confident" versus "Today I felt anxious") and facilitate the collection of personalized self-rating time series during therapy. Such methods align with the growing trend in personalized psychopathology research and leverage advancements in network modelling and time-series analysis. ISM enables the classification of general change profiles from a complex systems perspective, providing deeper insights into individual mechanisms of change. Research has shown that patients who transition to a different psychological state during treatment often achieve better outcomes than those who do not (Olthof et al., 2023). Applying ISM to NF1 research could help uncover patterns of symptom dynamics and transitions, informing both individual treatment strategies and broader therapeutic approaches.

By prioritizing comparison groups, investigating the interactions between fatigue, cognition, and behavior, and adopting personalized methodologies like ISM, future research can advance the understanding and clinical management of NF1. The integration of these approaches holds the potential to uncover new patterns of symptomatology and inform the development of tailored interventions, ultimately improving outcomes for individuals with NF1.





## Conclusions

Cognitive impairments in individuals with Neurofibromatosis Type 1 (NF1) are often subtle and may not be immediately evident in everyday life, contributing to the under recognition of their functional impact. This under recognition is further reinforced by the absence of externalizing psychopathology and by the tendency of individuals with NF1 not to express their psychological struggles. As a result, clinical attention is often delayed, despite the presence of significant challenges such as difficulties in adaptive coping, elevated fatigue, and a heightened risk of internalizing psychopathology. It is therefore essential to remain alert to more nuanced warning signs, such as academic difficulties, reduced social engagement, or a predominant focus on physical complaints without adequate attention to psychological wellbeing. To achieve a more comprehensive understanding of the needs of individuals with NF1, neuropsychological and genetic assessments should be integrated into routine medical evaluations. In particular, clinical neuro-psychological assessments are critical for identifying cognitive and behavioral vulnerabilities and can help inform individualized and targeted treatment plans.

By focusing on transdiagnostic constructs such as emotion regulation within a biosocial framework, psychological interventions can address the root causes of distress, rather than treating only the surface-level symptoms like anxiety or depression. Dialectical Behavior Therapy (DBT), with its emphasis on both acceptance and change, shows promise as a suitable intervention for adults with NF1. Preliminary findings suggest that DBT skills training may improve emotional functioning and reduce distress in this population. Including the environment as an active part of the treatment adds important value. By teaching participants and their relatives to understand and communicate about their emotions, opportunities for mutual validation can be created. This not only targets individual coping mechanisms but also creates a context more conducive to sustainable therapeutic change. To ensure broad and sustainable access to care, future treatment efforts could benefit from blended care approaches, combining face-to-face and digital formats, ideally delivered through specialized centres of expertise.

# References

## A


Alivuotila, L., Hakokari, J., Visnapuu, V., Korpijaakko-Huuhka, A. M., Aaltonen, O., Happonen, R. P., ... & Peltonen, J. (2010). Speech characteristics in neurofibromatosis type 1. *American Journal of Medical Genetics Part A, 152*(1), 42–51. https://doi.org/10.1002/ajmg.a.33178

American Psychiatric Association. (2022). *Diagnostic and statistical manual of mental disorders* (5th ed., text rev.; DSM-5-TR). American Psychiatric Publishing.

American Psychological Association. (2002). *Monitor on Psychology.* The Association.

Andersson, G., & Titov, N. (2014). Advantages and limitations of internet-based interventions for common mental disorders. *World Psychiatry, 13*(1), 4–11. https://doi.org/10.1002/wps.20083

Andersson, G., Carlbring, P., & Lindefors, N. (2016). History and current status of ICBT. In *Guided Internet-Based Treatments in Psychiatry* (pp. 1–16). Springer. https://doi.org/10.1007/978-3-319-06083-5_1

APA Presidential Task Force on Evidence-Based Practice. (2006). Evidence-based practice in psychology. *American Psychologist, 61*(4), 271–285. https://doi.org/10.1037/0003-066X.61.4.271

Arntz, A., van den Hoorn, M., Cornelis, J., Verheul, R., van den Bosch, L. M. C., & de Bie, A. J. H. T. (2003). Reliability and validity of the Borderline Personality Disorder Severity Index. *Journal of Personality Disorders, 17*(1), 45–59. https://doi.org/10.1521/pedi.17.1.45.24053

Austin, S. F., Jansen, J. E., Petersen, C. J., Jensen, R., & Simonsen, E. (2020). Mobile app integration into dialectical behavior therapy for persons with borderline personality disorder: Qualitative and quantitative study. *JMIR Mental Health, 7*(6), e14913. https://doi.org/10.2196/14913


## B


Bailey, R. C., & Grenyer, B. F. S. (2015). The relationship between expressed emotion and wellbeing for families and carers of a relative with Borderline Personality Disorder: Expressed emotion in borderline disorder. *Personality and Mental Health, 9*(1), 21–32. https://doi.org/10.1002/pmh.1273

Barak, A., Hen, L., Boniel-Nissim, M., & Shapira, N. A. (2008). A comprehensive review and a meta-analysis of the effectiveness of internet-based psychotherapeutic interventions. *Journal of Technology in Human Services, 26*(2–4), 109–160. https://doi.org/10.1080/15228830802094429

Baudou, E., Nemmi, F., Biotteau, M., Maziero, S., Peran, P., & Chaix, Y. (2020). Can the cognitive phenotype in neurofibromatosis type 1 (NF1) be explained by neuroimaging? A review. *Frontiers in Neurology, 10*, 1373. https://doi.org/10.3389/fneur.2019.01373

Baumeister, H., Terhorst, Y., Grässle, C., Freudenstein, M., Nübling, R., & Ebert, D. D. (2020). Impact of an acceptance facilitating intervention on psychotherapists' acceptance of blended therapy. *PLOS ONE, 15*(8), e0236995. https://doi.org/10.1371/journal.pone.0236995

Beauchaine, T. P., & Gatzke-Kopp, L. M. (2012). Instantiating the multiple levels of analysis perspective in a program of study on externalizing behavior. *Development and Psychopathology, 24*(3), 1003–1018. https://doi.org/10.1017/S0954579412000508

Beauchaine, T. P., & McNulty, T. (2013). Comorbidities and continuities as ontogenic processes: Toward a developmental spectrum model of externalizing psychopathology. *Development and Psychopathology, 25*(4pt2), 1505–1528. https://doi.org/10.1017/S0954579413000746

Beauchaine, T. P., Hinshaw, S. P., & Pang, K. L. (2010). Comorbidity of attention-deficit/hyperactivity disorder and early-onset conduct disorder: Biological, environmental, and developmental mechanisms. *Clinical Psychology: Science and Practice, 17*(4), 327–336. https://doi.org/10.1111/j.1468-2850.2010.01224.x

Beaussart, M. L., Barbarot, S., Mauger, C., & Roy, A. (2018). Systematic review and meta-analysis of executive functions in preschool and school-age children with Neurofibromatosis Type 1. *Journal of the International Neuropsychological Society, 24*(9), 977–994. https://doi.org/10.1017/S1355617718000383

Bell, M. (2001). Online Role-Play: Anonymity, Engagement and Risk. *Educational Media International, 38*(4), 251–260. https://doi.org/10.1080/09523980110105141

Ben-Porath, D. D. (2004). Intersession telephone contact with individuals diagnosed with borderline personality disorder: Lessons from dialectical behavior therapy. *Cognitive and Behavioral Practice, 11*(2), 222–230. https://doi.org/10.1016/S1077-7229(04)80033-6

Ben-Porath, D. D. (2011a). Special series: Dialectical behavior therapy and telephone coaching introduction. *Cognitive and Behavioral Practice, 18*(2), 165–167. https://doi.org/10.1016/j.cbpra.2010.06.001

Ben-Porath, D. D. (2015). Orienting clients to telephone coaching in dialectical behavior therapy. *Cognitive and Behavioral Practice, 22*(4), 407–414. https://doi.org/10.1016/j.cbpra.2014.02.004

Ben-Porath, D. D., & Koons, C. R. (2005). Telephone coaching in dialectical behavior therapy: A decision-tree model for managing inter-session contact with clients. *Cognitive and Behavioral Practice, 12*(4), 448–460. https://doi.org/10.1016/S1077-7229(05)80072-0

Berryhill, M. B., Culmer, N., Williams, N., Halli-Tierney, A., Betancourt, A., Roberts, H., & King, M. (2019). Videoconferencing psychotherapy and depression: A systematic review. *Telemedicine and e-Health, 25*(6), 435–446. https://doi.org/10.1089/tmj.2018.0058

Berryhill, M. B., Halli-Tierney, A., Culmer, N., Williams, N., Betancourt, A., King, M., & Ruggles, H. (2019). Videoconferencing psychological therapy and anxiety: A systematic review. *Family Practice, 36*(1), 53–63. https://doi.org/10.1093/fampra/cmy072

Bicudo, N. P., de Menezes Neto, B. F., da Silva de Avó, L. R., Germano, C. M. R., & Melo, D. G. (2016). Quality of life in adults with neurofibromatosis 1 in Brazil. *Journal of Genetic Counseling, 25*(5), 1063–1074. https://doi.org/10.1007/s10897-016-9939-8

Bolton, A. J., & Dorstyn, D. S. (2015). Telepsychology for posttraumatic stress disorder: A systematic review. *Journal of Telemedicine and Telecare, 21*(5), 254–267. https://doi.org/10.1177/1357633X15571996

Bos-Roubos, A. G., van Dongen, L., Verhoeven, W. M., & Egger, J. I. (2020). Genetic disorders and dual diagnosis: Building clinical management on etiology and neurocognition. In *Handbook of dual diagnosis: Assessment and treatment in persons with intellectual disorders* (pp. 57–76). Springer International Publishing.

Bottesi, G., Spoto, A., Trevisson, E., Zuccarello, D., Vidotto, G., Cassina, M., & Clementi, M. (2020). Dysfunctional coping is related to impaired skin-related quality of life and psychological distress in patients with neurofibromatosis type 1 with major skin involvement. *British Journal of Dermatology, 182*(6), 1449–1457. https://doi.org/10.1111/bjd.18363

Bouma, A., Mulder, J., Lindeboom, J., & Schmand, B. (2012). *Handboek neuropsychologische diagnostiek* (2nd ed.). Pearson Benelux.

Brown, J. F., Brown, M. Z., & Dibiasio, P. (2013). Treating individuals with intellectual disabilities and challenging behaviors with adapted dialectical behavior therapy. *Journal of Mental Health Research in Intellectual Disabilities, 6*(4), 280–303. https://doi.org/10.1080/19315864.2013.829723

## C

Carmel, A., Villatte, J. L., Rosenthal, M. Z., Chalker, S., & Comtois, K. A. (2016). Applying technological approaches to clinical supervision in dialectical behavior therapy: A randomized feasibility trial of the bug-in-the-eye (BITE) model. *Cognitive and Behavioral Practice, 23*(2), 221–229. https://doi.org/10.1016/j.cbpra.2015.08.001

Caspi, A., & Moffitt, T. E. (2018). All for one and one for all: Mental disorders in one dimension. *American Journal of Psychiatry, 175*(9), 831–844. https://doi.org/10.1176/appi.ajp.2018.17121383

Caspi, A., & Silva, P. A. (1995). Temperamental qualities at age three predict personality traits in young adulthood: Longitudinal evidence from a birth cohort. *Child Development, 66*(2), 486. https://doi.org/10.2307/1131592

Cavicchioli, M., Ramella, P., Vassena, G., Simone, G., Prudenziati, F., Sirtori, F., Movalli, M., & Maffei, C. (2020). Dialectical behaviour therapy skills training for the treatment of addictive behaviours among individuals with alcohol use disorder: The effect of emotion regulation and experiential avoidance. *American Journal of Drug and Alcohol Abuse, 46*(3), 368–384. https://doi.org/10.1080/00952990.2020.1712411

Chalker, S. A., Carmel, A., Atkins, D. C., Landes, S. J., Kerbrat, A. H., & Comtois, K. A. (2015). Examining challenging behaviors of clients with borderline personality disorder. *Behaviour Research and Therapy, 75*, 11–19. https://doi.org/10.1016/j.brat.2015.10.003





Chapman, A. L. (2018). *Phone coaching in dialectical behavior therapy.* Guilford Press.

Chisholm, A. K., Anderson, V. A., Pride, N. A., Malarbi, S., North, K. N., & Payne, J. M. (2018). Social function and autism spectrum disorder in children and adults with neurofibromatosis type 1: A systematic review and meta-analysis. *Neuropsychology Review, 28*, 317–340. https://doi.org/10.1007/s11065-018-9380-x

Chu, B. C., Rizvi, S. L., Zendegui, E. A., & Bonavitacola, L. (2015). Dialectical behavior therapy for school refusal: Treatment development and incorporation of web-based coaching. *Cognitive and Behavioral Practice, 22*(3), 317–330. https://doi.org/10.1016/j.cbpra.2014.08.002

Chugani, C. D., & Landes, S. J. (2016). Dialectical behavior therapy in college counseling centers: Current trends and barriers to implementation. *Journal of College Student Psychotherapy, 30*(3), 176–186. https://doi.org/10.1080/87568225.2016.1177429

Cipolletta, S., Spina, G., & Spoto, A. (2018). Psychosocial functioning, self-image, and quality of life in children and adolescents with neurofibromatosis type 1. *Child: Care, Health and Development, 44*(2), 260–268. https://doi.org/10.1111/cch.12496

Conway, C. C., Forbes, M. K., Forbush, K. T., Fried, E. I., Hallquist, M. N., Kotov, R., Mullins-Sweatt, S. N., Shackman, A. J., Skodol, A. E., South, S. C., Sunderland, M., Waszczuk, M. A., Zald, D. H., Afzali, M. H., Bornovalova, M. A., Carragher, N., Docherty, A. R., Jonas, K. G., Krueger, R. F., Patalay, P., … Eaton, N. R. (2019). A hierarchical taxonomy of psychopathology can transform mental health research. *Perspectives on Psychological Science, 14*(3), 419–436. https://doi.org/10.1177/1745691618810696

Copley-Merriman, C., Yang, X., Juniper, M., Amin, S., Yoo, H. K., & Sen, S. S. (2021). Natural history and disease burden of neurofibromatosis type 1 with plexiform neurofibromas: A systematic literature review. *Adolescent Health, Medicine and Therapeutics, 12*, 55–66. https://doi.org/10.2147/AHMT.S303456

Coutinho, V., Câmara-Costa, H., Kemlin, I., Billette de Villemeur, T., Rodriguez, D., & Dellatolas, G. J. A. N. C. (2017). The discrepancy between performance-based measures and questionnaires when assessing clinical outcomes and quality of life in pediatric patients with neurological disorders. *Applied Neuropsychology: Child, 6*(4), 255–261. https://doi.org/10.1080/21622965.2016.1146141

Crawford, H. A., Barton, B., Wilson, M. J., Berman, Y., McKelvey-Martin, V. J., Morrison, P. J., & North, K. N. (2015). The impact of neurofibromatosis type 1 on the health and wellbeing of Australian adults. *Journal of Genetic Counseling, 24*, 931–944. https://doi.org/10.1007/s10897-015-9829-5

Cristol, S. (2018). Patient's perspective on using mobile technology as an aid to psychotherapy. *JMIR Mental Health, 5*(4), e10015. https://doi.org/10.2196/10015

Cuthbert, B. N., & Insel, T. R. (2013). Toward the future of psychiatric diagnosis: The seven pillars of RDoC. *BMC Medicine, 11*, Article 126. https://doi.org/10.1186/1741-7015-11-126

## D

David, N., Bewernick, B. H., Cohen, M. X., Newen, A., Lux, S., Fink, G. R., Shah, N. J., & Vogeley, K. (2006). Neural representations of self versus other: Visual-spatial perspective taking and agency in a virtual ball-tossing game. *Journal of Cognitive Neuroscience, 18*(6), 898–910. https://doi.org/10.1162/jocn.2006.18.6.898

De Souza Costa, D., & De Paula, J. J. (2015). Usefulness of the reliable change index for psychology and psychiatry in clinical practice: A case report of cognitive-behavioral therapy. *Clinical Neuropsychiatry, 12*(5). https://doi.org/10.1590/1980-57642015DN93000008

De Vet, H. C., De Bie, R. A., Van Der Heijden, G. J., Verhagen, A. P., Sijpkes, P., & Knipschild, P. G. (1997). Systematic reviews on the basis of methodological criteria. *Physiotherapy, 83*(6), 284–289. https://doi.org/10.1016/S0031-9406(05)66175-5

De Witte, N. A., Carlbring, P., Etzelmueller, A., Nordgreen, T., Karekla, M., Haddouk, L., … Brugnera, A. (2021). Online consultations in mental healthcare during the COVID-19 outbreak: An international survey study on professionals' motivations and perceived barriers. *Internet Interventions, 25*, 100405. https://doi.org/10.1016/j.invent.2021.100405

Debard, G., De Witte, N., Sels, R., Mertens, M., Van Daele, T., & Bonroy, B. (2020). Making wearable technology available for mental healthcare through an online platform with stress detection algorithms: The Carewear project. *Journal of Sensors, 2020*, 8846077. https://doi.org/10.1155/2020/8846077

Deckers, J. W. M., Lobbestael, J., van Wingen, G. A., Kessels, R. P. C., Arntz, A., & Egger, J. I. M. (2015). The influence of stress on social cognition in patients with borderline personality disorder. *Psychoneuroendocrinology, 52*, 119–129. https://doi.org/10.1016/j.psyneuen.2014.11.003

Descheemaeker, M. J., Plasschaert, E., Frijns, J. P., & Legius, E. (2013). Neuropsychological profile in adults with neurofibromatosis type 1 compared to a control group. *Journal of Intellectual Disability Research, 57*(9), 874–886. https://doi.org/10.1111/j.1365-2788.2012.01648.x

Dheensa, S., & Williams, G. A. (2009). "I have NF. NF does not have me.": An interpretative phenomenological analysis of coping with neurofibromatosis type 1. *Health Psychology Update, 18*(1), 3–8.

Dimeff, L. A., Harned, M. S., Woodcock, E. A., Skutch, J. M., Koerner, K., & Linehan, M. M. (2015). Investigating bang for your training buck: A randomized controlled trial comparing three methods of training clinicians in two core strategies of dialectical behavior therapy. *Behavior Therapy, 46*(3), 283–295. https://doi.org/10.1016/j.beth.2015.01.001

Dimeff, L. A., Koerner, K., Woodcock, E. A., Beadnell, B., Brown, M. Z., Skutch, J. M., ... Harned, M. S. (2009). Which training method works best? A randomized controlled trial comparing three methods of training clinicians in dialectical behavior therapy skills. *Behaviour Research and Therapy, 47*(11), 921–930. https://doi.org/10.1016/j.brat.2009.07.011

Dimeff, L. A., Woodcock, E. A., Harned, M. S., & Beadnell, B. (2011). Can dialectical behavior therapy be learned in highly structured learning environments? Results from a randomized controlled dissemination trial. *Behavior Therapy, 42*(2), 263–275. https://doi.org/10.1016/j.beth.2010.06.004

Domon-Archambault, V., Gagnon, L., Benoît, A., & Perreault, S. (2018). Psychosocial features of neurofibromatosis type 1 in children and adolescents. *Journal of Child Neurology, 33*(3), 225–232. https://doi.org/10.1177/0883073817749367

Domsalla, M., Koppe, G., Niedtfeld, I., Vollstädt-Klein, S., Schmahl, C., Bohus, M., & Lis, S. (2014). Cerebral processing of social rejection in patients with borderline personality disorder. *Social Cognitive and Affective Neuroscience, 9*(11), 1789–1797. https://doi.org/10.1093/scan/nst176

Doser, K., Andersen, E. W., Kenborg, L., Dalton, S. O., Jepsen, J. R. M., Krøyer, A., ... & Bidstrup, P. E. (2020). Clinical characteristics and quality of life, depression, and anxiety in adults with neurofibromatosis type 1: A nationwide study. *American Journal of Medical Genetics Part A, 182*(7), 1704–1715. https://doi.org/10.1002/ajmg.a.61627

## E

Ebert, D. D., Berking, M., Cuijpers, P., Lehr, D., Pörtner, M., & Baumeister, H. (2015). Increasing the acceptance of internet-based mental health interventions in primary care patients with depressive symptoms: A randomized controlled trial. *Journal of Affective Disorders, 176*, 9–17. https://doi.org/10.1016/j.jad.2015.01.056

Eikelboom, W. S., van den Berg, E., Beauchamp, M. H., Bray, K. O., Kumfor, F., MacPherson, S. E., ... & Kessels, R. P. (2025). Providing a taxonomy for social cognition: how to bridge the gap between expert opinion, empirical data, and theoretical models. *Journal of Psychiatry and Neuroscience*, *50*(3), E157-E161. DOI: https://doi.org/10.1503/jpn.240156

Evans, D. G., Howard, E., Giblin, C., Clancy, T., Spencer, H., Huson, S. M., & Lalloo, F. (2010). Birth incidence and prevalence of tumorprone syndromes: Estimates from a UK family genetic register service. *American Journal of Medical Genetics Part A, 152A*(2), 327–332. https://doi.org/10.1002/ajmg.a.33139

## F

Fernández-Álvarez, J., & Fernández-Álvarez, H. (2021). Videoconferencing psychotherapy during the pandemic: Exceptional times with enduring effects? *Frontiers in Psychology, 12*, 589536. https://doi.org/10.3389/fpsyg.2021.589536

Ferner, E. F., & Evans, D. G. R. (2011). *Neurofibromatosis in clinical practice*. Springer-Verlag.

Ferner, R. E. (2007). Neurofibromatosis 1 and neurofibromatosis 2: A twenty first century perspective. *The Lancet Neurology, 6*(4), 340–351. https://doi.org/10.1016/S1474-4422(07)70075-3

First, M. B., Gibbon, M., Spitzer, R. L., Williams, J. B., & Benjamin, L. S. (1997). *Structured clinical interview for DSM-IV® axis II personality disorders SCID-II*. American Psychiatric Pub.





Fjermestad, K. W., Nyhus, L., Kanavin, Ø. J., Heiberg, A., & Hoxmark, L. B. (2018). Health survey of adults with neurofibromatosis 1 compared to population study controls. *Journal of Genetic Counseling, 27*, 1102–1110. https://doi.org/10.1007/s10897-018-0229-5

Flores, A., Linehan, M. M., Todd, S., & Hoffman, H. G. (2018). The use of virtual reality to facilitate mindfulness skills training in dialectical behavioral therapy for spinal cord injury: A case study. *Frontiers in Psychology, 9*, 531. https://doi.org/10.3389/fpsyg.2018.00531

Flynn, D., Joyce, M., Gillespie, C., Kells, M., Swales, M., Spillane, A., ... Weihrauch, M. (2020). Evaluating the national multisite implementation of dialectical behaviour therapy in a community setting: A mixed methods approach. *BMC Psychiatry, 20*(1), 235. https://doi.org/10.1186/s12888-020-02610-3

Flynn, D., Joyce, M., Spillane, A., Wrigley, C., Corcoran, P., Hayes, A., Flynn, M., Wyse, D., Corkery, B., & Mooney, B. (2019). Does an adapted Dialectical Behaviour Therapy skills training programme result in positive outcomes for participants with a dual diagnosis? A mixed methods study. *Addiction Science & Clinical Practice, 14*(1), 28. https://doi.org/10.1186/s13722-019-0156-2

Foji, S., Mohammadi, E., Sanagoo, A., & Jouybari, L. (2021). The patients' experiences of burden of neurofibromatosis: A qualitative study. *Iranian Journal of Nursing and Midwifery Research, 26*(4), 342–348. https://doi.org/10.4103/ijnmr.IJNMR_178_20

Forbes, E. E., & Dahl, R. E. (2005). Neural systems of positive affect: Relevance to understanding child and adolescent depression? *Development and Psychopathology, 17*(03). https://doi.org/10.1017/S095457940505039X

Fournier, H., Calcagni, N., Morice-Picard, F., et al. (2023). Psychosocial implications of rare genetic skin diseases affecting appearance on daily life experiences, emotional state, self-perception and quality of life in adults: A systematic review. *Orphanet Journal of Rare Diseases, 18*(1), Article 39. https://doi.org/10.1186/s13023-023-02650-8

Freije, H., Dietz, B., & Appelo, M. (2002). Behandeling van de borderline persoonlijkheidsstoornis met de vers: De Vaardigheidstraining emotionele regulatiestoornis. *Dth, 22*, 160–166.

Fruzzetti, A. E., Shenk, C., & Hoffman, P. D. (2005). Family interaction and the development of borderline personality disorder: A transactional model. *Development and Psychopathology, 17*(04). https://doi.org/10.1017/S0954579405050479

## G

Gomez, J., Hoffman, H. G., Bistricky, S. L., Gonzalez, M., Rosenberg, L., Sampaio, M., Garcia-Palacios, A., Navarro-Haro, M. V., Alhalabi, W., Rosenberg, M., Meyer, W. J., & Linehan, M. M. (2017). The use of virtual reality facilitates dialectical behavior therapy® "observing sounds and visuals" mindfulness skills training exercises for a Latino patient with severe burns: A case study. *Frontiers in Psychology, 8*, 1611. https://doi.org/10.3389/fpsyg.2017.01611

Görg, N., Priebe, K., Deuschel, T., Schüller, M., Schriner, F., Kleindienst, N., Ludäscher, P., Schmahl, C., & Bohus, M. (2016). Computer-assisted in sensu exposure for posttraumatic stress disorder: Development and evaluation. *JMIR Mental Health, 3*(2), e27. https://doi.org/10.2196/mental.5697

Gray, J. A., & McNaughton, N. (2007). *The neuropsychology of anxiety: An enquiry into the function of the septo-hippocampal system* (2nd ed., repr). Oxford Univ. Press.

Grob, A., Horowitz, D., & Punt, D. J. (2014). *FEEL-E. Fragebogen zur Erhebung der Emotionsregulation bei Erwachsenen*. Bern: Huber.

Gunderson, J. G. (2007). Disturbed relationships as a phenotype for borderline personality disorder. *American Journal of Psychiatry, 164*(11), 1637–1640. https://doi.org/10.1176/appi.ajp.2007.07071125

Gunderson, J. G. (2011). Ten-year course of borderline personality disorder: Psychopathology and function from the Collaborative Longitudinal Personality Disorders Study. *Archives of General Psychiatry, 68*(8), 827. https://doi.org/10.1001/archgenpsychiatry.2011.37

Gunderson, J. G., Zanarini, M. C., Choi-Kain, L. W., Mitchell, K. S., Jang, K. L., & Hudson, J. I. (2011). Family study of borderline personality disorder and its sectors of psychopathology. *Archives of General Psychiatry, 68*(7), 753. https://doi.org/10.1001/archgenpsychiatry.2011.65

Gutmann, D. H., Ferner, R. E., Listernick, R. H., Korf, B. R., Wolters, P. L., & Johnson, K. J. (2017). Neurofibromatosis type 1. *Nature Reviews Disease Primers, 3*(1), 1–17. https://doi.org/10.1038/nrdp.2017.5

## H

Hayes, S. C., Strosahl, K., Wilson, K. G., Bissett, R. T., Pistorello, J., Toarmino, D., ... & McCurry, S. M. (2004). Measuring experiential avoidance: A preliminary test of a working model. *The Psychological Record, 54*, 553–578. https://doi.org/10.1007/BF03395492

Helweg-Jørgensen, S., Schmidt, T., Lichtenstein, M. B., & Pedersen, S. S. (2019). Using a mobile diary app in the treatment of borderline personality disorder: Mixed methods feasibility study. *JMIR Formative Research, 3*(3), e12852. https://doi.org/10.2196/12852

Hendriks, A. L., Barnes-Holmes, Y., McEnteggart, C., De Mey, H. R. A., Janssen, G. T. L., & Egger, J. I. M. (2016). Understanding and remediating social-cognitive dysfunctions in patients with serious mental illness using relational frame theory. *Frontiers in Psychology, 7*. https://doi.org/10.3389/fpsyg.2016.00143

Hilty, D. M., Ferrer, D. C., Parish, M. B., Johnston, B., Callahan, E. J., & Yellowlees, P. M. (2013). The effectiveness of telemental health: A 2013 review. *Telemedicine and e-Health, 19*(6), 444–454. https://doi.org/10.1089/tmj.2013.0075

Hoffman, P. D., Fruzzetti, A., & Swenson, C. (1999). Dialectical behavior therapy—Family skills training. *Family Process, 38*(4), 399–414. https://doi.org/10.1111/j.1545-5300.1999.00399.x

Holsbrink-Engels, G. A. (2001). Using a computer learning environment for initial training in dealing with social-communicative problems. *British Journal of Educational Technology, 32*(1), 53–67. https://doi.org/10.1111/1467-8535.00176

Hooley, J. M., & Miklowitz, D. J. (2017). Perceived criticism in the treatment of a high-risk adolescent. *Journal of Clinical Psychology, 73*(5), 570–578.

Hooley, J. M., & Teasdale, J. D. (1989). Predictors of relapse in unipolar depressives: Expressed emotion, marital distress, and perceived criticism. *Journal of Abnormal Psychology, 98*(3), 229–235. https://doi.org/10.1037/0021-843X.98.3.229

Hughes, A. J., Botanov, Y., & Beier, M. (2022). Dialectical behavior therapy skills training for individuals with multiple sclerosis and their support partners: A pilot randomized controlled trial. *Multiple Sclerosis and Related Disorders, 59*, 103481. https://doi.org/10.1016/j.msard.2021.103481

Huijbregts, S. C., Loitfelder, M., Rombouts, S. A., Swaab, H., Verbist, B. M., Arkink, E. B., ... & Veer, I. M. (2015). Cerebral volumetric abnormalities in neurofibromatosis type 1: Associations with parent ratings of social and attention problems, executive dysfunction, and autistic mannerisms. *Journal of Neurodevelopmental Disorders, 7*(32), 1–9. https://doi.org/10.1186/s11689-015-9128-3

Hyman, S. L., Shores, A. E., & North, K. N. (2006). Learning disabilities in children with neurofibromatosis type 1: Subtypes, cognitive profile, and attention-deficit-hyperactivity disorder. *Developmental Medicine and Child Neurology, 48*(12), 973–977. https://doi.org/10.1017/S0012162206002131

Hyman, S. L., Shores, A., & North, K. N. (2005). The nature and frequency of cognitive deficits in children with neurofibromatosis type 1. *Neurology, 65*(7), 1037–1044. https://doi.org/10.1212/01.wnl.0000179303.72345.ce

## I

Ilagan, G. S., Iliakis, E. A., Wilks, C. R., Vahia, I. V., & Choi-Kain, L. W. (2020). Smartphone applications targeting borderline personality disorder symptoms: A systematic review and meta-analysis. *Borderline Personality Disorder and Emotion Dysregulation, 7*(1), 1–5. https://doi.org/10.1186/s40479-020-00127-5

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., Sanislow, C., & Wang, P. (2010). Research domain criteria (RDoC): Toward a new classification framework for research on mental disorders. *American Journal of Psychiatry, 167*(7), 748–751. https://doi.org/10.1176/appi.ajp.2010.09091379

## J

Jacobs, N., Kleen, M., De Groot, F., & A-Tjak, J. (2008). Measuring experiential avoidance. Dutch translation of the *Acceptance and Action Questionnaire-II* (AAQ-II). *Gedragstherapie, 41*, 349–361.

Jacobson, N. S., & Truax, P. (1991). Clinical significance: A statistical approach to defining meaningful change in psychotherapy research. *Journal of Consulting and Clinical Psychology, 59*, 12–19.

Jacobson, N. S., Follette, W. C., & Revenstorf, D. (1984). Psychotherapy outcome research: Methods for reporting variability and evaluating clinical significance. *Behavior Therapy, 15*(4), 336–352. https://doi.org/10.1016/S0005-7894(84)80002-7







Jett, K., & Friedman, J. M. (2010). Clinical and genetic aspects of neurofibromatosis 1. *Genetics in Medicine: Official Journal of the American College of Medical Genetics, 12*(1), 1–11. https://doi.org/10.1097/GIM.0b013e3181bf15e3

Joint Task Force for the Development of Telepsychology Guidelines for Psychologists. (2013). Guidelines for the practice of telepsychology. *American Psychologist, 68*(9), 791–800. https://doi.org/10.1037/a0035001

## K

Karekla, M., Kasinopoulos, O., Neto, D. D., Ebert, D. D., Van Daele, T., Nordgreen, T., Höfer, S., Øverland, S., & Jensen, K. L. (2019). Best practices and recommendations for digital interventions to improve engagement and adherence in chronic illness sufferers. *European Psychologist, 24*(1), 49–67. https://doi.org/10.1027/1016-9040/a000349

Kauth, M. R., Adler, G., McCandless, S. J., & Leopolous, W. S. (2017). Embedding new clinical practices: The role of facilitation in enhancing web-based training for mental health providers. *Journal of Mental Health Training, Education and Practice, 12*(1), 24–32. https://doi.org/10.1108/JMHTEP-01-2016-0001

Kells, M., Joyce, M., Flynn, D., Spillane, A., & Hayes, A. (2020). Dialectical behaviour therapy skills reconsidered: Applying skills training to emotionally dysregulated individuals who do not engage in suicidal and self-harming behaviours. *Borderline Personality Disorder and Emotion Dysregulation, 7*, 3. https://doi.org/10.1186/s40479-020-0119-y

Keng, S. L., Mohd Salleh Sahimi, H. B., Chan, L. F., Woon, L., Eu, C. L., Sim, S. H., & Wong, M. K. (2021). Implementation of brief dialectical behavior therapy skills training among borderline personality disorder patients in Malaysia: Feasibility, acceptability, and preliminary outcomes. *BMC Psychiatry, 21*(1), 486. https://doi.org/10.1186/s12888-021-03500-y

Kirtley, J., Chiocchi, J., Cole, J., & Sampson, M. (2019). Stigma, emotion appraisal, and the family environment as predictors of carer burden for relatives of individuals who meet the diagnostic criteria for borderline personality disorder. *Journal of Personality Disorders, 33*(4), 497–514. https://doi.org/10.1521/pedi_2018_32_355

Konradi, A. (2021). Stigma and psychological distress among pediatric participants in the FD/MAS Alliance Patient Registry. *BMC Pediatrics, 21*(1), Article 173. https://doi.org/10.1186/s12887-021-02634-y

Koons, C. R. (2011). The role of the team in managing telephone consultation in dialectical behavior therapy: Three case examples. *Cognitive and Behavioral Practice, 18*(2), 168–177. https://doi.org/10.1016/j.cbpra.2009.10.008

Kotov, R., Krueger, R. F., & Watson, D. (2018). A paradigm shift in psychiatric classification: The Hierarchical Taxonomy of Psychopathology (HiTOP). *World Psychiatry, 17*(1), 24–25. https://doi.org/10.1002/wps.20478

Kotov, R., Krueger, R. F., Watson, D., Achenbach, T. M., Althoff, R. R., Bagby, R. M., Brown, T. A., Carpenter, W. T., Caspi, A., Clark, L. A., Eaton, N. R., Forbes, M. K., Forbush, K. T., Goldberg, D., Hasin, D., Hyman, S. E., Ivanova, M. Y., Lynam, D. R., Markon, K., ... Zimmerman, M. (2017). The Hierarchical Taxonomy of Psychopathology (HiTOP): A dimensional alternative to traditional nosologies. *Journal of Abnormal Psychology, 126*(4), 454–477. https://doi.org/10.1037/abn0000258

## L

Lakeman, R., & Crighton, J. (2020). The impact of social distancing on people with borderline personality disorder: The views of dialectical behavioural therapists. *Issues in Mental Health Nursing*, 1–7. https://pubmed.ncbi.nlm.nih.gov/32878547/

Lakens, D. (2013). Calculating and reporting effect sizes to facilitate cumulative science: A practical primer for t-tests and ANOVAs. *Frontiers in Psychology, 4*, 863. https://doi.org/10.3389/fpsyg.2013.00863

Landes, S. J., Matthieu, M. M., Smith, B. N., McBain, S. A., & Ray, E. S. (2021). Challenges and potential solutions to implementing phone coaching in dialectical behavior therapy. *Cognitive and Behavioral Practice, 28*(1), 66–76. https://doi.org/10.1016/j.cbpra.2019.10.005

Landes, S. J., Matthieu, M. M., Smith, B. N., Trent, L. R., Rodriguez, A. L., Kemp, J., & Thompson, C. (2016). Dialectical behavior therapy training and desired resources for implementation: Results from a national program evaluation in the Veterans Health Administration. *Military Medicine, 181*(8), 747–752. https://doi.org/10.7205/MILMED-D-15-00267

Landes, S. J., Rodriguez, A. L., Smith, B. N., Matthieu, M. M., Trent, L. R., Kemp, J., & Thompson, C. (2017). Barriers, facilitators, and benefits of implementation of dialectical behavior therapy in routine care: Results from a national program evaluation survey in the Veterans Health Administration. *Translational Behavioral Medicine, 7*(4), 832–844. https://doi.org/10.1007/s13142-017-0465-5

Lannin, D., & Scott, N. (2014). Best practices for an online world. *Monitor on Psychology, 45*(2), 56–61.

Latzman, R. D., DeYoung, C. G., & HiTOP Neurobiological Foundations Workgroup. (2020). Using empirically derived dimensional phenotypes to accelerate clinical neuroscience: The Hierarchical Taxonomy of Psychopathology (HiTOP) framework. *Neuropsychopharmacology.* Advance online publication. https://doi.org/10.1038/s41386-020-0639-6

Legius, E., Messiaen, L., Wolkenstein, P., Pancza, P., Avery, R. A., Berman, Y., Blakeley, J., Babovic-Vuksanovic, D., Cunha, K. S., Ferner, R., Fisher, M. J., Friedman, J. M., Gutmann, D. H., Kehrer-Sawatzki, H., Korf, B. R., Mautner, V. F., Peltonen, S., Rauen, K. A., Riccardi, V., Schorry, E., … Plotkin, S. R. (2021). Revised diagnostic criteria for neurofibromatosis type 1 and Legius syndrome: An international consensus recommendation. *Genetics in Medicine: Official Journal of the American College of Medical Genetics, 23*(8), 1506–1513. https://doi.org/10.1038/s41436-021-01170-5

Lehtonen, A., Garg, S., Roberts, S. A., Trump, D., Evans, D. G., Green, J., & Huson, S. M. (2015). Cognition in children with neurofibromatosis type 1: Data from a population-based study. *Developmental Medicine & Child Neurology, 57*(7), 645–651. https://doi.org/10.1111/dmcn.12734

Lehtonen, A., Howie, E., Trump, D., & Huson, S. M. (2013). Behaviour in children with neurofibromatosis type 1: Cognition, executive function, attention, emotion, and social competence. *Developmental Medicine & Child Neurology, 55*(2), 111–125. https://doi.org/10.1111/j.1469-8749.2012.04399.x

Lewis, A. K., Porter, M. A., Williams, T. A., North, K. N., & Payne, J. M. (2016). Social competence in children with neurofibromatosis type 1: Relationships with psychopathology and cognitive ability. *Journal of Childhood & Developmental Disorders, 2*(2), 12. Retrieved from https://childhood-developmental-disorders.imedpub.com/social-competence-in-children-with-neurofibromatosis-type-1-relationships-with-psychopathology-and-cognitive-ability.php?aid=9014

Lezak, M. D., Howieson, D. B., Bigler, E. D., & Tranel, D. (2012). *Neuropsychological assessment* (5th ed.). Oxford University Press.

Limbrunner, H. M., Ben-Porath, D. D., & Wisniewski, L. (2011). DBT telephone skills coaching with eating disordered clients: Who calls, for what reasons, and for how long? *Cognitive and Behavioral Practice, 18*(2), 186–195. https://doi.org/10.1016/j.cbpra.2010.01.010

Linehan, M. (1993). *Skills training manual for treating borderline personality disorder.* Guilford Press.

Linehan, M. (2015). *DBT skills training manual* (Second edition). The Guilford Press.

Linehan, M. M. (1993). *Cognitive-behavioral treatment of borderline personality disorder.* Guilford Press.

Linehan, M. M. (1993). *Skills training manual for treating borderline personality disorder.* Guilford Press.

Linehan, M. M. (2011). Dialectical behavior therapy and telephone coaching. *Cognitive and Behavioral Practice, 18*(2), 207–208. https://doi.org/10.1016/j.cbpra.2010.06.003

Linehan, M. M. (2015). *DBT skills training handouts and worksheets.* Guilford Press.

Linehan, M. M., & Heard, H. L. (1993). Impact of treatment accessibility on clinical course of parasuicidal patients—in reply to R.E. Hoffman [Letter to the editor]. *Archives of General Psychiatry, 50*(2), 157–158. https://doi.org/10.1001/archpsyc.1993.01820140083011

Linehan, M. M., Armstrong, H. E., Suarez, A., Allmon, D., & Heard, H. L. (1991). Cognitive-behavioral treatment of chronically parasuicidal borderline patients. *Archives of General Psychiatry, 48*(12), 1060–1064. https://doi.org/10.1001/archpsyc.1991.01810360024003

Linehan, M. M., Dimeff, L., Waltz, J., & Koerner, K. (2000). *DBT skills training video: Opposite action.* Behavioral Technology Transfer Group.

Linehan, M. M., Heard, H. L., & Armstrong, H. E. (1993). Naturalistic follow-up of a behavioral treatment for chronically parasuicidal borderline patients. *Archives of General Psychiatry, 50*(12), 971–974. https://doi.org/10.1001/archpsyc.1993.01820240055007

Lis, S., & Bohus, M. (2013). Social interaction in borderline personality disorder. *Current Psychiatry Reports, 15*(2), 338. https://doi.org/10.1007/s11920-012-0338-z





Lopez, A., Rothberg, B., Reaser, E., Schwenk, S., & Griffin, R. (2020). Therapeutic groups via video teleconferencing and the impact on group cohesion. *mHealth, 6*, 13. https://doi.org/10.21037/mhealth.2019.11.04

Lorch, M., Ferner, R., Golding, J., & Whurr, R. (1999). The nature of speech and language impairment in adults with neurofibromatosis 1. *Journal of Neurolinguistics, 12*(3-4), 157–165. https://doi.org/10.1016/S0911-6044(99)00012-3

Lungu, A. (2015). *Computerized trans-diagnostic dialectical behavior therapy skills training for emotion dysregulation* [Doctoral dissertation, University of Washington].

## M

Maffei, C., Cavicchioli, M., Movalli, M., Cavallaro, R., & Fossati, A. (2018). Dialectical behavior therapy skills training in alcohol dependence treatment: Findings based on an open trial. *Substance Use & Misuse, 53*(14), 2368–2385. https://doi.org/10.1080/10826084.2018.1480035

Manning, S. Y. (2011). Common errors made by therapists providing telephone consultation in dialectical behavior therapy. *Cognitive and Behavioral Practice, 18*(2), 178–185. https://doi.org/10.1016/j.cbpra.2010.06.002

Martin, S., Allen, T., Toledo-Tamula, M. A., Struemph, K., Reda, S., Wolters, P. L., … & Widemann, B. C. (2021). Acceptance and commitment therapy for adolescents and adults with neurofibromatosis type 1, plexiform neurofibromas, and chronic pain: Results of a randomized controlled trial. *Journal of Contextual Behavioral Science, 22*, 93–101.

Masland, S. R., & Hooley, J. M. (2015). Perceived criticism: A research update for clinical practitioners. *Clinical Psychology: Science and Practice, 22*(3), 211.

Masland, S. R., Drabu, S., & Hooley, J. M. (2019). Is perceived criticism an independent construct? Evidence for divergent validity across two samples. *Journal of Family Psychology, 33*(2), 133.

Mautner, V. F., Asuagbor, F. A., Dombi, E., et al. (2008). Assessment of benign tumor burden by whole-body MRI in patients with neurofibromatosis 1. *Neuro-Oncology, 10*(4), 593–598. https://doi.org/10.1215/15228517-2008-003

McCay, E., Carter, C., Aiello, A., Quesnel, S., Howes, C., Beanlands, H., … Lord, C. (2017). Training frontline community agency staff in dialectical behaviour therapy: Building capacity to meet the mental health needs of street-involved youth. *Journal of Mental Health Training, Education and Practice, 12*(2), 121–132. https://doi.org/10.1108/JMHTEP-07-2015-0034

McMain, S. F., Links, P. S., Gnam, W. H., Guimond, T., Cardish, R. J., Korman, L., & Streiner, D. L. (2009). A randomized trial of dialectical behavior therapy versus general psychiatric management for borderline personality disorder. *American Journal of Psychiatry, 166*(12), 1365–1374. https://doi.org/10.1176/appi.ajp.2009.09010039

McNair, L., Woodrow, C., & Hare, D. (2017). Dialectical behaviour therapy [DBT] with people with intellectual disabilities: A systematic review and narrative analysis. *Journal of Applied Research in Intellectual Disabilities, 30*(5), 787–804. https://doi.org/10.1111/jar.12388

McNeill, A. M., Hudock, R. L., Foy, A. M. H., Shanley, R., Semrud-Clikeman, M., Pierpont, M. E., Berry, S. A., Sommer, K., Moertel, C. L., & Pierpont, E. I. (2019). Emotional functioning among children with neurofibromatosis type 1 or Noonan syndrome. *American Journal of Medical Genetics. Part A, 179*(12), 2433–2446. https://doi.org/10.1002/ajmg.a.61361

McRae, J., Smith, C., Emmanuel, A., & Beeke, S. (2020). The experiences of individuals with cervical spinal cord injury and their family during post-injury care in non-specialised and specialised units in the UK. *BMC Health Services Research, 20*, 1–9. https://doi.org/10.1186/s12913-020-05722-2

Miller, A. L., Rathus, J. H., & Linehan, M. M. (2007). *Dialectical behavior therapy with suicidal adolescents.* Guilford Press.

Montgomery-Graham, S. (2016). DBT and schema therapy for borderline personality disorder: Mentalization as a common factor. *Journal of Contemporary Psychotherapy, 46*(1), 53–60. https://doi.org/10.1007/s10879-015-9309-0

Morley, S. (2017). *Single case methods in clinical psychology: A practical guide.* Routledge.

Morris-Rosendahl, D. J., & Crocq, M.-A. (2022). Neurodevelopmental disorders—The history and future of a diagnostic concept. *Dialogues in Clinical Neuroscience, 24*(1), 19–27. https://doi.org/10.31887/DCNS.2022.24.1/dmorrisrosendahl

Mulay, A. L., Waugh, M. H., Fillauer, J. P., Bender, D. S., Bram, A., Cain, N. M., … & Skodol, A. E. (2019). Borderline personality disorder diagnosis in a new key. *Borderline Personality Disorder and Emotion Dysregulation, 6*(1), 1–16. https://doi.org/10.1186/s40479-019-0116-1

Mulay, A. L., Waugh, M. H., Fillauer, J. P., Bender, D. S., Bram, A., Cain, N. M., … Keeley, J. W. (2019). Borderline personality disorder diagnosis in a new key. *Borderline Personality Disorder and Emotion Dysregulation, 6*(1), 18. https://doi.org/10.1186/s40479-019-0116-1

## N

Nadort, M., Arntz, A., Smit, J. H., Giesen-Bloo, J., Eikelenboom, M., Spinhoven, P., van Asselt, T., Wensing, M., & van Dyck, R. (2009). Implementation of outpatient schema therapy for borderline personality disorder with versus without crisis support by the therapist outside office hours: A randomized trial. *Behaviour Research and Therapy, 47*(11), 961–973. https://doi.org/10.1016/j.brat.2009.07.013

Nam, S. H., Nam, J. H., & Kwon, C. Y. (2021). Comparison of the mental health impact of COVID-19 on vulnerable and non-vulnerable groups: A systematic review and meta-analysis of observational studies. *International Journal of Environmental Research and Public Health, 18*(20), 10830. https://doi.org/10.3390/ijerph182010830

National Institutes of Health Consensus Development Conference Statement: Neurofibromatosis. (1988). Bethesda, MD, USA, July 13–15, 1987. *Neurofibromatosis, 1*(3), 172–178.

Navarro-Haro, M. V., Hoffman, H. G., Garcia-Palacios, A., Sampaio, M., Alhalabi, W., Hall, K., & Linehan, M. (2016). The use of virtual reality to facilitate mindfulness skills training in dialectical behavioral therapy for borderline personality disorder: A case study. *Frontiers in Psychology, 7*, 1573. https://doi.org/10.3389/fpsyg.2016.01573

Navarro-Haro, M. V., Modrego-Alarcón, M., Hoffman, H. G., López-Montoyo, A., Navarro-Gil, M., Montero-Marin, J., García-Palacios, A., Borao, L., & García-Campayo, J. (2019). Evaluation of a mindfulness-based intervention with and without virtual reality dialectical behavior therapy® mindfulness skills training for the treatment of generalized anxiety disorder in primary care: A pilot study. *Frontiers in Psychology, 10*, 55. https://doi.org/10.3389/fpsyg.2019.00055

Nelson, E. L., & Sharp, S. (2016). A review of pediatric telemental health. *Pediatric Clinics of North America, 63*(5), 913–931.

Nicholas, J., Bell, I. H., Thompson, A., Valentine, L., Simsir, P., Sheppard, H., & Adams, S. (2021). Implementation lessons from the transition to telehealth during COVID-19: A survey of clinicians and young people from youth mental health services. *Psychiatry Research, 299*, 113848. https://doi.org/10.1016/j.psychres.2021.113848

## O

O'Hayer, C. V. (2021). Building a life worth living during a pandemic and beyond: Adaptations of comprehensive DBT to COVID-19. *Cognitive and Behavioral Practice*. https://doi.org/10.1016/j.cbpra.2020.12.005

Oliveira, P. N., & Rizvi, S. L. (2018). Phone coaching in dialectical behavior therapy: Frequency and relationship to client variables. *Cognitive Behaviour Therapy, 47*(5), 383–396. https://doi.org/10.1080/16506073.2018.1437469

## P

Pavol, M., Hiscock, M., Massman, P., Moore III, B., Foorman, B., & Meyers, C. (2006). Neuropsychological function in adults with von Recklinghausen's neurofibromatosis. *Developmental Neuropsychology, 29*(3), 509–526. https://doi.org/10.1207/s15326942dn2903_8

Payne, J. M., Moharir, M. D., Webster, R., & North, K. N. (2010). Brain structure and function in neurofibromatosis type 1: Current concepts and future directions. *Journal of Neurology, Neurosurgery & Psychiatry, 81*(3), 304–309. https://doi.org/10.1136/jnnp.2009.179630

Payne, J. M., Porter, M., Pride, N. A., & North, K. N. (2016). Theory of mind in children with neurofibromatosis type 1. *Neuropsychology, 30*(4), 439–448. https://doi.org/10.1037/neu0000262

Payne, J. M., Walsh, K. S., Pride, N. A., Haebich, K. M., Maier, A., Chisholm, A., … & Klein-Tasman, B. (2020). Social skills and autism spectrum disorder symptoms in children with neurofibromatosis type 1: Evidence for clinical trial outcomes. *Developmental Medicine & Child Neurology, 62*(7), 813–819. https://doi.org/10.1111/dmcn.14517





Peeters, F. P. M. L., Ponds, R. H. W. M., & Vermeeren, M. T. G. (1996). Affectiviteit en zelfbeoordeling van depressie en angst. *Tijdschrift voor Psychiatrie*, 240–250.

Potter, B. S., & Mendoza, L. (2019). Cognitive issues experienced by individuals living with neurofibromatosis. In F. Signorelli & R. Messina (Eds.), *Neurofibromatosis - Current Trends and Future Directions*. https://doi.org/10.5772/intechopen.90020

Pride, N. A., Crawford, H., Payne, J. M., & North, K. N. (2013). Social functioning in adults with neurofibromatosis type 1. *Research in Developmental Disabilities, 34*(10), 3393–3399. https://doi.org/10.1016/j.ridd.2013.07.011

Pride, N. A., Korgaonkar, M. S., Barton, B., Payne, J. M., Vucic, S., & North, K. N. (2014). The genetic and neuroanatomical basis of social dysfunction: Lessons from neurofibromatosis type 1. *Human Brain Mapping, 35*(5), 2372–2382. https://doi.org/10.1002/hbm.22334

Pulopulos, M. M., Boccagno, C., De Raedt, R., & Hooley, J. M. (2021). Attenuated beta-adrenergic response to stress and increased anticipation and perception of social threat in women high on perceived criticism. *Psychoneuroendocrinology, 133*, 105421.

## R

R Core Team (2023). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing, Vienna, Austria. Retrieved from https://www.R-project.org/

Rauen, K. A. (2013). The RASopathies. *Annual Review of Genomics and Human Genetics, 14*, 355–369. https://doi.org/10.1146/annurev-genom-091212-153523

Reelick, M. F., Faes, M. C., Esselink, R. A., Kessels, R. P., & Rikkert, M. G. O. (2011). How to perform a preplanned process evaluation for complex interventions in geriatric medicine: Exemplified with the process evaluation of a complex falls-prevention program for community-dwelling frail older fallers. *Journal of the American Medical Directors Association, 12*(5), 331–336. https://doi.org/10.1016/j.jamda.2011.01.006

Reichardt, C., Scherwath, A., Felix Mautner, V., Bullinger, M., & Petersen-Ewert, C. (2013). Psychische Belastung von Erwachsenen mit Neurofibromatose Typ 1: Eine Längsschnittstudie [Psychological distress in adults with neurofibromatosis type 1: A longitudinal study]. *Psychotherapie, Psychosomatik, Medizinische Psychologie, 63*(2), 85–92. https://doi.org/10.1055/s-0032-1321883

Renshaw, K. D. (2007). Perceived criticism only matters when it comes from those you live with. *Journal of Clinical Psychology, 63*(12), 1171–1179.

Rietman, A. B., Oostenbrink, R., van Noort, K., Franken, M. J. P., Catsman-Berrevoets, C. E., Aarsen, F. K., Hendriksen, J. G., & de Nijs, P. F. A. (2017). Development of emotional and behavioral problems in neurofibromatosis type 1 during young childhood. *American Journal of Medical Genetics. Part A, 173*(9), 2373–2380. https://doi.org/10.1002/ajmg.a.38323

Rietman, A. B., van der Vaart, T., Plasschaert, E., Nicholson, B. A., Oostenbrink, R., Krab, L. C., … & Nijs, P. F. D. (2018). Emotional and behavioral problems in children and adolescents with neurofibromatosis type 1. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 177*(3), 319–328. https://doi.org/10.1002/ajmg.b.32612

Rietman, A. B., van Helden, H., Both, P. H., Taal, W., Legerstee, J. S., van Staa, A., … & van Eeghen, A. M. (2018a). Worries and needs of adults and parents of adults with neurofibromatosis type 1. *American Journal of Medical Genetics Part A, 176*(5), 1150–1160. https://doi.org/10.1002/ajmg.a.38680

Rizvi, S. L., Dimeff, L. A., Skutch, J., Carroll, D., & Linehan, M. M. (2011). A pilot study of the DBT coach: An interactive mobile phone application for individuals with borderline personality disorder and substance use disorder. *Behavior Therapy, 42*(4), 589–600. https://doi.org/10.1016/j.beth.2011.01.003

Rizvi, S. L., Hughes, C. D., & Thomas, M. C. (2016). The DBT coach mobile application as an adjunct to treatment for suicidal and self-injuring individuals with borderline personality disorder: A preliminary evaluation and challenges to client utilization. *Psychological Services, 13*(4), 380–388. https://doi.org/10.1037/ser0000100

Rodante, D. E., Kaplan, M. I., Olivera Fedi, R., Gagliesi, P., Pascali, A., José Quintero, P. S., … Daray, F. M. (2020). CALMA, a mobile health application, as an accessory to therapy for reduction of suicidal and non-suicidal self-injured behaviors: A pilot cluster randomized controlled trial. *Archives of Suicide Research, 17*, 1–8. https://doi.org/10.1080/13811118.2020.1834476

Roelofs, R. L., Wingbermühle, E., Freriks, K., Verhaak, C. M., Kessels, R. P. C., & Egger, J. I. M. (2015). Alexithymia, emotion perception, and social assertiveness in adult women with Noonan and Turner syndromes. *American Journal of Medical Genetics. Part A, 167A*(4), 768–776. https://doi.org/10.1002/ajmg.a.37006

Rosenberg, A. G. W., Mochèl, K., Hähner, L. M., Davidse, K., Bos-Roubos, A. G., van Dijk, S. A., … & de Graaff, L. C. G. (2024). Endocrine and non-endocrine causes of fatigue in adults with Neurofibromatosis type 1. *Frontiers in Endocrinology, 14*, 11191159. https://doi.org/10.3389/fendo.2023.1119159

Rosenberg, A. G. W., Pater, M. R. A., Pellikaan, K., Davidse, K., Kattentidt-Mouravieva, A. A., Kersseboom, R., … & de Graaff, L. C. G. (2021). What every internist-endocrinologist should know about rare genetic syndromes in order to prevent needless diagnostics, missed diagnoses and medical complications: Five years of 'Internal Medicine for Rare Genetic Syndromes'. *Journal of Clinical Medicine, 10*(22), 5457. https://doi.org/10.3390/jcm10225457

Rosnau, K., Hashmi, S. S., Northrup, H., Slopis, J., Noblin, S., & Ashfaq, M. (2017). Knowledge and self-esteem of individuals with neurofibromatosis type 1 (NF1). *Journal of Genetic Counseling, 26*, 620–627. https://doi.org/10.1007/s10897-016-0036-9

Ruggero, C. J., Kotov, R., Hopwood, C. J., First, M., Clark, L. A., Skodol, A. E., … & Zimmermann, J. (2019). Integrating the Hierarchical Taxonomy of Psychopathology (HiTOP) into clinical practice. *Journal of Consulting and Clinical Psychology, 87*(12), 1069–1084. https://doi.org/10.1037/ccp0000452

## S

Salamin, V., Rossier, V., Joye, D., Nolde, C., Pierrehumbert, T., Gothuey, I., & Guenot, F. (2021). Adaptations of an outpatient dialectical behavioral therapy during the COVID-19 pandemic and consequences of the confinement on patients with borderline personality disorder. *Annales Médico-Psychologiques, 179*(2), 131. https://doi.org/10.1016/j.amp.2020.10.006

Sánchez-García, J. C., Cortés-Martín, J., Rodríguez-Blanque, R., Marín-Jiménez, A. E., Montiel Troya, M., & Díaz-Rodríguez, L. (2021). Depression and anxiety in patients with rare diseases during the COVID-19 pandemic. *International Journal of Environmental Research and Public Health, 18*(6), 3234. https://doi.org/10.3390/ijerph18063234

Schiepek, G. (1986). *Systemische Diagnostik in der Klinischen Psychologie*. Psychologie Verlags Union.

Schiepek, G., Eckert, H., Aas, B., Wallot, S., & Wallot, A. (2016). *Integrative psychotherapy: A feedback-driven dynamic systems approach*. Hogrefe.

Schmand, B., Agelink van Rentergem, J., de Vent, N., Murre, J., & Huizinga, H. (2017). Advanced Neuropsychological Diagnostics Infrastructure (ANDI): Voor een scherpere neuropsychologische diagnostiek. *Tijdschrift voor Neuropsychologie, 12*(2), 114–124.

Schroeder, J., Wilkes, C., Rowan, K., Toledo, A., Paradiso, A., Czerwinski, M., Mark, G., & Linehan, M. M. (2018). Pocket skills: A conversational mobile web app to support dialectical behavioral therapy. In *Proceedings of the 2018 CHI Conference on Human Factors in Computing Systems* (pp. 1–15). https://doi.org/10.1145/3173574.3173972

Schütze, M., de Souza Costa, D., de Paula, J. J., Malloy-Diniz, L. F., Malamut, C., Mamede, M., Miranda, D. M., Brammer, M., & Romano-Silva, M. A. (2018). Use of machine learning to predict cognitive performance based on brain metabolism in neurofibromatosis type 1. *PloS One, 13*(9), e0203520. https://doi.org/10.1371/journal.pone.0203520

Schwetye, K. E., & Gutmann, D. H. (2014). Cognitive and behavioral problems in children with neurofibromatosis type 1: Challenges and future directions. *Expert Review of Neurotherapeutics, 14*(10), 1139–1152. https://doi.org/10.1586/14737175.2014.953931

Shilyansky, C., Lee, Y. S., & Silva, A. J. (2010). Molecular and cellular mechanisms of learning disabilities: A focus on NF1. *Annual Review of Neuroscience, 33*, 221–243. https://doi.org/10.1146/annurev-neuro-060909-153215

Shore, J. H., Yellowlees, P., Caudill, R., Johnston, B., Turvey, C., Mishkind, M., … Hilty, D. (2018). Best practices in videoconferencing-based telemental health April 2018. *Telemedicine and e-Health, 24*(11), 827–832. https://doi.org/10.1089/tmj.2018.0237

Sinnaeve, R., Vaessen, T., Van Diest, I., Myin-Germeys, I., Van den Bosch, L. M. C., Vrieze, E., … & Claes, S. (2021). Investigating the stress-related fluctuations of level of personality functioning: A critical review and agenda for future research. *Clinical Psychology & Psychotherapy, 28*(5), 1181–1193.





Sinnaeve, R., van den Bosch, L. M. C., Hakkaart-van Roijen, L., & Vansteelandt, K. (2018). Effectiveness of step-down versus outpatient dialectical behaviour therapy for patients with severe levels of borderline personality disorder: A pragmatic randomized controlled trial. *Borderline Personality Disorder and Emotion Dysregulation, 5*(1), 12. https://doi.org/10.1186/s40479-018-0089-5

Sloan, E., Hall, K., Moulding, R., Bryce, S., Mildred, H., & Staiger, P. K. (2017). Emotion regulation as a transdiagnostic treatment construct across anxiety, depression, substance, eating and borderline personality disorders: A systematic review. *Clinical Psychology Review, 57*, 141–163. https://doi.org/10.1016/j.cpr.2017.09.002

Smoktunowicz, E., Barak, A., Andersson, G., Banos, R. M., Berger, T., Botella, C., et al. (2020). Consensus statement on the problem of terminology in psychological interventions using the internet or digital components. *Internet Interventions, 21*, 100331. https://doi.org/10.1016/j.invent.2020.100331

Soler, J., Pascual, J. C., Tiana, T., Cebrià, A., Barrachina, J., Campins, M. J., … & Pérez, V. (2009). Dialectical behaviour therapy skills training compared to standard group therapy in borderline personality disorder: A 3-month randomised controlled clinical trial. *Behaviour Research and Therapy, 47*(5), 353–358. https://doi.org/10.1016/j.brat.2009.01.013

Stefanopoulou, E., Hogarth, H., Taylor, M., Russell-Haines, K., Lewis, D., & Larkin, J. (2020). Are digital interventions effective in reducing suicidal ideation and self-harm? A systematic review. *Journal of Mental Health, 29*(2), 207–216. https://doi.org/10.1080/09638237.2020.1714009

Steinberg, J. A., Steinberg, S. J., & Miller, A. L. (2011). Orienting adolescents and families to DBT telephone consultation: Principles, procedures, and pitfalls. *Cognitive and Behavioral Practice, 18*(2), 196–206. https://doi.org/10.1016/j.cbpra.2009.10.007

Stewart, D. R., Korf, B. R., Nathanson, K. L., Stevenson, D. A., & Yohay, K. (2018). Care of adults with neurofibromatosis type 1: A clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genetics in Medicine, 20*(6), 671–682. https://doi.org/10.1038/gim.2017.28

Storebø, O. J., Stoffers-Winterling, J. M., Völlm, B. A., Kongerslev, M. T., Mattivi, J. T., Jørgensen, M. S., Faltinsen, E., Todorovac, A., Sales, C. P., Callesen, H. E., Lieb, K., & Simonsen, E. (2020). Psychological therapies for people with borderline personality disorder. *Cochrane Database of Systematic Reviews, 2020*(11). https://doi.org/10.1002/14651858.CD012955.pub2

Strauss, E., Sherman, E. M. S., & Spreen, O. (2006). *A compendium of neuropsychological tests: Administration, norms, and commentary* (3rd ed.). Oxford University Press.

Swales, M. A. (Ed.). (2018). *The Oxford handbook of dialectical behaviour therapy.* Oxford University Press.

## T

Tate, R. L. (2010). *A compendium of tests, scales and questionnaires: The practitioner's guide to measuring outcomes after acquired brain impairment* (1st ed.). Psychology Press; Abingdon, UK.

Teding van Berkhout, E., & Malouff, J. M. (2016). The efficacy of empathy training: A meta-analysis of randomized controlled trials. *Journal of Counseling Psychology, 63*(1), 32–41. https://doi.org/10.1037/cou0000093

Thome, J., Liebke, L., Bungert, M., Schmahl, C., Domes, G., Bohus, M., & Lis, S. (2016). Confidence in facial emotion recognition in borderline personality disorder. *Personality Disorders: Theory, Research, and Treatment, 7*(2), 159–168. https://doi.org/10.1037/per0000142

Thompson, H. L., Viskochil, D. H., Stevenson, D. A., & Chapman, K. L. (2010). Speech-language characteristics of children with neurofibromatosis type 1. *American Journal of Medical Genetics. Part A, 152A*(2), 284–290. https://doi.org/10.1002/ajmg.a.33235

Torres Nupan, M. M., Velez Van Meerbeke, A., López Cabra, C. A., & Herrera Gomez, P. M. (2017). Cognitive and behavioral disorders in children with neurofibromatosis type 1. *Frontiers in Pediatrics, 5*, 227. https://doi.org/10.3389/fped.2017.00227

Tricco, A. C., Lillie, E., Zarin, W., O'Brien, K. K., Colquhoun, H., Levac, D., … Moher, D. (2018). PRISMA extension for scoping reviews (PRISMA-ScR): Checklist and explanation. *Annals of Internal Medicine, 169*(7), 467–473. https://doi.org/10.7326/M18-0850

Tsamakis, K., Tsiptsios, D., Ouranidis, A., Mueller, C., Schizas, D., Terniotis, C., … & Rizos, E. (2021). COVID-19 and its consequences on mental health. *Experimental and Therapeutic Medicine, 21*(3), 1–1. https://doi.org/10.3892/etm.2021.9675

## U

United Nations Educational Scientific and Cultural Organization (UNESCO). (2012). *International Standard Classification of Education-ISCED 2011*. Montreal. https://doi.org/10.15220/978-92-9189-123-8-en

## V

Valentine, J. C., & Thompson, S. G. (2013). Issues relating to confounding and meta-analysis when including non-randomized studies in systematic reviews on the effects of interventions. *Research Synthesis Methods, 4*(1), 26–35. https://doi.org/10.1002/jrsm.1064

Valentine, S. E., Bankoff, S. M., Poulin, R. M., Reidler, E. B., & Pantalone, D. W. (2015). The use of dialectical behavior therapy skills training as stand-alone treatment: A systematic review of the treatment outcome literature. *Journal of Clinical Psychology, 71*(1), 1–20. https://doi.org/10.1002/jclp.22114

Van Daele, T., Karekla, M., Kassianos, A. P., Compare, A., Haddouk, L., Salgado, J., ... De Witte, N. A. (2020). Recommendations for policy and practice of telepsychotherapy and e-mental health in Europe and beyond. *Journal of Psychotherapy Integration, 30*(2), 160–173. https://doi.org/10.1037/int0000218

Van den Bergh, R., Olthof, M., Goldbeck, F., Hegewald, K., Pommerien-Becht, F., Daniels Wredenhagen, N., Weggemans, R. J., Daalmans, S., Otten, R., Aas, B. G., & Lichtwarck Aschoff, A. (2022). The content of personalised network-based case formulations. *PsyArXiv.* https://doi.org/10.31234/osf.io/yan4k

Van den Bosch, L. M., Verheul, R., Schippers, G. M., & Van Den Brink, W. (2002). Dialectical behavior therapy of borderline patients with and without substance use problems: Implementation and long-term effects. *Addictive behaviors*, *27*(6), 911-923.

Van den Bosch, L. M. C., Sinnaeve, R., Hakkaart-van Roijen, L., & van Furth, E. F. (2014). Efficacy and cost-effectiveness of an experimental short-term inpatient Dialectical Behavior Therapy (DBT) program: Study protocol for a randomized controlled trial. *Trials, 15*(1), 152. https://doi.org/10.1186/1745-6215-15-152

Van Leeuwen, H., Van den Bosch, W., Ossewaarde, L., & Egger, J. I. (2022). Perceived criticism in relation to the dialectical behaviour therapy network training in a residential program: A pre-post study. *International Journal of Psychology and Psychological Therapy, 22*(3), 267–276.

Van Leeuwen, J. P. A., Urganci, Y., Ossewaarde, L., Boumans, C. E., Van Den Bosch, L. M. C., & Egger, J. I. M. (2024). Behandeling van emotieregulatieproblemen bij mensen met neurofibromatosis type 1. *Tijdschrift voor Psychiatrie, 66*(8), 331–335.

Van Ments, M. (1999). *The effective use of role play: Practical techniques for improving learning*. Kogan Page.

Van Minkelen, R., Van Bever, Y., Kromosoeto, J. N. R., Withagen-Hermans, C. J., Nieuwlaat, A., Halley, D. J. J., & Van den Ouweland, A. M. W. (2014). A clinical and genetic overview of 18 years neurofibromatosis type 1 molecular diagnostics in the Netherlands. *Clinical Genetics, 85*(4), 318–327. https://doi.org/10.1111/cge.12187

Vassallo, G., Mughal, Z., Robinson, L., Weisberg, D., Roberts, S. A., Hupton, E., Eelloo, J., Burkitt Wright, E. M., Garg, S., Lewis, L., Evans, D. G., & Stivaros, S. M. (2020). Perceived fatigue in children and young adults with neurofibromatosis type 1. *Journal of Paediatrics and Child Health, 56*(6), 878–883. https://doi.org/10.1111/jpc.14764

Verhage, F. (1964). *Intelligentie en leeftijd [Intelligence and age]* (Doctoral dissertation). Van Gorcum.

Vermeulen, K., Kleefstra, T., Janzing, J. G., Rietman, M., van Dongen, L., van Bokhoven, H., ... & Staal, W. G. (2021). The impact of rare genetic disorders on family functioning. *Medical Research Archives, 9*(11). https://doi.org/10.18103/mra.v9i11.2598

## W

Waltz, J., Dimeff, L. A., Koerner, K., Linehan, M. M., Taylor, L., & Miller, C. (2009). Feasibility of using video to teach a dialectical behavior therapy skill to clients with borderline personality disorder. *Cognitive and Behavioral Practice, 16*(2), 214–222. https://doi.org/10.1016/j.cbpra.2008.08.004

Wang, D. L., Smith, K. B., Esparza, S., Leigh, F. A., Muzikansky, A., Park, E. R., & Plotkin, S. R. (2012). Emotional functioning of patients with neurofibromatosis tumor suppressor syndrome. *Genetics in Medicine: Official Journal of the American College of Medical Genetics, 14*(12), 977–982. https://doi.org/10.1038/gim.2012.85







Wang, X., Wu, Q., Tang, H., Zhao, F., Yang, Z., Wang, B., Li, P., Wang, Z., Wu, Y., Fan, J., & Liu, P. (2019). Selective impairment of the executive attentional network in adult patients with neurofibromatosis type 1. *Neuroreport, 30*(14), 921–926. https://doi.org/10.1097/WNR.0000000000001275

Warner, N., & Murphy, M. (2022). Dialectical behaviour therapy skills training for individuals with substance use disorder: A systematic review. *Drug and Alcohol Review, 41*(2), 501–516. https://doi.org/10.1111/dar.13362

Washburn, M., & Parrish, D. E. (2013). DBT self-help application for mobile devices. *Journal of Technology in Human Services, 31*(2), 175–183. https://doi.org/10.1080/15228835.2013.775904

Waszczuk, M. A., Eaton, N. R., Krueger, R. F., Shackman, A. J., Waldman, I. D., Zald, D. H., Lahey, B. B., Patrick, C. J., Conway, C. C., Ormel, J., Hyman, S. E., Fried, E. I., Forbes, M. K., Docherty, A. R., Althoff, R. R., Bach, B., Chmielewski, M., DeYoung, C. G., Forbush, K. T., Hallquist, M., ... Kotov, R. (2020). Redefining phenotypes to advance psychiatric genetics: Implications from hierarchical taxonomy of psychopathology. *Journal of Abnormal Psychology, 129*(2), 143–161. https://doi.org/10.1037/abn0000486

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: The PANAS scales. *Journal of Personality and Social Psychology, 54*(6), 1063. https://doi.org/10.1037/0022-3514.54.6.1063

Weertman, A., Arntz, A., & Kerkhofs, M. (2000). *Gestructureerd diagnostisch interview voor DSM-IV persoonlijkheidsstoornissen (SCID II) [Structural and Clinical Interview for DSM-IV personality disorders (SCID II)]*. Lisse, The Netherlands: Swets Test.

White, A., Dunn, N., Matsunaga, E., & Dimeff, L. (2023). Innovations in practice: Feasibility and provision of dialectical behavior therapy skills training for adolescents and their families. *Child and Adolescent Mental Health, 28*(3), 458–460. https://doi.org/10.1111/camh.12605

Wilks, C. R., Lungu, A., Ang, S. Y., Matsumiya, B., Yin, Q., & Linehan, M. M. (2018). A randomized controlled trial of an internet delivered dialectical behavior therapy skills training for suicidal and heavy episodic drinkers. *Journal of Affective Disorders, 232*, 219–228. https://doi.org/10.1016/j.jad.2018.02.053

Wilks, C. R., Yin, Q., & Zuromski, K. L. (2020). User experience affects dropout from internet-delivered dialectical behavior therapy. *Telemedicine and e-Health, 26*(6), 794–797. https://doi.org/10.1089/tmj.2019.0124

Wilks, C., Yin, Q., Ang, S. Y., Matsumiya, B., Lungu, A., & Linehan, M. M. (2017). Internet-delivered dialectical behavioral therapy skills training for suicidal and heavy episodic drinkers: Protocol and preliminary results of a randomized controlled trial. *JMIR Research Protocols, 6*(10), e207. https://doi.org/10.2196/resprot.7767

Williams, V. C., Lucas, J., Babcock, M. A., Gutmann, D. H., Bruce, B., & Maria, B. L. (2009). *Neurofibromatosis type 1 revisited. Pediatrics, 123*(1), 124–133. https://doi.org/10.1542/peds.2007-3204

Wingbermühle, E., Roelofs, R. L., Oomens, W., Kramer, J., Draaisma, J. M. T., Leenders, E., Kleefstra, T., Kessels, R. P. C., & Egger, J. I. M. (2022). Cognitive phenotype and psychopathology in Noonan syndrome spectrum disorders through various Ras/MAPK pathway associated gene variants. *Journal of Clinical Medicine, 11*, 4735. https://doi.org/10.3390/jcm11164735

Worrall, J. M., & Fruzzetti, A. E. (2009). Improving peer supervisor ratings of therapist performance in dialectical behavior therapy: An internet-based training system. *Psychotherapy, 46*(4), 476–479. https://doi.org/10.1037/a0017948

## Z

Zale, E. L., Pierre-Louis, C., Macklin, E. A., Riklin, E., & Vranceanu, A. M. (2018). The impact of a mind–body program on multiple dimensions of resiliency among geographically diverse patients with neurofibromatosis. *Journal of Neuro-oncology, 137*, 321–329. https://doi.org/10.1007/s11060-017-2720-5

## Nederlandse Samenvatting

Het doel van dit proefschrift is het vergroten van het inzicht in de cognitieve en psychologische uitdagingen waarmee volwassenen met Neurofibromatose type 1 (NF1) geconfronteerd worden, alsmede het onderzoeken van de toepasbaarheid van een vaardigheidstraining gebaseerd op Dialectische Gedragstherapie (DGT) als transdiagnostische interventie voor deze doelgroep. Hoewel NF1 primair bekendstaat als een genetische aandoening die de huid en het zenuwstelsel aantast, krijgt de psychosociale problematiek van deze groep in de reguliere zorg nog onvoldoende aandacht. Verwijzing naar de geestelijke gezondheidszorg vindt veelal pas plaats bij duidelijke psychische klachten of onverklaarde lichamelijke symptomen, zoals vermoeidheid of stemmingsstoornissen, en een passende vervolgbehandeling blijft vaak uit. In dit proefschrift werd onderzoek gedaan naar cognitie en gedrag van mensen met NF1. Daarnaast werd nagegaan in hoeverre DGT, als geïntegreerde transdiagnostische aanpak gericht op emotieregulatie, kan aansluiten bij de behoeften van deze groep. DGT biedt een vaardigheids-training waarin vaardigheden worden geleerd op het gebied van mindfulness, emotieregulatie, interpersoonlijke effectiviteit en crisisvaardigheden. De dialectische basis van DGT, waarbij een balans wordt gezocht tussen acceptatievaardigheden en veranderingsvaardigheden, maakt het mogelijk om mensen te helpen hun gedrag te veranderen én tegelijkertijd de realiteit te accepteren. DGT richt zich zowel op individuele als op systeemfactoren, waaronder de invloed van de omgeving op het in stand houden of beïnvloeden van gedrag. Een behandelvorm die zich richt op emotionele regulatie en gedragsverandering kan mensen met NF1 mogelijk helpen om meer grip te krijgen op hun interne emotionele ervaringen en zo hun algehele psychologisch functioneren te verbeteren.

Het eerste hoofdstuk van dit proefschrift start met een systematische en gedetailleerde beoordeling van cognitief functioneren, gedrag en psychopathologie bij mensen met NF1. Vervolgens wordt de toepasbaarheid van DGT verkend aan de hand van diepte interviews met twee patiënten die een DGT vaardigheidstraining hebben gevolgd, evenals met hun naasten. Het daaropvolgende hoofdstuk benadrukt het belang van het betrekken van naasten bij de behandeling. Daarna volgt een systematische review van de huidige toepassingen van telepsychologie binnen de context van DGT. Het proefschrift sluit af met een haalbaarheidsstudie waarin de uitvoerbaarheid en potentiële therapeutische waarde van een (*blended*) DGT vaardigheidstraining worden geëvalueerd, met als doel bij te dragen aan meer toegankelijke en op maat gemaakte psychologische zorg voor volwassenen met NF1.

## Samenvatting en belangrijkste bevindingen

Een gedetailleerde beschrijving van cognitie, gedrag en psychopathologie in een groep van 62 NF1 patiënten is weergegeven in **hoofdstuk 2**. Resultaten lieten lagere intelligentieniveaus en specifieke cognitieve beperkingen zien. Deze betroffen onder meer tekorten in aandacht en verwerkingssnelheid, verbale vloeiendheid, leer- en geheugenfuncties, en sociale cognitie. In tegenstelling tot de verwachtingen bleek het executief functioneren op het gebied van planning, organisatie en inhibitie relatief intact. Meer specifiek toonden de resultaten aan dat de cognitieve prestaties van de NF1-groep significant lager waren dan normatieve gemiddelden op het gebied van leessnelheid, visuospatiële perceptie, visueel leren en visueel geheugen. De beoordeling van gedrag en psychopathologie liet verhoogde niveaus zien van problemen in emotieperceptie, subjectief ervaren problemen met uitvoerende functies, internaliserende psychopathologie (met name angst en depressie), en vermoeidheid ten opzichte van de algemene populatie. Nadere analyse van de emotieregulatie wees uit dat de NF1-groep in hogere mate gebruik maakte van maladaptieve copingstrategieën, en in mindere mate van adaptieve strategieën, vergeleken met de normatieve groep. In het bijzonder werd een beperkt gebruik van actieve en emotiegerichte coping waargenomen, Ook werd in hogere mate dan in de algemene populatie weinig differentiatie in emoties ervaren. Hoewel er op domeinniveau geen significante afwijking werd vastgesteld in emotieregulatie, kan de copingstijl van individuen met NF1 overwegend als passief worden gekarakteriseerd. Samenvattend verschilden de cognitieve en gedragsmatige prestaties van volwassenen met NF1 op meerdere meetniveaus van die van de normpopulatie. Een relatief groot deel van de NF1-groep behaalde lagere dan verwachte cognitieve testresultaten en vertoonde meer gedrags-problemen dan doorgaans wordt waargenomen in de algemene bevolking. Deze bevindingen wijzen op een verhoogde kwetsbaarheid bij volwassenen met NF1 en onderstrepen het belang van geïndividualiseerde neuropsychologische diagnostiek en op maat gemaakte interventies.

Vervolgens werden in **hoofdstuk 3** de psychologische uitdagingen van twee volwassenen met NF1 uitvoerig beschreven, als ook hun ervaringen met een vaardigheidstraining gebaseerd op Dialectische Gedragstherapie (DGT) middels een diepte interview. Niet enkel beide patiënten werden geïnterviewd, ook familieleden werden meegenomen in het interview. Beide deelnemers kampten met substantiële problematiek gerelateerd aan NF1, waaronder zorgen over hun ziekteverloop, invaliderende vermoeidheid en een algemeen verminderd functioneren. Na het volgen van de DGT- vaardigheidstraining rapporteerden beide deelnemers verbeteringen in het observeren en reguleren van emoties.





Zij gaven aan beter afstand te kunnen nemen van moeilijke situaties, waardoor piekeren en emotionele overweldiging afnamen, met name bij zorgen over ziekte--verloop of sociale beoordeling. De tijdens de training aangeleerde mindfulness vaardigheden ondersteunden hen in het bewuster omgaan met gedachten en gevoelens. Daarnaast leidde het verbeterde vermogen om emoties te benoemen tot effectievere communicatie en het duidelijker uiten van behoeften. Eén deelnemer had in het bijzonder baat bij de oefening van de “wijze geest” en leerde een evenwicht te vinden tussen emotioneel en rationeel denken. Door het toepassen van vaardigheden zoals “tegengesteld handelen” en “feiten checken” kon zij zich met meer zelfvertrouwen bewegen in sociale situaties en openbare ruimten. Beide deelnemers rapporteerden een toegenomen acceptatie van de realiteit en minder bezorgdheid over de mening van anderen, wat hen in staat stelde zich meer te richten op persoonlijke doelen. Eén deelnemer beschreef bovendien een toename in zelfvertrouwen ten aanzien van haar uiterlijk en een afgenomen behoefte aan externe bevestiging. Tegelijkertijd gaven beide deelnemers aan dat de online DGT bijeenkomsten als minder effectief werden ervaren dan de fysieke bijeenkomsten. Zij misten informele sociale interactie tijdens pauzes en ondervonden meer moeite met concentratie. Beiden spraken hun voorkeur uit voor een blended behandelmodel, met voldoende face-to-face contactmomenten ter versterking van de behandelrelatie en uitwisseling van ervaringen. Familieleden rapporteerden positieve veranderingen bij de deelnemers, waaronder verbeterde emotieregulatie, toegenomen assertiviteit en afname van interpersoonlijke spanningen, wat bijdroeg aan duidelijkere communicatie, betere besluitvorming en versterkte relaties.

**In hoofdstuk 4** werd het belang van het betrekken van belangrijke anderen in de behandeling onderzocht, met specifieke aandacht voor de rol van waargenomen kritiek (*perceived criticism, PC*) als contextuele factor. Deze pre-poststudie onderzocht 33 patiënten en 61 naasten die deelnamen aan een DGTnetwerk-training. De studie richtte zich specifiek op veranderingen in waargenomen kritiek (namelijk, hoe kritisch men zich opstelde tegenover naasten en hoe kritisch men dacht dat naasten tegenover hen waren). De DGT netwerktraining richtte zich op het aanleren van emotieregulatie vaardigheden voor alle betrokkenen. Na afloop werd een significante afname waargenomen in het niveau van waargenomen kritiek, zowel ten aanzien van hoe kritisch men zichzelf ten opzichte van anderen ervoer, als hoe kritisch men zich door anderen beoordeeld voelde. De gemeten effectgroottes waren groot, wat wijst op klinisch relevante veranderingen, ook al zijn de achterliggende mechanismen nog onvoldoende verklaard. Voorafgaand aan de training lagen de PC-scores voor beide groepen boven de grenswaarde van 6, een niveau dat samenhangt met verhoogde terugvalrisico’s. Na de training

daalden deze scores tot een niveau dat geassocieerd wordt met gunstiger behandeluitkomsten.

Tijdens het onderzoek naar een mogelijke psychologische behandeling voor mensen met NF1 (Dialectische Gedragstherapie) trad covid-19 op. **Hoofdstuk 5** richtte zich middels een systematische review op de rol van telepsychologie binnen DGT behandeling, mede in het licht van de COVID-19-pandemie. Daarbij werd onder andere bekeken hoe telefonische en video ondersteuning tussen sessies kan bijdragen aan generalisatie van vaardigheden. Hoewel telefonische coaching een vast onderdeel vormt van DGT, bestaat er een tekort aan kwantitatieve gegevens en ontbreken gerandomiseerde gecontroleerde onderzoeken (RCT's) die de effectiviteit ervan onderbouwen. Desondanks wijzen bestaande studies op positieve effecten, waaronder vermindering van uitval en verbetering van behandeluitkomsten. Verder werd literatuur onderzocht over de inzet van telepsychologie in onderdelen van DGT die doorgaans face-to-face worden aangeboden (zoals individuele therapie, vaardigheidstraining en consultatieteams). De bestaande evidentie rondom videobijeenkomsten en blended care is vooral gericht op haalbaarheid en acceptatie; RCT's die effectiviteit van blended aanbod vergelijken met traditionele face-to-face behandelingen ontbreken nog. Voorlopige bevindingen suggereren echter dat videobegeleiding en online modules bijdragen aan het leren van vaardigheden en de voorkeur hebben boven het ontbreken van behandeling. Verder werden innovaties binnen digitale toepassingen in DGT besproken. Mobiele applicaties met gepersonaliseerde berichten blijken het gebruik van vaardigheden te bevorderen en de voortgang te versnellen. Andere veelbelovende ontwikkelingen zijn gamification, draagbare technologie voor passieve monitoring (wearables) en virtual reality (VR) toepassingen voor mindfulness training. VR studies suggereren dat VR de het aanleren van nieuwe vaardigheden kan versterken en de therapietrouw kan vergroten bij specifieke patiëntengroepen. Deze bevindingen onderstrepen het potentieel van telepsychologie in de verdere ontwikkeling van DGT, maar benadrukken tevens de noodzaak van robuust en systematisch onderzoek ter onderbouwing van effectiviteit en implementatie in de klinische praktijk.

In het voorlaatste hoofdstuk, **hoofdstuk 6**, werd de haalbaarheid van DGT vaardigheidstraining voor mensen met NF1 geëvalueerd middels een single case pilot studie met 7 NF1 patiënten. Alle deelnemers voltooiden de interventie, namen consequent deel aan de sessies en besteedden aandacht aan huiswerkopdrachten. Ondanks de kleine steekproefomvang en de uitdagingen in het werven van deelnemers, vermoedelijk mede beïnvloed door de COVID-19-pandemie, was de motivatie onder deelnemers hoog. De training werd succesvol uitgevoerd en de





inhoud, bestaande uit modules over mindfulness, interpersoonlijke effectiviteit, emotieregulatie en frustratietolerantie, werd als begrijpelijk en toegankelijk ervaren. Deelnemers waren over het algemeen tevreden over de interventie, ongeacht variabelen zoals geslacht, cognitief functioneren of eerdere behandelervaring. Hoewel er aanwijzingen waren voor verbetering van emotieregulatie, lieten de eerste bevindingen beperkte effecten zien op bredere constructen zoals acceptatie, positief affect en negatief affect, met aanzienlijke individuele variatie in respons.

## Algemene discussie

Het cognitieve en gedragsmatige functioneren van volwassenen met Neurofibromatose type 1 (NF1) wijkt significant af van dat van de normpopulatie, met een opvallend hogere prevalentie van stoornissen. Deze bevindingen wijzen op een verhoogde kwetsbaarheid binnen deze groep en onderstrepen het belang van individuele diagnostiek en psychologische interventies. Gezien de chronische aard van NF1 en de brede psychosociale impact, wordt een behandelaanpak aanbevolen die gedragstherapeutische principes combineert met een systemisch perspectief. Dialectische Gedragstherapie (DGT) komt hierbij naar voren als een geschikte behandeling, vanwege de dialectische focus op acceptatie en verandering, en de flexibiliteit om afgestemd te worden op uiteenlopende cognitieve profielen. Een behandeling die zich breed richt op de regulatie van emotie en gedrag via mindfulness, emotieregulatie, frustratietolerantie en interpersoonlijke effectiviteit kan individuen ondersteunen in het herwinnen van regie over hun emotionele belevingswereld.

Ter verdere interpretatie van de bevindingen en ter ondersteuning van toekomstige ontwikkelingen in onderzoek en de klinische praktijk voor mensen met NF1, worden in dit proefschrift enkele centrale reflectiepunten besproken. Allereerst wordt emotieregulatie beschouwd als een relevante contextuele factor binnen behandeling. Door te focussen op een transdiagnostisch en dimensioneel construct zoals emotieregulatie, kan problematiek bij de kern worden aangepakt, in plaats van uitsluitend te reageren op de uiteenlopende symptomen die daaruit voortvloeien. Vervolgens wordt het transdiagnostisch perspectief verder uitgewerkt door middel van een reflectie op categorische versus dimensionele benaderingen. Daarna worden de onderliggende mechanismen van sociaal functioneren verder belicht, met specifieke aandacht voor het onderscheid tussen sociale cognitie en sociaal gedrag, omdat dit onderscheid kan bijdragen aan een verfijning van zowel diagnostische overwegingen en indicatiestelling. Tot slot wordt stilgestaan bij de modernisering van de geestelijke gezondheidszorg en de

potentiële rol van telepsychologie bij het ontwikkelen van toegankelijke en flexibele behandelvormen.

### Emotieregulatie in context als doel voor interventie

Psychologische interventies specifiek voor mensen met Neurofibromatose type 1 (NF1) zijn in de literatuur zelden beschreven, ondanks het feit dat psychische klachten zoals angst en stemmingsstoornissen veelvuldig worden gerapporteerd. Een opvallende uitzondering betreft het onderzoek van Martin et al. (2021), waarin de effectiviteit van Acceptance and Commitment Therapy (ACT) werd geëvalueerd bij adolescenten en volwassenen met NF1 en chronische pijn. De ACT-interventie leidde tot significante verbeteringen in pijninterferentie in het dagelijks functioneren; deze uitkomsten werden gemedieerd door toename in pijnacceptatie en afname in psychologische inflexibiliteit. Er werden echter geen verbeteringen gevonden in pijnintensiteit, pijn gerelateerde angst of depressieve symptomen. Deze resultaten suggereren dat ACT mogelijk bijdraagt aan verlichting van specifieke functionele beperkingen, echter met een beperkte invloed op emotieregulatie als transdiagnostisch construct.

Tot op heden is behandeling bij mensen met NF1 niet gericht geweest op emotie-regulatieproblemen als onderliggend mechanisme van uiteenlopende klachten, zoals angst of depressie. Hoewel in hoofdstuk 2 van dit proefschrift geen statistisch significante tekorten in emotieregulatie op domeinniveau werden vastgesteld, toonden nadere analyses aan dat personen met NF1, in vergelijking met normatieve gegevens, minder gebruik maakten van adaptieve coping strategieën en juist vaker terugvielen op maladaptieve strategieën zoals emotie-onderdrukking en sociale terugtrekking. Met name lage niveaus van actieve en emotiegerichte coping werden waargenomen, evenals een tendens om emoties als ongedifferentieerd te ervaren. Wanneer wel sprake was van adaptieve coping, werd voornamelijk taakgerichte coping toegepast, een probleemoplossende aanpak die echter minder effectief kan zijn in het omgaan met stressoren die voortkomen uit een chronische en onveranderlijke genetische aandoening. Dit kan leiden tot verhoogde frustratie en bijdragen aan psychisch leed. Hoewel het vermogen tot emotieregulatie bij mensen met NF1 geen grote tekorten laat zien, is het beperkte gebruik van effectieve coping strategieën zorgwekkend, gezien de aanzienlijke emotionele belasting die deze populatie ervaart. De chronische en onvoorspelbare aard van NF1, in combinatie met de vaak voorkomende cognitieve kwetsbaarheden, verhoogt het risico op overbelasting en het overschrijden van persoonlijke grenzen. Ook streven ze er veelal naar om volwaardig deel te nemen aan de maatschappij. Het versterken van coping vaardigheden kan derhalve een belangrijke beschermende factor vormen voor





de geestelijke gezondheid in diverse levensdomeinen, en bijdragen aan het verminderen van de psychologische impact van het leven met NF1.

Het beperkte repertoire aan coping strategieën duidt op een vaardigheidstekort, en benadrukt daarmee het potentieel van interventies gericht op het trainen van emotieregulatie vaardigheden. Hoewel bestaande programma's, zoals de VERS-training (Vaardigheidstraining Emotie Regulatie Stoornis; Freije et al., 2002), relevant kunnen zijn, ligt de nadruk daarin vaak uitsluitend op gedragsverande-ring. Een dergelijke benadering loopt het risico bredere tekorten, zoals in emotie-herkenning en interpersoonlijke effectiviteit (zoals vastgesteld in hoofdstuk 2), over het hoofd te zien. Bovendien kan een louter op vaardigheden gerichte aanpak bij deze doelgroep onbedoeld het gevoel versterken 'niet goed genoeg' te zijn, wat problematisch is voor een populatie die reeds worstelt met zelf ondermijnende overtuigingen.

Dialectische Gedragstherapie (DGT) biedt een genuanceerd, responsief behandelkader dat gebaseerd is op het biosociale model en goed aansluit bij de complexiteit van NF1. De biologische kwetsbaarheden van NF1 omvatten niet alleen cognitieve beperkingen, maar ook lichamelijke manifestaties, zoals ca-fé-au-laitvlekken, zichtbare en potentieel levensbedreigende neurofibromen, atypische sproeten en skeletafwijkingen (Fournier et al., 2023). Dergelijke zichtbare kenmerken maken individuen bijzonder kwetsbaar voor sociale uitsluiting en discriminatie (Konradi, 2021). Invaliderende omgevingen, door een te hoge mate van bescherming of juist een gebrek aan ondersteuning, beperken de mogelijkheid om adequate coping vaardigheden te ontwikkelen, wat de emotionele ontregeling kan versterken.

Het dialectische principe van DGT, waarin het streven naar een balans tussen acceptatie en verandering centraal staat, sluit aan bij mensen met NF1 waarbij zowel ruimte is voor het valideren van de ervaringen en tegelijkertijd wordt gewerkt aan het leren van nieuwe vaardigheden. Zoals in hoofdstuk 4 wordt besproken, biedt DGT bovendien ruimte voor actieve betrokkenheid van het sociale netwerk. Het betrekken van familieleden en andere belangrijke naasten kan leiden tot wederzijdse validatie en het doorbreken van oordelende of ondermijnende overtuigingen. Door het netwerk inzicht te geven in de emotionele kwetsbaarheid van de persoon en samen te werken aan het aanleren van vaardigheden, kan de negatieve impact van een invaliderende omgeving worden verminderd. DGT richt zich daarmee niet alleen op het individu, maar creëert ook een context waarin duurzame gedragsverandering en psychologisch herstel beter kunnen worden ondersteund.

## Transdiagnostisch denken: één benadering voor vele uitdagingen?

Huidige diagnostische systemen, zoals de Diagnostic and Statistical Manual of Mental Disorders (DSM; American Psychiatric Association, 2022), zijn gebaseerd op vaste, categorische classificaties. Hoewel deze systemen breed worden toegepast in de klinische praktijk, blijken ze in toenemende mate beperkt in hun voorspellende waarde met betrekking tot het beloop van psychische aandoeningen en de effectiviteit van behandelingen (Conway et al., 2019). Twee centrale uitdagingen in de geestelijke gezondheidszorg, namelijk hoe psychische problematiek wordt geclassificeerd en hoe de onderliggende oorzaken worden begrepen, staan hierbij nauw met elkaar in verband. Om tot een betere definiëring en groepering van psychische aandoeningen te komen, is diepgaander inzicht nodig in de etiologie en ontwikkelingsdynamiek van deze problematiek. Deze kennis vormt tevens de basis voor de ontwikkeling van meer effectieve, op maat gemaakte behandelinterventies. Door diagnostiek en etiologisch onderzoek systematisch te integreren, zoals bepleit door Latzman et al. (2020) en Waszczuk et al. (2020), kan vooruitgang worden geboekt in het begrijpen en behandelen van complexe psychische aandoeningen.

Een belangrijke tekortkoming van uitsluitend categorisch denken is dat het riskeert om personen die niet voldoen aan alle criteria van een specifieke classificatie onvoldoende recht te doen. Dit geldt in het bijzonder voor klinische profielen die zich kenmerken door een breed scala aan gedragsmatige en emotionele problemen, zoals vaak het geval is bij individuen met NF1. Veel van deze individuen ontvangen diagnoses als depressie of angststoornis, terwijl dergelijke symptomen mogelijk secundair zijn aan onderliggende problematiek, zoals sociale relationele spanningen, chronische vermoeidheid of een negatief zelfbeeld. In zulke gevallen slagen categorische diagnoses er niet in het volledige spectrum van klinisch relevante ervaringen te vatten, wat de mogelijkheden voor passende behandeling beperkt.

Alternatieve raamwerken zoals de Hierarchical Taxonomy of Psychopathology (HiTOP) en de Research Domain Criteria (RDoC) bieden een veelbelovend perspectief doordat zij voorbijgaan aan rigide classificatiedrempels en zich richten op transdiagnostische dimensies en onderliggende mechanismen (Kotov et al., 2017; Insel et al., 2010). Binnen het domein van neurobiologische ontwikkelingsstoornissen (NDD's) en in het bijzonder bij NF1, maken dergelijke modellen een genuanceerdere beoordeling van psychisch functioneren mogelijk. Zo wordt in plaats van de vraag of iemand voldoet aan de criteria voor bijvoorbeeld een persoonlijkheidsstoornis, onderzocht in hoeverre het persoonlijkheidsfunctioneren zelf (zoals identiteit, zelfsturing, empathie en intimiteit) is verstoord, in overeenstemming met recente modellen voor persoonlijkheidspathologie (Zimmerman et al., 2012; Sinnaeve et al., 2021). Evenzo wordt aanbevolen om bij stemmings- of angstklachten het bredere gedragsspectrum in ogenschouw te nemen, zoals internaliserende of externaliserende tendensen, en deze te interpreteren binnen de biologische, psychosociale en ontwikkelingscontext van het individu.





Deze dimensiegerichte benadering is van bijzondere waarde bij genetische en neurobiologische kwetsbaarheden, zoals bij NF1, waar psychische symptomen vaak voortkomen uit een complexe interactie tussen lang bestaande biologische gevoeligheden en omgevingsinvloeden. Ze stelt clinici in staat om recht te doen aan de heterogeniteit in patiëntenpresentaties die anders onzichtbaar blijven binnen rigide diagnostische categorieën.

Dit proefschrift onderstreept daarom het belang van een multidisciplinaire benadering in de zorg voor mensen met NF1. In de huidige praktijk vindt behandeling voornamelijk plaats in het somatische domein, met nadruk op zichtbare medische symptomen. Echter, ook relatief milde fenotypische uitingen en subtiele cognitieve beperkingen kunnen wijzen op onderliggende neurologische en genetische pathologie, hetgeen pleit voor een bredere kijk op diagnostiek en behandeling (Bos-Roubos et al., 2020). Naast medische beoordeling is daarom structurele inzet van neuropsychologisch en genetisch onderzoek noodzakelijk om een volledig beeld te verkrijgen van de uitdagingen waarmee deze patiënten worden geconfronteerd. In het bijzonder kunnen klinisch neuropsychologische evaluaties waardevolle informatie opleveren over cognitief en gedragsmatig functioneren, wat aanknopingspunten biedt voor gepersonaliseerde behandelstrategieën die recht doen aan de complexiteit van de aandoening.

## Interpersoonlijke effectiviteit: problemen in sociaal gedrag of sociale cognitie?

Een specifiek voorbeeld van de beperkingen van categorale classificatiesystemen in de context van NF1 betreft de sociale moeilijkheden die bij deze populatie frequent worden waargenomen. Veel van het bestaande onderzoek richt zich op het vaststellen van comorbiditeit met autismespectrumstoornis (ASS) en/of aandachtstekort-/hyperactiviteitsstoornis (ADHD). Klinische beschrijvingen rapporteren een verhoogde prevalentie van ASS (10–40%) en ADHD (38–67%) bij individuen met NF1 (Eijk et al., 2018; Morris et al., 2016; Hyman et al., 2005; Koth et al., 2000; Lidzba et al., 2012; Mautner et al., 2002). Deze categorische benadering heeft echter als beperking dat zij zich vooral richt op classificatie, terwijl de diagnostiek naar de onderliggende aard van het sociaal functioneren onvoldoende wordt belicht.

In plaats van uitsluitend te onderzoeken of een categorale diagnose kan worden gesteld, zou het relevanter zijn om de specifieke sociaal cognitieve en gedragsmatige processen te identificeren die ten grondslag liggen aan deze moeilijkheden. In dit kader is het zinvol een onderscheid te maken tussen sociale cognitie en sociaal gedrag. Sociale cognitie verwijst naar de mentale processen die betrokken zijn bij het interpreteren, voorspellen en gepast reageren op het gedrag van anderen (Frith & Frith, 2007), terwijl sociaal gedrag de observeerbare gedragingen in sociale contexten omvat, beïnvloed door zowel individuele kenmerken als omgevingsfactoren (Eisenberg et al., 2006).

De bevindingen in hoofdstuk 2 van dit proefschrift suggereren dat de Theory of Mind (ToM), een kerncomponent van sociale cognitie, niet globaal verstoord is bij volwassenen met NF1. Dit wijst erop dat het primaire probleem mogelijk niet ligt in het begrijpen van de mentale toestanden van anderen, maar eerder in de uitvoering van sociaal gedrag, dat beïnvloed wordt door een samenspel van individuele kwetsbaarheden en contextuele eisen. Deze interpretatie wordt ondersteund door recente bevindingen van Remaud et al. (2024), waarin werd aangetoond dat kinderen met NF1 zwaktes vertonen in sociale informatieverwerking en moreel redeneren, maar vergelijkbare prestaties leverden als gezonde controles op standaard ToM-taken. Bij volwassenen werden subtiele moeilijkheden aangetoond bij het toeschrijven van eerste-orde valse overtuigingen, zonder significante verschillen op complexere ToM-taken zoals het herkennen van tweede-orde valse overtuigingen of sociale misstappen.

Daarnaast werd in hoofdstuk 2 een verhoogde prevalentie van alexithymie vastgesteld. Deze beperkte emotionele bewustwording kan sociale interactie aanzienlijk belemmeren, aangezien emotionele herkenning en expressie cruciale voorwaarden zijn voor wederkerigheid in sociale relaties. Bovendien spelen verhoogde angstniveaus mogelijk een rol in de sociale terughoudendheid bij NF1. Negatieve reacties op zichtbare lichamelijke kenmerken, zoals sociale uitsluiting of discriminatie, kunnen leiden tot angst om fouten te maken of niet te voldoen aan sociale verwachtingen (Konradi, 2021). Dit suggereert dat sociale moeilijkheden bij NF1 niet louter voortkomen uit cognitieve beperkingen in sociaal begrip, maar eerder een bredere emotionele kwetsbaarheid en gedragsmatige remming weerspiegelen.

Recente theoretische kaders benadrukken het belang van het functioneel analyseren van sociale vaardigheden. Zo pleiten Hendriks et al. (2016), vanuit het perspectief van de *Relational Frame Theory* (RFT), voor een functionele analyse van perspectiefname. RFT beschrijft hoe mensen door middel van subtiele





contextuele signalen relaties leren leggen tussen gebeurtenissen of stimuli, ook wanneer die relaties arbitrair of abstract zijn. In aansluiting hierop ontwikkelden Eikelboom et al. (2025) het HITS-model van sociale cognitie, dat sociale vaardigheden opsplitst in onderscheiden componenten zoals emotieherkenning, perspectiefneming en empathie. Dit model biedt een bruikbaar kader voor toekomstig onderzoek, omdat het de focus verlegt van classificatie naar het begrijpen van onderliggende vaardigheden en mechanismen, en daarmee bijdraagt aan een genuanceerder begrip van sociale moeilijkheden.

Een bredere conceptualisering van emotionele kwetsbaarheid en gedragsremming bij NF1 sluit aan bij bevindingen binnen verwante rasopathieën, zoals het Noonan-syndroom, waar eveneens verstoringen in sociaal-emotionele ontwikkeling worden gerapporteerd (Foy et al., 2022; Pierpont et al., 2018). Individuen met het Noonan-syndroom vertonen bijvoorbeeld ook kenmerken van alexithymie. Gerichte interventies zoals het SENS-programma zijn ontwikkeld om deze sociaal-emotionele ontwikkelingsproblemen aan te pakken (Roelofs et al., 2019). Dergelijke parallellen onderstrepen de noodzaak van behandelmodellen die zich niet beperken tot cognitieve vaardigheden, maar gericht zijn op het bevorderen van emotioneel bewustzijn, zelfexpressie en contextueel adequaat sociaal gedrag.

### *Blended* zorg in het digitale tijdperk: mogelijkheden voor telepsychologie

Het gebruik van telepsychologie, waarbij psychologische behandelingen worden aangeboden via digitale technologieën zoals internet, mobiele applicaties en virtual reality, neemt de laatste jaren gestaag toe (Andersson & Titov, 2014; Geraldo et al., 2024; Van Daele et al., 2020). *Blended therapy,* een vorm van behandeling waarin face-to-face zorg wordt gecombineerd met digitale componenten, biedt verschillende voordelen, waaronder kostenbesparing en verbeterde effectiviteit. Desondanks is er nog onvoldoende overtuigend wetenschappelijk bewijs dat de grootschalige implementatie van dergelijke interventies volledig rechtvaardigt (Van Daele & Assche, 2019). Het blijft te betwijfelen of het implementeren van online interventies op grote schaal, zoals sinds covid-19 in toenemende mate gebeurd, te ondersteunen valt. Dit sluit aan bij de gepresenteerde bevindingen in hoofdstuk 6 waarin binnen DGT behandeling geadviseerd wordt om terug te gaan naar face-to-face behandeling zodra deze mogelijkheid bestaat.

Uit bestaand onderzoek blijkt dat online interventies het meest onderzocht zijn bij angst- en stemmingsstoornissen, waarbij ze vaak effectiever blijken dan wachtlijstcontroles. Er is ook ondersteunend bewijs voor de inzet van digitale interventies bij posttraumatische stressstoornis (PTSS), slaapstoornissen, eetstoornissen, chronische pijn en middelenmisbruik. Voor andere aandoeningen zoals obsessie-

ve-compulsieve stoornis (OCD), tinnitus, psychose en pathologisch gokken is de bewijsbasis aanzienlijk beperkter (Ebert et al., 2018; Nelson & Sharp, 2016; Berryhill et al., 2015; Berryhill et al., 2019; Bolton & Dorstyn, 2015). Bovendien richten de meeste studies zich voornamelijk op korte termijn effecten, wat de noodzaak benadrukt voor meer longitudinaal en kwaliteitsvol onderzoek.

In het licht van het toenemende gebruik van telepsychologie en de praktische beperkingen die de COVID-19-pandemie met zich meebracht, werd het relevant om de haalbaarheid en effectiviteit van Dialectische Gedragstherapie (DGT) op afstand nader te onderzoeken zoals beschreven in hoofdstuk 6. De inzichten uit het beschikbare bewijs over tele-DGT leverden niet alleen informatie op over de mogelijke voordelen van deze benadering, maar boden ook aanknopingspunten voor de ontwikkeling van richtlijnen en strategieën die de toegankelijkheid, continuïteit en kwaliteit van zorg waarborgen.

Voor mensen met NF1 biedt blended care een veelbelovende mogelijkheid om landelijk toegankelijke, gespecialiseerde zorg te garanderen. Door behandelingen te leveren vanuit expertisecentra die persoonlijke sessies combineren met digitale ondersteuning, ontstaat een flexibel zorgmodel dat kan worden aangepast aan individuele behoeften. De integratie van mobiele technologieën binnen deze blended formats opent bovendien nieuwe perspectieven voor het versterken van therapeutische processen en het monitoren van voortgang. De onderzoeksbevindingen, zoals gepresenteerd in hoofdstuk 6, onderstrepen het praktische nut van videoconferenties als alternatief wanneer face-to-face sessies niet haalbaar zijn. Tegelijkertijd benadrukken de in hoofdstuk 5 beschreven patiënt-interviews het belang van voldoende persoonlijke interactie binnen blended behandeltrajecten. Persoonlijke ontmoetingen bevorderen niet alleen de therapeutische alliantie, maar ook het gevoel van verbondenheid, groepscohesie en de mogelijkheid tot informeel uitwisselen van ervaringen vóór en na groepsbijeenkomsten.

Een geïntegreerde aanpak waarin digitale en persoonlijke zorgmodaliteiten elkaar aanvullen, lijkt dan ook het meest geschikt. Deze evenwichtige benadering benut de sterke kanten van beide vormen van zorg en draagt bij aan een toegankelijke, flexibele en effectieve behandelpraktijk voor mensen met NF1.





### Beperkingen en sterke punten

Dit onderzoek kent een aantal belangrijke beperkingen en sterke punten die in acht moeten worden genomen bij de interpretatie van de bevindingen. Belangrijk om rekening mee te houden is de mogelijke selectiebias binnen de steekproef, aangezien alle deelnemers werden verwezen naar de polikliniek vanwege vermoeidheidsklachten of psychosociale symptomen die niet somatisch verklaard konden worden. Hierdoor is de kans groot dat de steekproef oververtegenwoordigd is met individuen die een verhoogde gedragsmatige kwetsbaarheid en een hoger niveau van vermoeidheid vertonen in vergelijking met de bredere NF1-populatie. Daarnaast werden uitsluitend NF1-patiënten met een somatische belasting geïncludeerd. Het ontbreken van een controlegroep bestaande uit patiënten zonder dergelijke belasting beperkt dan ook de generaliseerbaarheid van de resultaten naar de gehele populatie van mensen met NF1.

Een belangrijke kracht van deze studie ligt in de gedetailleerde en uitgebreide beschrijving van het individuele neuropsychologische profiel van de NF1-groep. Door het gebruik van zorgvuldig geselecteerde analysemethoden konden zowel subtiele als uitgesproken tekorten worden geïdentificeerd, waarbij kwetsbaarheden op meerdere cognitieve en gedragsmatige domeinen aan het licht kwamen die vermoedelijk niet zichtbaar zouden zijn geweest bij louter analyse op groepsniveau via gemiddelde scores.

De kleine steekproefomvang, met name in de haalbaarheidsstudie naar de DGT-vaardigheidstraining, vormde een beperking, aangezien dit de statistische kracht en de generaliseerbaarheid van de resultaten beperkte. Tevens kon variabiliteit in behandelgeschiedenis van de deelnemers mogelijk invloed hebben gehad op de uitkomsten. Desondanks moet worden opgemerkt dat het, gezien de zeldzaamheid van NF1 als genetische aandoening, des te waardevoller is dat de studie kon beschikken over een relatief grote en demografisch evenwichtige steekproef. Dit draagt bij aan de betrouwbaarheid van de bevindingen en biedt een representatief beeld van de NF1-populatie.

Een andere beperking betreft het gebruik van uitsluitend zelfrapportagevragenlijsten, waarvan de gevoeligheid mogelijk beperkt was om subtiele pre- en post-interventieveranderingen nauwkeurig vast te stellen. In de haalbaarheidsstudie naar de DGT-vaardigheidstraining werd echter gebruikgemaakt van een single-case design, waarmee individuele variatie zichtbaar kon worden gemaakt en waardevolle informatie werd verkregen over patronen in behandelrespons, hetgeen bijdraagt aan hypothesevorming voor toekomstig onderzoek.

Verder ontbraken in bepaalde deelstudies, zoals die naar waargenomen kritiek en de DGT-netwerktraining, controlegroepen. Hierdoor is het niet met zekerheid vast te stellen in hoeverre de waargenomen veranderingen toe te schrijven zijn aan de interventies zelf of aan externe factoren. De externe validiteit van de bevindingen omtrent de DGT-netwerktraining is mogelijk beperkt, aangezien deze werd uitgevoerd in een nationaal residentieel standaard DGT-programma met hoogopgeleid personeel en zeer gemotiveerde deelnemers die een aanzienlijke ziektelast ervoeren—omstandigheden die mogelijk niet representatief zijn voor reguliere behandelsettings. Daarnaast kent de gebruikte schaal voor waargenomen kritiek (Perceived Criticism Scale) methodologische beperkingen. Door de eenvoudige opbouw van slechts twee items ontbrak de fijnmazigheid die nodig is om complexere vormen van interpersoonlijke dynamiek en bredere constructen van kritiek adequaat te onderscheiden, waardoor het risico bestaat dat een complex fenomeen te simplistisch is weergegeven.

Tegenover deze beperkingen staat een belangrijke kracht: de toekomstgerichte benadering van het onderzoek met betrekking tot de integratie van telepsychologie. Inzichten in het gebruik van mobiele applicaties, virtual reality en gamification tonen veelbelovende richtingen voor de doorontwikkeling van DGT-interventies. De studie laat zien dat het mogelijk is om interventies voor zeldzame genetische aandoeningen zoals NF1 te innoveren en aan te passen aan digitale zorgmodellen, waarmee een bijdrage wordt geleverd aan de verbetering van zowel toegankelijkheid als effectiviteit van psychologische behandeling.

### Toekomstig onderzoek

Toekomstig onderzoek naar (neuro)psychologische fenotypering en behandeling voor mensen met NF1 moet een veelzijdige aanpak hebben om de huidige hiaten op te vullen en het begrip en management van deze complexe aandoening te verbeteren. Een belangrijke prioriteit is het opnemen van zorgvuldig geselecteerde vergelijkingsgroepen in neuropsychologische studies. Gezien de variabiliteit in genetische expressie en symptoompresentatie bij NF1, zou het opnemen van volwassenen met NF1 die geen vermoeidheid ervaren, evenals IQ-gematchte controlegroepen met en zonder vermoeidheid, waardevolle inzichten opleveren. Deze aanpak zou een nauwkeurigere analyse mogelijk maken van de relaties tussen vermoeidheid, cognitief functioneren en gedragsstoornissen.

Het huidige onderzoek identificeerde hoge niveaus van vermoeidheid als een prominent kenmerk bij individuen met NF1. Toekomstige studies zouden de mogelijke tweerichtingsrelaties tussen vermoeidheid, cognitieve stoornissen en gedragsstoornissen moeten onderzoeken. Vermoeidheid kan zowel een voorspeller als





een gevolg zijn van tekortkomingen in coping, sociaal cognitief functioneren en internaliserende psychopathologie, zoals stemmings- en angststoornissen. Een uitgebreid begrip van deze interacties zou helpen verduidelijken hoe deze factoren gezamenlijk het dagelijks functioneren, de betrokkenheid bij het werk en het vermogen om aan maatschappelijke verwachtingen te voldoen beïnvloeden. Daarnaast is er behoefte aan een bredere focus op de wisselwerking tussen cognitief functioneren, copingmechanismen en mentaal welzijn bij NF1. Gedragsproblemen, zoals inadequate copingstrategieën, verergeren waarschijnlijk psychologische stress en vermoeidheid. Tekorten in sociaal cognitief functioneren zijn op vergelijkbare wijze gekoppeld aan internaliserende psychopathologie. Onderzoek naar deze onderlinge verbanden zou kunnen leiden tot op maat gemaakte interventies die zich richten op de onderliggende mechanismen die deze uitdagingen veroorzaken, in lijn met het Research Domain Criteria (RDoC) raamwerk, dat dimensionale, transdiagnostische constructen op meerdere niveaus van functioneren benadrukt analysis (Cuthbert & Insel, 2013; Insel et al., 2010).

In termen van behandeling moet toekomstig onderzoek gepersonaliseerde en adaptieve benaderingen onderzoeken. Naast DGT-vaardigheidstraining zou individuele DGT-coaching de generalisatie van vaardigheden kunnen verbeteren en beter kunnen inspelen op individuele behoeften. Technieken zoals dagelijkse dagboekkaarten, die in standaard DGT worden gebruikt, zouden kunnen worden geïntegreerd om specifiek gedrag en de toepassing van vaardigheden in reële contexten te analyseren. Deze gepersonaliseerde feedbacklus zou een dieper inzicht geven in de individuele vooruitgang en interventies verfijnen voor een grotere doeltreffendheid.

Gezien het nichekarakter van NF1 en de grote heterogeniteit binnen deze doelgroep, blijft onderzoek op N=1 niveau geschikt door gebruik te maken van het single-case experimenteel design (SCED). Traditionele methoden die vertrouwen op algemene vragenlijsten kunnen echter tekortschieten om de nuances van deze populatie vast te leggen. In plaats daarvan biedt het gebruik van innovatieve methoden zoals Idiographic System Modeling (ISM) een veelbelovend alternatief (Schiepek, 1986; Schiepek et al., 2016; van den Bergh et al., 2022). ISM is een bottom-up casusformuleringsmethode die een gepersonaliseerde conceptuele kaart van de situatie van een patiënt creëert, die vervolgens wordt gebruikt om samen met de patiënt geïndividualiseerde vragenlijsten te maken. Deze vragenlijsten bevatten zowel positieve en negatieve items (bijv. “Vandaag voelde ik me zelfverzekerd” versus “Vandaag voelde ik me angstig”) en vergemakkelijken het verzamelen van gepersonaliseerde zelfbeoordelende tijdreeksen tijdens de therapie. Dergelijke methoden sluiten aan bij de groeiende trend in gepersonali-

seerd psychopathologisch onderzoek en maken gebruik van de vooruitgang in netwerkmodellering en tijdreeksanalyse. ISM maakt het mogelijk om algemene veranderingsprofielen te classificeren vanuit een complex systeemperspectief, waardoor betere inzichten worden verkregen in individuele veranderingsmechanismen. Onderzoek heeft aangetoond dat patiënten die tijdens de behandeling naar een andere psychologische toestand overgaan, vaak betere resultaten behalen dan patiënten die dat niet doen (Olthof et al., 2023). Het toepassen van ISM op NF1 onderzoek zou kunnen helpen bij het blootleggen van patronen van symptoomdynamiek en transities, waardoor zowel individuele behandelstrategieën als bredere therapeutische benaderingen worden geïnformeerd.

Door het prioriteren van vergelijkingsgroepen, het onderzoeken van de interacties tussen vermoeidheid, cognitie en gedrag, en het toepassen van gepersonaliseerde methodologieën zoals ISM, kan toekomstig onderzoek het begrip en de klinische behandeling van NF1 bevorderen. De integratie van deze benaderingen heeft het potentieel om nieuwe patronen van symptomatologie bloot te leggen en de ontwikkeling van op maat gemaakte interventies te informeren, waardoor uiteindelijk de resultaten voor mensen met NF1 verbeteren.

## Conclusies

Cognitieve beperkingen bij personen met Neurofibromatose type 1 (NF1) zijn vaak subtiel van aard en niet onmiddellijk zichtbaar in het dagelijks functioneren, wat bijdraagt aan het risico dat de functionele impact ervan wordt onderschat. Deze onderkenning wordt versterkt door het veelal ontbreken van externaliserende psychopathologie en door de neiging van personen met NF1 om psychische klachten niet expliciet te uiten. Hierdoor wordt klinische aandacht vaak vertraagd, ondanks de aanwezigheid van significante uitdagingen, zoals geringe adaptieve coping, chronische vermoeidheid en een verhoogd risico op internaliserende psychopathologie.

Het is daarom van belang alert te blijven op meer genuanceerde signalen die kunnen wijzen op psychisch disfunctioneren, zoals school- of werkproblemen, teruggetrokken sociaal gedrag, of een sterke focus op lichamelijke klachten zonder duidelijke somatische verklaring. Voor een vollediger beeld van de ondersteuningsbehoeften van deze groep is het van belang om neuropsychologische en genetische evaluaties structureel te integreren in de medische zorg. In het bijzonder zijn klinisch neuropsychologische beoordelingen essentieel voor het detecteren van cognitieve en gedragsmatige kwetsbaarheden, en vormen zij een belangrijk uitgangspunt voor het ontwikkelen van geïndividualiseerde en doelgerichte behandelstrategieën.





Psychologische interventies zouden idealiter niet uitsluitend gericht moeten zijn op symptoombestrijding, maar op onderliggende transdiagnostische mechanismen, zoals emotieregulatie, binnen een biosociaal kader. Dialectische Gedragstherapie (DGT) is vanuit dit perspectief een veelbelovende behandelvorm voor volwassenen met NF1, gezien de geïntegreerde focus op acceptatie en gedragsverandering. Voorlopige bevindingen wijzen erop dat DGT-vaardigheidstraining het emotioneel functioneren kan verbeteren en stressniveaus kan verlagen in deze populatie.

Een belangrijk element binnen DGT is de actieve betrokkenheid van het sociale netwerk van de patiënt. Door patiënten en hun naasten te leren hoe zij emoties kunnen herkennen, benoemen en reguleren, worden mogelijkheden gecreëerd voor wederzijdse validatie en gedeeld begrip. Dit versterkt niet alleen de individuele copingvaardigheden, maar draagt ook bij aan een context die gunstiger is voor duurzame gedragsverandering.

Tot slot is het, met het oog op de landelijke toegankelijkheid van zorg voor mensen met NF1, wenselijk om blended care-modellen te ontwikkelen waarin face-to-face en digitale behandelvormen gecombineerd worden. Idealiter worden deze aangeboden vanuit gespecialiseerde expertisecentra, om zowel de inhoudelijke kwaliteit als de continuïteit van zorg te waarborgen en tegelijkertijd flexibel in te spelen op individuele behoeften.

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En dan mijn fantastische paranimfen: Loes en Nikita! Loes, onze vriendschap ontstond tijdens de gesprekken op de universiteit. We delen een liefde voor wetenschap, opleiden, ‘ons’ centrum voor neuropsychiatrie, bankhangen, de Vierdaagse en natuurlijk voor ratten. Oh nee, die laatste niet. Vanaf het moment dat ik wist dat ik dit promotie traject aan zou gaan, heb ik je gevraagd of je me mentaal wilde bijstaan. En dat heb je gedaan, met volle overtuiging! Niemand kijkt zo reikhalzend uit naar mijn verdediging en het vieren van mijn dr.-titel als jij. Ik ben dankbaar voor onze vriendschap, je aanstekelijke enthousiasme en de verbinding die we delen. Nikita, waar moet ik beginnen? Vanaf het allereerste moment dat ik je zag in het eerste jaar van de studie psychologie, sprong je er voor mij uit. Beiden eigenwijs, beiden ambitieus, beiden met een grote liefde voor ons vakgebied en een enorme waardering voor elkaar. De afgelopen jaren was je mijn steun en toeverlaat. Of het nu ging over de kinderen, werk, reizen of mijn proefschrift: jij stond voor me klaar. Ik voel me zo fijn met jou om me heen en kan volledig mezelf zijn. Zoveel dank daarvoor. En ook jouw wederhelft wil ik niet onbenoemd laten. Robert-Jan, onze vriendschap heeft me de afgelopen jaren veel gebracht. Je kalmte, vertrouwen en humor hebben op talloze momenten bijgedragen aan lucht, verbinding en plezier. Dank je wel daarvoor.

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## Curriculum Vitae

Hanneke Hoeijmakers werd op 4 november 1989 geboren in Venray. Na het behalen van haar VWO-diploma aan het Dendron College in Horst in 2008, startte zij met de studie Psychologie aan de Radboud Universiteit in Nijmegen. Binnen de bacheloropleiding koos zij voor de specialisatie ‘Brein’, waarna zij in 2013 cum laude afstudeerde in de master Gezondheidszorgpsychologie aan dezelfde universiteit.

Gedurende haar studie en aansluitend aan haar afstuderen was zij steeds werkzaam bij GGz-instelling Vincent van Gogh, waar zij sinds 2006 ervaring had opgedaan in diverse begeleidersfuncties binnen de langdurige zorg. Als masterpsycholoog werkte zij vervolgens op verschillende afdelingen, waarbij haar interesse voor ernstige en complexe psychiatrische problematiek verder werd verdiept. In 2016 startte zij de postmasteropleiding tot gezondheidszorgpsycholoog, die zij in 2018 succesvol afrondde. In dezelfde periode begon zij aan een traject tot trainer en supervisor in Dialectische Gedragstherapie (DGT) en trad zij toe tot het bestuur van Dialexis, het opleidingsinstituut voor DGT in Nederland en België.

Haar ambitie om patiëntenzorg te combineren met wetenschappelijk onderzoek gaf zij vorm als Gezondheidszorgpsycholoog in Opleiding tot Specialist en Klinisch Onderzoeker (GIOSKO). Binnen dit Nijmeegse traject, waarin het scientist practitioner model centraal staat, combineerde zij de postmaster specialisatieopleiding tot klinisch psycholoog met het verrichten van promotieonderzoek. Dit onderzoek werd uitgevoerd binnen het Topklinisch Centrum voor Neuropsychiatrie van Vincent van Gogh en was ingebed in het Donders Institute voor Brain, Cognition and Behaviour van de Radboud Universiteit. De opleiding tot klinisch psycholoog en het daarin vormgegeven GIOSKO-traject volgde zij bij het Radboud Centrum Sociale Wetenschappen.

Sinds 2022 vervolgt ze haar loopbaan in de patiëntenzorg, nu als klinisch psycholoog–psychotherapeut, bij het Topklinisch Centrum voor Neuropsychiatrie. Haar werkzaamheden richten zich op (neuro)psychologische diagnostiek en behandeling van mensen met complexe, onbegrepen of zeldzame aandoeningen en ze is onderdeel van het DGT team. Naast haar klinische en wetenschappelijke activiteiten vervult zij bestuurlijke taken als bestuursvoorzitter van Dialexis en is zij actief als docent binnen het postacademisch onderwijs. Sinds 2024 is zij tevens praktijkopleider klinische psychologie van Vincent van Gogh en regievoerend P-opleider van het Consortium Psychologische Vervolgopleidingen (CPVO). In deze functie draagt zij verantwoordelijkheid voor de continuïteit en kwaliteit van de praktijkopleidingscontext binnen elf aangesloten zorginstellingen.

Zij is getrouwd met Sjoerd van Leeuwen en samen hebben zij drie kinderen.

Mrs. Hanneke Hoeijmakers was born on 4 November 1989 in Venray. After completing the Atheneum at the Dendron College in Horst in 2008, she studied Psychology at the Radboud University Nijmegen. Within the bachelor's programme, she chose to specialise in "Brain", and subsequently graduated with honours in 2013 with a master's degree in Health Care Psychology from the same university.

During her studies and after graduation, she continued to work at the Vincent van Gogh Institute for Mental Health, where she had gained experience in patient care since 2006. As a psychologist, she then worked across several departments, further deepening her interest in severe and complex psychiatric conditions. In 2016, she began a post-master healthcare psychology training program, which she successfully completed in 2018. During the same period, she started as a trainer in training in Dialectical Behavior Therapy (DBT) and joined the board of Dialexis, the DBT training institute for the Netherlands and Belgium.

She realised her ambition to combine patient care with scientific research as a healthcare psychologist in training to become a specialist and clinical researcher (GIOSKO). Within this programme, which emphasises the scientist practitioner model, she combined the post-master specialisation in clinical psychology with a PhD trajectory. This research was conducted within the Centre of Excellence for Neuropsychology of Vincent van Gogh, embedded in the Donders Institute for Brain, Cognition and Behaviour at the Radboud University. She completed her training as a clinical psychologist and the GIOSKO programme at the Radboud Centre for Social Sciences.

Since 2022, she has continued her career in patient care as a clinical psychologist and psychotherapist at the Centre of Excellence for Neuropsychology of Vincent van Gogh. Her work focuses on (neuro)psychological diagnostics and the treatment of individuals with complex, misunderstood, or rare disorders and she is a member of the DBT team. In addition to her clinical and scientific activities, she serves as chair of the board of Dialexis and lectures in postgraduate education. Since 2024, she has also been an educational supervisor in clinical psychology at Vincent van Gogh and head of educational supervisors at the Consortium for Psychological Postgraduate Education (CPVO). In this role, she is responsible for ensuring the continuity and quality of the practical training context across eleven affiliated healthcare institutions.

She is married to Sjoerd van Leeuwen, and together they have three children.





## Research Data Management

This research was conducted in accordance with applicable legal and ethical guidelines, and data management followed the FAIR principles (Findable, Accessible, Interoperable, Reusable; doi.org/10.1038/sdata.2016.18). The sections below detail how these principles were implemented.

### Ethics

This thesis is based on human subject research conducted in accordance with the Declaration of Helsinki. Institutional protocols of the Vincent van Gogh Institute for Psychiatry were strictly followed, and the studies in chapter 2, 3, and 6 were performed in the context of standard clinical care within the Centre of Excellence for Neuropsychiatry and were approved by the Vincent van Gogh Institutional Review Board (CWOP-EM/hl/2019.00.02/RvB/19.01818). Chapter 4 comprised secondary data analysis of a study that was part of an RCT at GGZ Rivierduinen (https://doi.org/10.1186/1745-6215-15-152). Ethical approval was obtained from the ethical review board of the Leiden University Medical Center and the board of Rivierduinen agreed to support the execution of the study. There are no conflicts of interest related to the conduct of scientific research on the implementation of Dialectical Behavior Therapy (DBT). Concerning competing interests, LvdB is the founder of Dialexis, the training institute for DBT in the Netherlands, and was formerly a shareholder. HvL is currently a shareholder of Dialexis. Dialexis developed the DBT Travel Guide, a mobile application that is offered free of charge. Neither author received reimbursements, fees, or funding directly related to telepsychology or DBT, nor do they hold patents pertaining to telecommunications or digital technologies in DBT.

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### Findable and Accessible

Anonymized data from all empirical chapters are stored on the internal research database of Vincent van Gogh Institute for Psychiatry (project/network drive on local server; data manager Wouter Oomens, MSc). Data were accessible only to the contributing authors and data manager and will be preserved for at least 10 years. Paper-based informed consent for the anonymous use of data was obtained

in accordance with institutional procedures, with signed forms archived at the Centre of Excellence for Neuropsychiatry. All neuropsychological assessment forms are likewise securely stored at the Centre.

### Interoperable and Reusable

Raw data are retained in long-term accessible formats such as .sav, .csv, and .tif to ensure future usability. Detailed descriptions of experimental procedures are available in the associated publications.

### Privacy

Participant privacy was safeguarded through the use of individual subject codes. The key linking these codes to identities is stored separately from the research data and is accessible only to authorized project personnel, in accordance with internal privacy protocols. All materials are archived at the Centre of Excellence for Neuropsychiatry.





## Donders Graduate School

For a successful research Institute, it is vital to train the next generation of scientists. To achieve this goal, the Donders Institute for Brain, Cognition and Behaviour established the Donders Graduate School in 2009. The mission of the Donders Graduate School is to guide our graduates to become skilled academics who are equipped for a wide range of professions. To achieve this, we do our utmost to ensure that our PhD candidates receive support and supervision of the highest quality.

Since 2009, the Donders Graduate School has grown into a vibrant community of highly talented national and international PhD candidates, with over 500 PhD candidates enrolled. Their backgrounds cover a wide range of disciplines, from physics to psychology, medicine to psycholinguistics, and biology to artificial intelligence. Similarly, their interdisciplinary research covers genetic, molecular, and cellular processes at one end and computational, system-level neuroscience with cognitive and behavioural analysis at the other end. We ask all PhD candidates within the Donders Graduate School to publish their PhD thesis in de Donders Thesis Series. This series currently includes over 600 PhD theses from our PhD graduates and thereby provides a comprehensive overview of the diverse types of research performed at the Donders Institute. A complete overview of the Donders Thesis Series can be found on our website: https://www.ru.nl/donders/donders-series

The Donders Graduate School tracks the careers of our PhD graduates carefully. In general, the PhD graduates end up at high-quality positions in different sectors, for a complete overview see https://www.ru.nl/donders/destination-our-former-phd. A large proportion of our PhD alumni continue in academia (>50%). Most of them first work as a postdoc before growing into more senior research positions. They work at top institutes worldwide, such as University of Oxford, University of Cambridge, Stanford University, Princeton University, UCL London, MPI Leipzig, Karolinska Institute, UC Berkeley, EPFL Lausanne, and many others. In addition, a large group of PhD graduates continue in clinical positions, sometimes combining it with academic research. Clinical positions can be divided into medical doctors, for instance, in genetics, geriatrics, psychiatry, or neurology, and in psychologists, for instance as healthcare psychologist, clinical neuropsychologist, or clinical psychologist. Furthermore, there are PhD graduates who continue to work as researchers outside academia, for instance at non-profit or government organizations, or in pharmaceutical companies. There are also PhD graduates who work in education, such as teachers in high school, or as lecturers in higher education. Others continue in a wide range of positions, such as policy advisors, project

managers, consultants, data scientists, web- or software developers, business owners, regulatory affairs specialists, engineers, managers, or IT architects. As such, the career paths of Donders PhD graduates span a broad range of sectors and professions, but the common factor is that they almost all have become successful professionals.

For more information on the Donders Graduate School, as well as past and upcoming defences please visit: **http://www.ru.nl/donders/graduate-school/phd/**

“In clinical practice, it becomes evident that many individuals with Neurofibromatosis type 1 (NF1) long to feel “normal”. They wish to participate in society, to blend in, and not to stand out as different. This desire for belonging is a shared human experience, yet it often carries the subtle burden of wanting to be something one is not, like a tulip striving to become a rose in a garden where roses dominate.

As Marsha Linehan insightfully reminds us, “the goal is not to become a rose.” The true challenge lies in developing the skills to cultivate a thriving garden, one that embraces a diversity of flowers. This garden is not about uniformity, but about understanding who we are, recognizing what nourishes us, and discovering how we can flourish in our own unique way. Learning to tend to this diverse garden filled with tulips, roses, and countless other flowers fosters the resilience needed to grow into who we are, rather than who we think we should be”

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