

# Social cognitive training for adults with Noonan syndrome: a feasibility study

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**Purpose:** Noonan syndrome (NS) is a genetic disorder that is associated with social cognitive problems. While treatment aimed at the improvement of social cognition is available for other neuropsychiatric disorders, no such interventions yet exist for NS patients. In this study, the development of the first social cognitive training for NS patients is described and its applicability and feasibility evaluated.

**Methods:** Eleven adult patients with NS participated in this controlled proof-of-principle study. Six patients were included in the treatment group and five in the control group. Neuropsychological testing was performed in both groups at baseline and posttreatment. Social cognition was a primary outcome measure and nonsocial cognition and psychopathology secondary outcome measures. Differences between pre- and posttest were investigated with Wilcoxon signed-rank tests, and a process evaluation was performed to aid interpretation of the results.

**Results:** Both groups were comparable with regard to age, estimated intelligence, and baseline performance. Although no significant differences were found between pre- and posttest scores on primary and secondary outcome measures in either group, a medium-large effect size was found on emotion recognition in the treatment group. Also, the process evaluation demonstrated the feasibility of the training.

**Conclusion:** This first social cognitive training for adult patients with NS has proven to be feasible for this population and showed some encouraging results regarding emotion recognition, although the training protocol could be optimized. Further investigation is required using a randomized controlled design in a larger sample, in order to substantiate the overall effectiveness of the training.

**Keywords:** social cognition, alexithymia, cognition, social cognitive intervention, genetic syndrome

## Introduction

Noonan syndrome (NS) is an autosomal-dominant genetic disorder characterized by distinctive facial features, congenital heart disease, short stature, and varying degrees of developmental delay. Other features include chest deformities, a broad or webbed neck, cryptorchidism, coagulation defects, and lymphatic dysplasia.<sup>1,2</sup> The estimated prevalence is one in 1,000–2,500 live births.<sup>3</sup> NS is caused by germ-line mutations encoding components of the Ras–MAPK pathway, a signal-transduction cascade involved in several developmental processes, such as cell-cycle regulation, differentiation, growth, apoptosis, and cell senescence.<sup>2,4</sup> NS is one of the “RASopathies”, referring to a class of related developmental disorders that are caused by gene mutations, resulting in dysregulation of the Ras–MAPK pathway.<sup>5</sup> To date, mutations in 17 genes have been associated with NS, of which those in *PTPN11* (50%), *SOS1* (10%), and *RAF1* (10%) are most frequently identified.<sup>6</sup> In approximately 75% of patients with NS,

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a genetic mutation can be identified, although diagnosis is still primarily based on clinical criteria.<sup>7-9</sup>

In children with NS, difficulties have been found in several cognitive domains, ie, language, motor function, attention, executive function, and social cognition.<sup>10</sup> Regarding the cognitive profile of adults with NS, (low) average intelligence and lowered speed of information processing were found in comparison to matched controls.<sup>11</sup> Performance on other cognitive domains, such as memory, executive functioning, and visuoconstruction, seems to be relatively intact in adulthood, although patients report subjective executive problems.<sup>11</sup> With regard to social cognition – the mental processes underlying social functioning<sup>12</sup> – in adults with NS, difficulty in identifying and describing one's own emotional feelings (ie, higher levels of alexithymia), slight overall problems in facial emotion recognition and social discomfort have been described.<sup>13</sup> Alexithymia (from Greek for 'no words for emotions') is a dimensional personality trait, reflecting weaknesses in cognitive processing and regulation of one's own emotions. Alexithymia is characterized by difficulties in identifying and describing feelings, limited imaginal capacity, and an externally oriented cognitive style.<sup>20</sup> In a variety of clinical and healthy populations, alexithymia has been related to social cognitive impairments, such as problems in the automatic processing of emotional stimuli, affect recognition, empathy, and mentalizing.<sup>65-76</sup> Studies on a behavioral level in patients with NS showed higher prevalence of autism traits and weaker social skills, although it should be noted that these studies focused predominantly on children and only two included a (normally developing) control group.<sup>14-17</sup> Even though only a few studies have investigated the presence of psychiatric disorders in adults with NS, mood and anxiety problems are suggested to be rather frequent.<sup>3,18,19</sup> Despite the mental health risks associated with social cognitive impairments and alexithymia,<sup>12,20</sup> no social cognitive intervention incorporating alexithymia training is yet available for patients with NS.

Various social cognitive interventions have demonstrated improvements in social cognition in adult neuropsychiatric patients (ie, patients with schizophrenia-spectrum disorders, autism-spectrum disorders, and acquired brain injury).<sup>21</sup> These treatments included targeted interventions, focusing on one social cognitive subdomain, eg, emotion recognition or theory of mind (ToM), comprehensive interventions that addressed more than one social cognitive subdomain, eg, emotion recognition and ToM training, and broad-based interventions in which social cognition training was embedded in the context of other interventions, such as

neurocognitive remediation or social skill training. In general, these social cognitive interventions were most effective in improving emotion perception, but ToM, social perception, and social functioning could also be trained effectively. Training of emotion perception appears to be an important component of effective social cognitive interventions, while addressing social functioning and providing sufficient practice opportunities in daily life are beneficial for generalization.<sup>21</sup> Some well-described social cognitive interventions for various neuropsychiatric disorders include social cognition and interaction training,<sup>22</sup> treatment of affect recognition,<sup>23</sup> cognitive enhancement therapy,<sup>24</sup> and treatment for impairments in social cognition and emotion regulation.<sup>25</sup> Several social cognitive interventions exist for children with autism-spectrum disorder, but well-studied treatments for adults are scarce, although results seem promising.<sup>21,26</sup> Given the fact that alexithymia is related to social cognitive difficulties, it is remarkable that social cognitive interventions for neuropsychiatric disorders do not address alexithymia.

Almost four decades ago, Krystal<sup>27</sup> recommended the use of specific therapeutic techniques in alexithymic patients, such as making patients aware of their alexithymic problems and emotional feelings, developing affect tolerance, and providing psychoeducation regarding emotions (ie, their signal function, duration, and intensity), and helping patients to recognize and verbalize their emotions. A more recent narrative review on psychological interventions aimed at reducing alexithymia in psychiatric, medical, and healthy populations suggests that alexithymia is partly modifiable and that reductions in alexithymia scores can be obtained when alexithymia is directly trained.<sup>28</sup> Some studies have used relaxation techniques and mindfulness to diminish stress levels and increase awareness of inner experiences and physical sensations.<sup>29-31</sup> Psychoeducation regarding emotions and their function, as well as the identification of antecedents of alexithymia (eg, emotional expression in family of origin), have also been described.<sup>30-32</sup> Since alexithymia is correlated with decrements in emotion recognition, many alexithymia interventions incorporate training of emotion perception, identification, and differentiation.<sup>29-33</sup> Mentalizing and differentiating bodily feelings, thoughts, emotions, and behavior have also been addressed.<sup>31,32</sup> In order to improve verbalization of emotions, training affect labeling, extension of the "emotional vocabulary", and training of self-expression skills are used.<sup>31-33</sup> Listening to music, creating fantasy stories, creative writing, noting dreams, reading literary fiction, or creating poetry can stimulate fantasizing.<sup>29,34</sup> Lastly, Taylor and Bagby<sup>20</sup> suggested that alexithymia interventions are

preferably provided in a group-therapy setting, because a group offers relevant interpersonal practice. However, they suggest that the groups should be small and consist of no more than three patients.

Because the existing social cognitive treatments do not incorporate alexithymia training, they are not completely suitable for NS patients, in whom specific difficulties in the identification and verbalization of their own emotions have been demonstrated. For this reason, a social cognitive training was developed, based on the promising results of previous social cognitive and alexithymia interventions and tailored to the specific (social) cognitive profile of adult patients with NS. The training consists of ten weekly group sessions comprising the three phases of social cognition: perception of one's own emotions and the emotions of others, interpretation and integration of socially relevant information, and execution and regulation of social behavior.<sup>35</sup> In this proof-of-principle study, the development, applicability, and feasibility of the new training protocol will be described in a group of patients with NS in comparison to an NS control group. Social cognition, operationalized by the three aforementioned phases of affective information processing, was a primary outcome measure. Given the cognitive profile of patients with NS and relation with social cognition, nonsocial cognition (speed of information processing, inhibition, planning abilities), psychopathology ([social] anxiety, depression), quality of life, and self-efficacy were the secondary outcome measures.

## Methods

### Design and procedure

Pilot sessions of the training were held at meetings of the Dutch Noonan Syndrome Foundation to investigate both interest and support for a social cognitive training, as well as to obtain input from patients and their relatives regarding important aspects of everyday functioning, eg, inclusion of training partners. Subsequently, a training protocol was designed by RR and EW, including important elements of evidence-based social cognitive interventions (eg, training of emotion recognition, ToM, social behavior) and exercises from alexithymia treatments. This resulted in a structured, 10-week group intervention of 90-minute sessions in which the three phases of social cognition were addressed (perception, interpretation, and reaction). The training protocol included psychoeducation and in-session exercises, incorporating emotion-recognition training, ToM and mentalizing strategies, and exercises to improve identification, labeling, and expression of (own) emotional feelings (see Table 1 for topics and content per session). Participants also performed

homework exercises aimed at increasing awareness of one's own emotional feelings and social behavior and allowed them to practice with the training topics. Each training session was structured similarly, starting with the evaluation of homework exercises, psychoeducation concerning a social cognitive phase and/or subdomain, practice in the group, and introducing new homework. The group size was intentionally limited, with a maximum of five patients per group. Participants were asked to select a training partner, who was invited for two training sessions and performed homework exercises with the patients, in order to provide practice opportunities in daily life.

The current study had a controlled pre- vs posttest within-subject design with a treatment group and a control group. Patients in the control group received treatment as usual (eg, psycho-education, psychological counseling, consultation with general practitioner and/or medical specialist). Before and after training, a neuropsychological test battery, including several (social) cognitive tasks and self-report questionnaires, was administered in both groups. The primary outcome measures reflected all three phases of affective information processing, thus including emotion recognition, ToM, social perception, alexithymia, and social behavioral problems. As secondary outcome measures, subjective and objective measures of nonsocial cognition, psychopathology, quality of life, and self-efficacy were included. Proxies of patients in the treatment group were asked to complete two questionnaires as well. Training sessions were held at a central location in the Netherlands within an acceptable travel distance for all participants. For patients in the treatment group, pre- and posttests were planned at the same location and combined with the first and the last training session, if possible. Participants in the control group were tested at a location of their preference. However, most testing took place at the same location as for the treatment group and at about the same time. Control participants received a gift voucher as compensation for their travel expenses. Further information regarding the procedure is provided in the process analysis in Table 2.

### Participants

Eleven patients with NS participated in this study. Four more patients were eligible for inclusion, but did not participate, due to current work or study obligations or nonresponse. Due to the small number of patients who volunteered to participate in the training study, it was not possible to allocate patients randomly to the treatment and control conditions. The treatment group consisted of six patients, who followed the

**Table 1** Overview of topic and content of each training session

Session	Topic	Content
1	Introduction	Identification of treatment aims Psychoeducation on social cognition (perception, interpretation, and reaction) in NS Relaxation exercise
	<b>Perception</b>	
2	Emotion perception in other people	Psychoeducation on emotions and emotion perception in others Exercises aimed at emotion perception via different modalities
3	Perception of own emotions	Introduction of emotion word of the day (repeated exercise) Psychoeducation on (affective) alexithymia Exercises regarding the identification of emotional feelings and mindfulness
4	Training partner session (with patients)	Psychoeducation on social cognition (in NS) Providing information regarding the training and the role of training partners
	<b>Interpretation</b>	
5	Theory of mind/perspective taking	Psychoeducation on analyzing emotions, mentalizing, theory of mind, and perception of social information Exercises aimed at the perception of social faux pas, perspective taking, and social context
6	Theory of mind/perspective taking	Psychoeducation on perspective taking and attributional biases Exercises concerning perspective taking, theory of mind, attributional biases, and social faux pas
	<b>Reaction</b>	
7	Alexithymia	Psychoeducation on (cognitive) alexithymia, emotion regulation, and inhibition Exchanging emotion-regulation strategies (coping with emotions) in family of origin Exercises aimed at extending the emotional vocabulary and alternative ways of expressing emotions
8	Alexithymia	Psychoeducation on coping strategies (reappraisal, acceptance, and action) Exercises regarding emotional expression
9	Recapitulation	Summary of training information Evaluation of individual treatment aims Exercises concerning emotional expression and repeating exercises from previous phases
10	Evaluation with training partners and patients	Summary of training information Evaluation of individual mood boards (personal, nonverbal expression of the six basic emotions) Evaluating the role of training partners and treatment aims

**Abbreviation:** NS, Noonan syndrome.

training in two consecutive groups. The control group comprised five patients. Participants were recruited by the Centre of Excellence for Neuropsychiatry of Vincent van Gogh Institute for Psychiatry, the Department of Medical Genetics of Radboud University Medical Center, Nijmegen, and the Dutch Noonan Syndrome Foundation. Written informed consent was obtained, and the study was approved by the Institutional Review Board of Vincent van Gogh Institute for Psychiatry, in accordance with the Declaration of Helsinki.

Inclusion criteria were a confirmed clinical diagnosis of NS or other RASopathy, minimum age of 16 years, and sufficient verbal capacities estimated during the intake procedure by two neuropsychologists (RR and EW). The presence of subjective or objective social cognitive impairments was required for participation in the treatment group. More information regarding the recruitment and inclusion procedures is presented in Table 2.

The mean age in the treatment group was 47.7 years (SD 12.8, range 29–60) and 35.8 years in the control group (SD 9.8, range 23–46). Mean IQ, estimated by the Dutch version of the National Adult Reading Test (NART),<sup>36</sup> was 85.33 in the treatment group (SD 17.86, range 69–113) and 83.40 (SD 17.59, range 55–103) in the control group. Education level, according to the Dutch educational system and ranging from category 1 (<6 years of primary education) to 7 (academic degree),<sup>37</sup> varied from 3 to 7 in the treatment group (mode 4) and from 2 to 5 in the control group (mode 5). In the treatment group, 17% of the participants were men, while in the control group 60% men were included. Half the participants in the treatment group had a mutation in the *PTPN11* gene compared to 40% in the control group. One patient in the treatment group was diagnosed with NS with multiple lentiginos and one patient in the control group with NS with loose anagen hair. After a Mann–Whitney *U* test,

**Table 2** Results from the process analysis organized as per process-evaluation components, related process measures, and process variables

Process components	Findings
Study population	<b>1. Recruitment and selection rate</b>
	<b>1a. Number of eligible persons in screened population</b> Fifty-five patients from the Department of Clinical Genetics of Radboud University Medical Center and all contributors to the Dutch Noonan Syndrome Foundation were contacted by letter or email with information regarding the training. This information was also displayed on the websites of the Centre of Excellence for Neuropsychiatry of the Vincent van Gogh Institute for Psychiatry and the Dutch Noonan Syndrome Foundation and presented in newsletters and at meetings of the Dutch Noonan Syndrome Foundation. In total, approximately 150 patients were approached, of whom a maximum 25% were thought to be eligible, because children and adolescents aged <16 years, adult patients without social cognitive complaints, or patients who were not interested in this intervention were not eligible for participation.
	<b>1b. Number of participants from sample of eligible persons</b> Initially, 15 patients were interested in participating in the training. Five patients were excluded due to age (<16 years) or low verbal intelligence. Four other patients were eligible for inclusion but did not (yet) participate, because they could not combine the training with current work or study obligations or because they did not respond to invitations. Given the small number of patients who volunteered, it was not possible to allocate patients randomly to a treatment group and a waiting-list control group. Therefore, control participants were actively recruited at meetings of the Dutch Noonan Syndrome Foundation, and five patients were included in the control group. The control group did not follow the training at a later point in time. One patient of the control group subsequently participated in the training. No pre- or posttest information was obtained from this participant after the training because they had already been included in the control group and repeated neuropsychological assessment after participation in the training would have affected the results. The training was provided in two treatment groups (n=4 and n=3), which started consecutively. In sum, 11 patients were included in this study: six in the treatment group and five in the control group.
	<b>1c. Number of participants vs aimed-at number</b> The aim was to include 20 patients (ten in the treatment group and ten in the control group). The recruitment objective was not reached.
	<b>2. Barriers and facilitators in recruitment and selection</b>
	<b>2a. Difference in baseline characteristics between nonparticipating and participating eligible persons</b> No information was available regarding differences between participating and nonparticipating eligible patients. There were no significant differences in demographics or baseline variables between the control group and treatment group, although this could reflect a power problem due to the small study sample size. Because the groups could not be allocated randomly, a selection bias might be present, as patients with more severe social cognitive deficits may be more inclined to participate in the treatment group.
	<b>2b. Motivation of nonparticipating and participating eligible persons</b> Some patients who were initially interested in the training could not make the required time investment in combination with current work or study activities. There also seemed to be some hesitation for participation in group training. Possibly, the nature of the (social) cognitive problems of patients with NS could provide an explanation for these findings.
	<b>2c. Experience with recruitment and selection</b> Although there appeared to be much interest for the social cognitive training, the number of patients that volunteered in the feasibility study was lower than expected.
	<b>3. Number of participants completing follow-up vs number started</b>
	<b>3a.</b> All participants completed the neuropsychological measures at pre- and posttest. However, not all self-report and proxy questionnaires were returned.
	<b>4. Barriers to and facilitators of follow-up</b>
<b>4a. Reasons for dropout and motivation for continued participation</b> There were no dropouts. All participants in the treatment group completed the training and wanted to improve their social cognitive functioning. Patients in both groups valued the importance of this study to increase the treatment options for patients with NS and were driven to contribute.	
Complex intervention	<b>1. Quality of delivery of the interventional components</b>
	<b>1a. Part of each component and complete intervention delivered by instructors</b> All three phases of the intervention (perception, interpretation, reaction) were delivered successfully. The number and difficulty of exercises could be adjusted flexibly to the level of social cognitive functioning of the group or to individual participants.

(Continued)

**Table 2** (Continued)

Process components	Findings
	<p><b>1b. Satisfaction with delivery</b>                      All phases appeared to be feasible. It was observed that participants were inclined to spend a lot of time on sharing their experiences at the expense of practicing social cognitive exercises. A possible explanation for this observation could be that patients with NS seldom met other patients and enjoyed exchanging experiences. However, it could also reflect avoidance of (possibly distressing) exercises or be the result of verbosity, due to executive difficulties. The time spent on psychoeducation could be shortened in favor of more (group) exercises. The training initially incorporated one proxy session without participants and one evaluation session with proxies and participants together. After evaluation of the first training group, both proxy sessions were provided in the presence of the participants.</p>
	<p><b>2. Barriers and facilitators for delivery of interventional components</b></p>
	<p><b>2a. Reasons for diverging from or applying (planned) components</b>                      The three phases of the training were all delivered, although the exercises were slightly adjusted to the level of social cognitive functioning of the group. Despite differences in intellectual capacities and education level, participants had comparable training aims and found many similarities between one another's social cognitive difficulties.</p>
	<p><b>3. Adherence to interventional components</b></p>
	<p><b>3a. Number of sessions followed</b>                      Three participants (50%) followed all sessions. One participant missed one-and-a-half sessions due to problems with public transport. Two participants missed two sessions, because of work-related activities or health issues. When sessions were missed, participants received the information and exercises of that week by email, studied them independently, and had the opportunity to ask questions via email or telephone. On average, less than one session was missed (mean 9.08±1.02 sessions). Not all training partners attended both proxy sessions, due to the required time investment, work obligations, or cognitive difficulties.</p>
	<p><b>3b. Intervention components (partly) followed</b>                      The participants received all three training phases.</p>
	<p><b>3c. Compliance with individual recommendations</b>                      Individual recommendations were followed up.</p>
	<p><b>3d. Homework adherence</b>                      All participants did homework exercises, although some needed additional guidance or support. The number and nature of the homework exercises slightly differed each week. Some patients viewed the number of exercises as too many. Also, there seemed to be a tendency to avoid exercises with training partners. Some proxies were thus less involved in the training than intended. Adequate involvement of a training partner seemed to be supportive and beneficial for the participant.</p>
	<p><b>4. Barriers and facilitators for adherence to interventional components</b></p>
	<p><b>4a. Motivation for (lack of) attendance and compliance</b>                      Patients appeared motivated to attend the training. They valued the importance of the training and seemed to enjoy the sessions.</p>
	<p><b>5. Experience of participants and instructors with interventional components</b></p>
	<p><b>5a. Perceived benefit</b>                      All participants reported that they benefited from the training. They mentioned, eg, an increased awareness of social cognitive difficulties (related to NS) and the acquisition of useful strategies to improve social cognitive functioning in daily life. In addition to the content of the training, participants seemed to benefit from recognition of one another's experiences and the support from their group members. For some participants, this training was the first time they had come in contact with other patients with NS. Patients also mentioned that the training was intensive and demanding with regard to emotional load and time investment required. Two participants suggested more time and elaboration, eg, on social rules and social interaction. Furthermore, it was suggested by one participant that it be stated more clearly that the homework exercises could be time-consuming and to provide a contact person who patients could reach when they felt worse or relapsed. Three of the training partners who evaluated the training posttest felt that the participants benefited from the training. The training partners judged the proxy sessions as sufficient in frequency, although one partner mentioned that more proxy sessions were preferred. For the three other patients, no evaluative information was provided by their training partners. On average, general satisfaction with the training, evaluated by five participants in the treatment group, was judged as 8.9 (ranging from 0 to 10). Satisfaction with the therapeutic relationship 7.8, satisfaction with aims and topics of training 7.6, and satisfaction with approach and methods 8.4.</p>
	<p><b>5b. Strong and weak aspects of the interventional components (structure and content) and the total intervention</b>                      Strong aspects of the training concerned its (small) group-based format, in which patients learned from each other's experiences, increased their awareness of social cognitive difficulties, and were able to practice learned strategies. The training stimulated three participants for additional psychotherapy to continue practicing with the training topics.</p>

(Continued)

**Table 2** (Continued)

Process components	Findings
	For two patients, information and elements from the training were incorporated into already-existing coaching or counseling trajectories. In addition, patients used the psychoeducation provided during the training to inform other people (eg, healthcare professionals or family members) or in cases of relapse. Every 6 months, participants were invited to follow up evaluation-group sessions at meetings of the Dutch Noonan Syndrome Foundation. If patients were not able to participate in this session, individual (telephone) contact was offered. Besides the small sample, a weak aspect of the training may be the slight imbalance between time spent on psychoeducation and discussion of social cognitive complaints and the amount of practice time. More concise and practical psychoeducation in combination with additional exercises may be helpful. Also, some training partners were less involved in the training than intended.
<b>Evaluation data</b>	<b>1. Outcome measure: coverage of interventional components</b>
	<b>1a. Average number of outcomes per component</b> Primary outcome measures covered all three phases of social cognition that were addressed in the training: perception (Emotion Recognition Task and alexithymia questionnaire), interpretation (social perception task, theory-of-mind task, and alexithymia questionnaire), and reaction (questionnaire of social behavioral problems and alexithymia). The five secondary outcome measures concerned nonsocial cognition (speed of information processing, inhibition, and planning), psychopathology ([social] anxiety and mood problems), quality of life, and self-efficacy.
	<b>2. Completeness of data collection</b>
	<b>2a. Number and characteristics of missing data</b> Neuropsychological test data were complete. With regard to the questionnaires, for one patient in the treatment group the BVAQ and DEX-SC were missing posttest, while the SIB was missing both pre- and posttest in this individual. For one control participant the BVAQ, DEX-SC, and SIB were missing. One individual in the treatment group missed one page of the questionnaire book, which was replaced with the pretest scores. In addition, there were nine incidental missing data points (five in the treatment group and four in the control group): six at pretest and three at posttest. Most missing data were on the BVAQ, SIB, and DEX-SC. If it was not possible to recontact participants, incidental missing data points were replaced with the score at pre- or posttest (depending on which score was missing) or with the average score on other items of that questionnaire. When two answers were given, the average score was calculated.
	<b>3. Barriers to and facilitators of data collection</b>
	<b>3a. Feasibility of outcome measures</b> The test battery lasted approximately 2 hours but was not considered too long by participants. Questionnaires were filled out mostly at home, which possibly led to a lower response rate. Three participants in the treatment group reported trouble with some of the questionnaires, and one received help from a friend. One proxy had difficulty filling out the questionnaires and thus did not complete the posttest.
	<b>3b. Reasons data were missing</b> Reasons for attrition in returning the questionnaires at posttest were difficulty with completing the questionnaires, lack of supervision while filling out the questionnaires, psychosocial problems, and unfortunate practical complications with mail-order services.
	<b>3c. Reasons participants were excluded from analysis</b> There were no participants excluded from analyses for reasons other than missing data. With regard to heterogeneity in patient characteristics in this sample, outliers could be present. However, for the purpose of this feasibility study, all data were included.
<b>4. Comparison of qualitative and quantitative effectiveness data</b> The perceived benefit by patients and training partners was not reflected by the quantitative data. Finding no significant improvement on primary or secondary outcome measures may be the result of a power problem due to the small sample. Furthermore, it is possible that some tests in the current battery were not able to detect differences adequately between pre- and posttest.	

**Abbreviations:** BVAQ, Bermond-Vorst Alexithymia Questionnaire; DEX-SC, Dysexecutive Questionnaire – social conventions; NS, Noonan syndrome; SIB, Scale for Interpersonal Behavior.

there appeared to be no significant differences between the treatment group and the control group with regard to NART IQ (treatment median 78, control median 85,  $U=13$ ,  $z=-0.37$ ,  $r=-0.11$ ;  $P=0.76$ ), and age (treatment median 50 years, control median 40 years,  $U=7.50$ ,  $z=-1.38$ ,  $r=-0.42$ ;  $P=0.19$ ), although the effect size for age was medium-large.

Five patients in the treatment group reported previous psychological problems (mood problems, anxiety, stress-related

psychological complaints, alcohol abuse), and three had current psychological complaints (mainly mood problems). Two patients were still receiving psychosocial counseling, which did not focus on improving social cognition. All participants in the control group had received psychological treatment once in their lives for anxiety and compulsions, posttraumatic stress disorder, suicidal ideation, attention deficit/hyperactivity disorder, or a history of being bullied.

Two participants in the control group reported current psychological problems, and one was still receiving psychological and psychiatric treatment, not aimed at reducing social cognitive problems, at another mental healthcare facility.

## Baseline measures

The Dutch version of the NART was administered at baseline as an estimate of intellectual functioning.<sup>36</sup>

## Primary outcome measures

### Emotion recognition

The Emotion Recognition Task (ERT) was used as a measure of facial emotion recognition.<sup>38</sup> The ERT is a computer task in which participants are presented with dynamic images of the faces of four actors expressing the six basic emotional expressions: anger, disgust, fear, happiness, sadness, and surprise. A computer program enables real-time interactive morphing between a neutral expression and the emotional expression in four intensities (40%, 60%, 80%, and 100%).<sup>38</sup> After each video clip, the participant is asked to choose among the six emotions, displayed as buttons on the test computer. Performance is defined by the total number of correctly identified emotional expressions. Scores range from 0 to 96, and higher scores represent better facial emotion recognition. The ERT has been validated in a wide range of clinical groups and normative data of healthy participants are available.<sup>38</sup>

### Theory of mind

Two subtests of the short Dutch version of The Awareness of Social Inference Test (TASIT-NL) were used as measures of ToM.<sup>39,40</sup> A combined score of the subtests social inference – minimal (SI-M) and social inference – enriched (SI-E) was used, because these subtests measure aspects of ToM, while the first subtest – the emotion-evaluation test – addresses emotion recognition.<sup>40</sup> The TASIT-NL is the only ToM test that uses videos of actual persons in familiar social situations. Subtest SI-M includes nine videos with three sincere, three sarcastic, and three paradoxical sarcastic scenes. After each video, the participant has to answer four questions about what the actor was doing, saying, thinking, and feeling. Subtest SI-E consists of eight other videos (four lies, four sarcastic scenes) with additional contextual cues to assist the understanding of the situation. After each video, the participant has to answer the same four questions (do, say, think, feel). The combined score for the two subtests ranges from 0 to 68, with higher scores reflecting better ToM abilities. The TASIT-NL has two parallel forms: form A (used at pretest) and form B

(at posttest). Although some differences were found between the two forms regarding difficulty at item level and presence of a sequence effect for subtest SI-M (lower performance on form B when participants first completed form A), no differences were found between forms A and B on subtest total scores and overall score, indicating that both forms are comparable. Overall performance on the alternate forms was correlated moderately ( $r=0.45$ ).<sup>40</sup>

### Social perception

The social interpretation test (SIT) was used as a measure of social perception.<sup>41</sup> The SIT consists of a colored drawing depicting a social situation (an accident and reactions of people in the street). Nine open questions are asked to the participant, such as “Can you tell me something about the picture?”; “Do you think there is something striking or strange in the picture?”; and “How are these people involved in the situation?”. The SIT contains a scoring system with 24 statements, and correct answers are scored as 1 point. The SIT has a parallel version using a different yet comparable drawing. Form A was used at pretest and form B at posttest. A maximum score of 21 could be obtained, because only those statements that were thought to be plausible analogies between the two forms were used.<sup>41</sup> Performance on the two forms was highly correlated ( $r=0.82$ ).<sup>41</sup>

### Alexithymia

The Bermond–Vorst Alexithymia Questionnaire (BVAQ) was administered to measure alexithymia.<sup>42</sup> This questionnaire consists of 40 items, which are rated on a 5-point Likert scale. The BVAQ includes five factor-based subscales (emotionalizing, fantasizing, identifying, analyzing, and verbalizing), and two higher-order scales (affective and cognitive dimensions). The total score on the BVAQ (40–200) was used in this study, with higher scores reflecting higher levels of alexithymia. Patients in both groups completed a self-report version of this questionnaire. In addition, for participants in the treatment group, a partner or other person close to the patient (ie, their training partner) was asked to complete a proxy version of this list constructed by the researchers. The reliability and validity of the self-report version of the BVAQ are acceptable, and normative data of healthy participants are available.<sup>42,43</sup>

### Social behavioral problems

Based on the factor-analysis study of Bodenbun and Dopsloff,<sup>44</sup> a subscale of the Dysexecutive Questionnaire was calculated measuring social conventions and the ability



to incorporate social interaction in one's own behavior (DEX-SC).<sup>45</sup> The subscale consists of four items. Total scores range from 0 to 16, with higher scores reflecting more social behavioral problems. Patients in the treatment and control groups completed the self-report version of the DEX-SC, and for participants in the treatment group a proxy version of this list was completed by a partner or other person close to the patient (ie, their training partner).

## Secondary outcome measures

### Speed of information processing and inhibition

The Stroop color-word test (CWT) was assessed to measure processing speed and response inhibition.<sup>46,47</sup> The average time to complete the first two conditions is used as a measure of mental speed. A ratio score (completion time on third condition divided by the average time on conditions 1 and 2) was calculated to reflect the ability to inhibit an automatic response. Lower ratio scores reflect better inhibition. The reliability of the Stroop CWT is considered good and construct validity sufficient.<sup>48</sup>

### Planning

An adapted version of the modified six-elements test (MSET), a subtest of the behavioral assessment of the dysexecutive-syndrome battery, was used to measure planning abilities.<sup>45,49</sup> The adapted MSET was used, because it has two parallel forms (version 1 was used at pretest and version 2 at posttest), reduced ceiling effects in mildly impaired individuals, and a more differentiated scoring system.<sup>50</sup> In the adapted MSET, the original dictation subtask has been replaced with a sorting task. The other subtasks include arithmetic (version 1), categorizing pictures (version 1), picture naming (version 2), and categorizing words (version 2). The test procedure of the adapted MSET is comparable to the original task. In this study, the scoring method of the adapted MSET ([time of longest subtasks – time of shortest subtasks]/[number of executed tasks – rule breaks]) was used.<sup>50</sup> Lower adapted MSET scores indicate better planning performance. Normative data of healthy participants are available.<sup>50</sup>

### Social distress

The Scale for Interpersonal Behavior (SIB) was used to reflect engagement in social behavior and related distress.<sup>51</sup> The SIB includes 50 items reflecting social behavior, of which the participant has to evaluate (on two separate 5-point scales) the probability of engaging in this behavior (performance scale) and the level of stress it evokes (distress scale). For the purpose of this study, only the distress scale was used.

Higher scores reflect higher levels of social distress. The construct validity and reliability of the SIB are considered good and criterion validity sufficient.<sup>52</sup> Normative data of healthy participants are available.<sup>77</sup>

### Anxiety and depression

The Dutch version of the Symptom Checklist 90 – revised (SCL-90-R) was used to measure general psychological complaints.<sup>53</sup> The questionnaire consists of 90 items, which are rated on a 5-point scale. For the purpose of this study, only the depression (16 items) and anxiety (10 items) subscales were administered. Higher scores reflect a higher level of complaints. The reliability, construct validity, and criterion validity of the SCL-90-R are considered good.<sup>54</sup> Normative data of healthy participants are available.<sup>53</sup>

### Quality of life and self-efficacy

Two short self-report questionnaires of quality of life (three items) and self-efficacy regarding social cognitive functioning (eight items) were administered. These questionnaires were developed by the authors, based on items of the Dutch version of the Acceptance and Action Questionnaire and the Lancashire Quality of Life Questionnaire,<sup>55,56</sup> and adjusted to the NS population. Higher scores on these questionnaires reflect a higher level of quality of life or self-efficacy.

## Data analyses

Pretest scores on the primary and secondary outcome measures of the treatment and control groups were compared using a Mann–Whitney U tests. Wilcoxon signed-rank tests were performed to investigate pre- vs posttest differences in the treatment and control groups. Effect sizes were calculated manually using the equation:  $r = z / (\sqrt{n})$ .<sup>57,58</sup> Analyses were performed with SPSS version 23.0.0.0.

For tests for which normative data of healthy participants were available and no adjusted scores were used in the current study (ie, ERT, BVAQ, MSET, SIB, SCL-90-R), individual test scores were classified as low ( $< -2$  SD), below average ( $-1.5$  to  $-2$  SD), above average ( $1.5$ – $2$  SD), or high ( $> 2$  SD). A process evaluation (ie, a structured exploration of each process of an intervention) was added, as it can provide valuable information regarding the understanding of both positive and negative outcome results.<sup>59</sup> In the current study, the process evaluation was structured into three components, as suggested by Reelick et al:<sup>59</sup> success rate of recruitment and quality of study population, quality of execution of complex intervention, and process of acquisition of evaluation data.

## Results

### Baseline testing

The results of the treatment group and control group at baseline are displayed in Table 3. On primary and secondary outcome measures, no significant differences were found between the groups, even though medium–large effect sizes were present for differences on the ERT, DEX-SC, quality of life, self-efficacy, SCL-90-R – anxiety, and Stroop CWT – inhibition.

Compared to normative data, one patient in the treatment group had below-average performance on the ERT and one patient in this group performed at a low level. Two patients had above-average alexithymia levels on the BVAQ and two patients had high levels. For two patients, proxy reports showed above-average levels of alexithymia, while for two patients high levels of alexithymia were reported by proxies. Two patients reported high levels of depression on the SCL-90-R. In the control group, two patients reported high levels of alexithymia. Two patients in this group reported high levels of depression on the SCL-90-R and one patient reported high levels of anxiety on the same questionnaire. One patient reported an above-average level of social distress on the SIB and one patient reported high levels of social distress. One patient showed a low planning performance on the MSET. The classifications are displayed in Tables 4–7.

### Pretest vs posttest

There appeared to be no significant differences on primary outcome measures between pre- and posttest scores in the

treatment group or the control group (Tables 4 and 5). However, the effect size of improvement on the ERT was medium–large in the treatment group, while it was only small–medium in the control group.

Regarding secondary outcome measures, there were no significant differences between pre- and posttest scores in either group, although improvement on the adapted MSET in the treatment group and the faster performance of the control group on Stroop CWT processing speed almost reached significance and effect sizes were large (Tables 6 and 7). Despite the lack of significant results, the effect size of the improvement in inhibition scores on the Stroop CWT in the treatment group was medium–large, while decreased performance on this task in the control group showed a large effect. Furthermore, large effects were found in the control group with regard to the (nonsignificant) improvement in planning abilities on the adapted MSET and the decrease in anxiety on the SCL-90-R, while a medium effect was found for the decrease in depression. Since both groups showed a (medium to) large effect on improvement on the adapted MSET, this most likely reflected a practice effect.

### Process evaluation

In Table 2, detailed information regarding the process evaluation is displayed. The results of the process analysis regarding selection of the study population showed that the number of included patients was smaller than intended. It is hypothesized that the lower inclusion may have been influenced by the nature of the (social) cognitive deficits

**Table 3** Baseline performance of treatment group compared to control group

Outcome measures	Treatment <sup>a</sup> (n=6)	Control <sup>a</sup> (n=5)	U	z	P-value	r <sup>b</sup>
ERT	47	52	9	-1.10	0.31	-0.33
TASIT-NL	49	52	11	-0.74	0.50	-0.22
SIT	12.5	13	11.5	-0.65	0.54	-0.20
BVAQ	119	104	12	-0.55	0.62	-0.17
DEX-SC	9	7	9.5	-1.02	0.37	-0.31
Stroop CWT processing speed	55.5	48.5	12	-0.55	0.66	-0.17
Stroop CWT inhibition	1.75	1.59	6	-1.64	0.13	-0.49
Adapted MSET	18.5	15	11.5	-0.64	0.57	-0.19
SIB distress	109	117	11	-0.31	0.84	-0.09
SCL-90-R anxiety	17.5	12	9	-1.10	0.32	-0.33
SCL-90-R depression	28	22	11	-0.73	0.51	-0.22
Quality of life	12.5	16	9	-1.11	0.33	-0.33
Self-efficacy	36	39	9.5	-1.01	0.35	-0.30

**Note:** <sup>a</sup>Medians; <sup>b</sup>effect size.

**Abbreviations:** BVAQ, Bermond -Vorst Alexithymia Questionnaire; CWT, color-word test; DEX-SC, Dysexecutive Questionnaire – social conventions; ERT, Emotion Recognition Task; MSET, modified six-elements test; SCL-90-R, Symptom Checklist 90, revised; SIB, Scale for Interpersonal Behavior; SIT, social interpretation test; TASIT-NL, The Awareness of Social Inference Test (Dutch version).

**Table 4** Results of treatment-group patients on primary outcome measures at pre- and posttest

Patient number	ERT		TASIT-NL		SIT		BVAQ <sup>a</sup>		DEX-SC <sup>a</sup>		BVAQ proxy <sup>a</sup>		DEX-SC proxy <sup>a</sup>	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	51	51	56	56	12	11	93	119	9	11	113 <sup>b</sup>	111	10	13
2	31 <sup>c</sup>	45	47	52	9	10	117 <sup>b</sup>	127	10	7	150 <sup>c</sup>	150	14	8
3	41 <sup>b</sup>	55	49	46	9	10	122 <sup>c</sup>	–	9	–	100	115	8	9
4	43	39	43	42	13	11	121 <sup>b</sup>	127	7	9	124 <sup>c</sup>	–	7	–
5	61	59	60	55	15	16	146 <sup>c</sup>	127	10	12	108	102	11	9
6	51	61	49	45	16	16	103	90	8	9	118 <sup>b</sup>	121	13	11
Median	47.00	53.00	49.00	49.00	12.50	11.00	117.00	127.00	9.00	9.00	113.00	115.00	11.00	9.00
Interquartile range	15.00	16.00	11.00	11.00	6.25	6.00	35.50	22.50	2.50	3.50	30.00	29.00	4.50	3.50
$T^e$	3.00		4.50		7.50		7.00		5.00		4.00		5.00	
$z$	–1.22		–0.81		0		–0.14		–0.69		–0.37		–0.68	
$P$ -value	0.31		0.50		1.00		1.00		0.56		0.88		0.63	
$r^d$	–0.35		–0.23		0		–0.04		–0.22		–0.12		–0.22	

**Note:** <sup>a</sup>Median, interquartile range, and test statistics calculated for five patients; <sup>b</sup>below/above-average performance at pretest; <sup>c</sup>low/high performance at pretest; <sup>e</sup>effect size; <sup>d</sup>Test statistic of Wilcoxon signed-rank test reflecting the smallest sum of ranks.

**Abbreviations:** BVAQ, Bermond–Vorst Alexithymia Questionnaire; DEX-SC, Dysexecutive Questionnaire – social conventions; ERT, Emotion Recognition Task; SIT, social interpretation test; TASIT-NL, The Awareness of Social Inference Test (Dutch version).

in patients with NS. There were no dropouts among the included patients.

With regard to the evaluation of the intervention itself, the results of the process evaluation indicated that all three phases of the training were delivered successfully. All participants reported benefiting from the training. Increased awareness of social cognitive difficulties (related to NS) and the acquisition of useful strategies to improve social cognitive functioning were mentioned most frequently, though participants also reported that they had experienced the training as intensive and demanding in terms of the emotional load and practical

issues (eg, time investment). In addition to the content of the training, participants also benefited from the support they felt from their group members. It was observed that patients were inclined to spend much time on sharing their experiences in a detailed manner during the sessions, at the expense of training time. Supposedly, most patients with NS seldom meet other patients and greatly valued the recognition of one another's experiences and (social cognitive) problems. Alternatively, the observed tendency to share experiences extensively may reflect avoidance of (potentially distressing) exercises during the training or may be the result of verbosity, caused by

**Table 5** Results of control-group patients on primary outcome measures at pre- and posttest

Patient number	ERT		TASIT-NL		SIT		BVAQ <sup>a</sup>		DEX-SC <sup>a</sup>	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	45	27	45	44	13	9	124 <sup>b</sup>	144	9	6
2	56	61	52	59	13	11	104	–	6	–
3	52	49	58	49	11	11	89	90	12	12
4	47	53	52	60	14	16	126 <sup>b</sup>	105	7	8
5	59	65	58	54	16	16	89	91	5	5
Median	52.00	53.00	52.00	54.00	13.00	11.00	106.50	98.00	8.00	7.00
Interquartile range	11.50	25.00	9.50	13.00	3.00	6.00	36.50	44.00	5.75	5.75
$T^d$	6.00		7.00		1.50		4.00		1.00	
$z$	–0.41		–0.14		–0.82		–0.37		–0.45	
$P$ -value	0.75		1.00		0.75		0.88		1.00	
$r^c$	–0.13		–0.04		–0.26		–0.13		–0.16	

**Note:** <sup>a</sup>Median, interquartile range, and test statistics calculated for four patients; <sup>b</sup>low/high performance at pretest; <sup>c</sup>effect size; <sup>d</sup>Test statistic of Wilcoxon signed-rank test reflecting the smallest sum of ranks.

**Abbreviations:** BVAQ, Bermond–Vorst Alexithymia Questionnaire; DEX-SC, Dysexecutive Questionnaire – social conventions; ERT, Emotion Recognition Task; SIT, social interpretation test; TASIT-NL, The Awareness of Social Inference Test (Dutch version).

**Table 6** Results of treatment-group patients on secondary outcome measures at pre- and posttest

Patient number	Stroop CWT processing speed		Stroop CWT inhibition		Adapted MSET		SIB distress <sup>a</sup>		SCL-90-R anxiety <sup>a</sup>		SCL-90-R depression <sup>a</sup>		Quality of life <sup>a</sup>		Self-efficacy <sup>a</sup>	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	53.5	48.5	1.38	1.42	20.67	6.67	121	179	19	25	41 <sup>b</sup>	43	12	10	36	32
2	62.5	61.5	1.79	1.61	12.67	20.00	87	84	13	10	24	18	15	17	34	43
3	46.5	58.0	2.00	1.45	23.80	14.33	-	-	20	-	53 <sup>b</sup>	-	7	-	29	-
4	69.0	61.0	1.78	1.67	21.75	12.17	107	145	14	15	19	21	12	14	38	34
5	47.5	45.0	1.62	1.67	7.33	2.33	109	94	17	13	32	29	13	12	42	44
6	57.5	54.5	1.72	1.61	16.33	6.00	133	123	18	20	24	24	14	15	36	38
Median	55.50	56.25	1.75	1.61	18.50	9.42	109.00	123.00	17.00	15.00	24.00	24.00	13.00	14.00	36.00	38.00
Interquartile range	16.88	13.50	0.28	0.23	10.93	10.67	30.00	73.00	5.00	11.00	15.00	16.50	2.50	5.00	5.00	10.50
T <sup>d</sup>	6.00	3.00	3.00	2.00	2.00	2.00	6.00	6.00	7.00	7.00	3.00	3.00	5.50	5.50	7.00	7.00
Z	-0.94	-1.57	-1.57	-1.78	-1.78	-1.78	-0.41	-0.41	-0.14	-0.14	-0.74	-0.74	-0.55	-0.55	-0.14	-0.14
P-value	0.44	0.16	0.16	0.09	0.09	0.09	0.81	0.81	1.00	1.00	0.63	0.63	0.81	0.81	1.00	1.00
r <sup>e</sup>	-0.27	-0.45	-0.45	-0.51	-0.51	-0.51	-0.13	-0.13	-0.04	-0.04	-0.23	-0.23	-0.17	-0.17	-0.04	-0.04

Note: <sup>a</sup>Median and interquartile range calculated for five participants; <sup>b</sup>low/high performance at pretest; <sup>c</sup>effect size; <sup>d</sup>Test statistic of Wilcoxon signed-rank test reflecting the smallest sum of ranks. Abbreviations: CWT, color-word test; MSET, modified six-elements test; SCL-90-R, Symptom Checklist 90, revised; SIB, Scale for Interpersonal Behavior.

**Table 7** Results of control-group patients on secondary outcome measures at pre- and posttest

Patient number	Stroop CWT processing speed		Stroop CWT inhibition		Adapted MSET		SIB distress <sup>a</sup>		SCL-90-R anxiety <sup>a</sup>		SCL-90-R depression <sup>a</sup>		Quality of life <sup>a</sup>		Self-efficacy <sup>a</sup>	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	103.0	98.0	1.59	1.62	489.0 <sup>c</sup>	46.50	96	80	12	10	17	20	18	16	48	39
2	44.5	40.0	1.60	1.83	16.00	7.33	117	-	11	-	22	-	16	-	39	-
3	48.5	43.0	1.69	1.81	5.83	8.17	137 <sup>b</sup>	132	20 <sup>c</sup>	18	45 <sup>c</sup>	34	9	11	35	35
4	54.0	49.0	1.52	1.65	12.67	4.67	168 <sup>c</sup>	190	18	17	42 <sup>c</sup>	30	12	15	34	37
5	47.0	45.5	1.49	1.47	15.00	11.50	77	79	11	11	18	17	17	17	46	46
Median	48.50	45.50	1.59	1.65	15.00	8.17	116.50	106.00	15.00	14.00	30.00	25.00	14.50	15.50	40.50	38.00
Interquartile range	32.75	32.00	0.14	0.27	243.25	23.00	78.50	96.25	8.25	7.50	27.00	15.25	8.00	4.75	13.25	8.75
T <sup>d</sup>	0.00	1.00	1.00	1.00	1.00	1.00	5.00	5.00	0.00	0.00	2.00	2.00	1.50	1.50	1.00	1.00
Z	-2.03	-1.75	-1.75	-1.75	-1.75	-1.75	0	0	-1.63	-1.63	-1.10	-1.10	-0.82	-0.82	-0.45	-0.45
P-value	0.06	0.13	0.13	0.13	0.13	0.13	1.00	1.00	0.25	0.25	0.38	0.38	0.75	0.75	1.00	1.00
r <sup>e</sup>	-0.64	-0.55	-0.55	-0.55	-0.55	-0.55	0	0	-0.58	-0.58	-0.39	-0.39	-0.29	-0.29	-0.16	-0.16

Note: <sup>a</sup>Median and interquartile range calculated for four participants; <sup>b</sup>below/above-average performance at pretest; <sup>c</sup>low/high performance at pretest; <sup>d</sup>effect size; <sup>e</sup>Test statistic of Wilcoxon signed-rank test reflecting the smallest sum of ranks.

Abbreviations: CWT, color-word test; MSET, modified six-elements test; SCL-90-R, Symptom Checklist 90, revised; SIB, Scale for Interpersonal Behavior.

difficulties in executive functioning. Although homework exercises were performed satisfactorily, participants tended to avoid exercises with their training partners. Patients who involved their training partners seemed to profit from the participation of their proxies. Three of the five training partners who shared their experiences after training reported that the participants benefited from the training in their opinion.

Lastly, the results of the process evaluation of outcome measures showed that the neuropsychological test data were complete, but that not all questionnaires were returned. This could suggest a difficulty with completing the questionnaires. The missing data may have influenced the findings in this study, because conservative methods were used to compensate for these. The perceived benefit by patients and their training partners was not reflected by the quantitative data.

## Discussion

In the present study, applicability and feasibility of a new social cognitive training for adult patients with NS was evaluated. The training appeared feasible, and promising results were found with regard to enhancement of emotion recognition, although the overall effectiveness of the training could not be quantified, due to the small sample.

With regard to baseline measures, no significant differences were found between the treatment and control groups. However, several outcome measures showed medium–large effect sizes when comparing the two groups, which may suggest that meaningful differences between the treatment and control groups on these variables could not be demonstrated due to a power problem. Baseline variables that potentially differed were higher age, poorer emotion recognition, lower levels of quality of life and self-efficacy, more social behavioral problems, more anxiety, and a worse inhibition score in the treatment group in comparison to the control group. Possible baseline differences between the groups might have resulted from the inclusion of patients with subjective or objective social cognitive impairments in the treatment group.

Within each group, no significant differences between pre- and posttest were found for primary outcome measures. However, the medium–large effect size of the pre- vs posttest-difference on ERT in the treatment group compared to the small–medium effect sizes in the control group may indicate that the effects on emotion recognition were stronger in the treatment group. An improvement in emotion recognition was expected, because it has been a consistent finding in other social cognitive interventions.<sup>21</sup> Finding no significant improvement in the treatment group on subjective measures

of social cognitive functioning may reflect increased awareness of social cognitive difficulties. Awareness of one's (social) cognitive problems can be considered an initial step toward behavioral change.

Regarding secondary outcome measures, no significant differences were found between pre- and posttest in either group. However, the improvement in adapted MSET scores in the treatment group and faster processing on the Stroop CWT in the control group almost reached significance. In addition, the medium–large effect sizes of the (nonsignificant) improvement on the Stroop CWT – inhibition in the treatment group and the (nonsignificant) improvement on the adapted MSET and SCL-90-R and (nonsignificant) decrease on Stroop CWT – inhibition in the control group may reflect differences that could not be demonstrated by the Wilcoxon signed-rank test due to power problems. Moreover, large effects were found in both groups with regard to the (nonsignificant) improvement in planning abilities on the adapted MSET, which most likely reflected a practice effect.

The process evaluation showed that there were no drop-outs, all three phases of the intervention were feasible, and patients reported benefits from the training. Strong aspects concerned the (small) group-based format, in which NS patients learned from one another's experiences, gained more awareness of their social cognitive difficulties, and were able to practice strategies. The number of patients included in this study was smaller than intended, which could be related to the nature of the (social) cognitive deficits in patients with NS. Providing more information concerning the beneficial effects of group training and considering alternative training locations in order to reduce the time investment may be helpful in this regard. eHealth interventions can also be considered, although exercising social skills in real-life interaction remains necessary. The evaluation also showed that more time may be spent on practicing social cognitive skills and performing exercises and to a lesser extent on psychoeducation and discussion of experiences and social cognitive complaints. Additional exercises can be considered, focusing for instance on emotion-regulation strategies, task-concentration training, and elements of acceptance and commitment therapy, which may be helpful in diminishing alexithymic problems and social anxiety and in increasing acceptance of emotions. Furthermore, training partners were less involved in the training than intended, which could have hampered the generalization of training effects to daily life. The selection of appropriate training partners, their role, and the benefits of their involvement should be addressed more elaborately during both the intake procedure and the sessions

in which they are present. It also appeared that patients had some difficulty with filling out the questionnaires. Supervised administration of the questionnaires and the use of shorter instruments, eg, replacing the BVAQ with the shorter Toronto Alexithymia Scale 20, may be helpful in this regard.<sup>60</sup> Furthermore, a revision of the test battery is suggested. Although the TASIT has many benefits (ie, alternate forms and videos of real-life social situations) and is used frequently, the Dutch version is still time-consuming and its suitability for repeated administration is questionable.<sup>61</sup> Other ToM tasks may be considered, eg, a recognition of faux pas task.<sup>62–64</sup>

Despite the fact that this is the first controlled study to evaluate a new social cognitive training for adult patients with NS, there are also some limitations. Firstly, the study sample was small, which has consequences for the power. Furthermore, because subjective or objective social cognitive impairments were required for inclusion in the treatment group, a selection bias could be present, which limits the interpretation of pre- vs posttest results to this group. Although no baseline differences were found between the groups, the presence of several medium–large effect sizes on baseline comparisons may suggest that meaningful differences between the groups could not be demonstrated due to limited statistical power. Also, patients were not randomly allocated to the groups, and we emphasize that these preliminary findings should be interpreted with caution and replicated in a randomized controlled trial. Because only nonparametric analyses were performed, no interaction effects between group (treatment vs control) and time (pre vs post) could be explored. As a result of the large heterogeneity in cognitive functioning in the NS population, possible outliers may have influenced the results of the analyses. However, these effects are considered minimal, due to the use of nonparametric testing. Lastly, all participants in the treatment group underwent neuropsychological assessment at the Center of Excellence of Neuropsychiatry for different periods before the training (approximately 1–8 years). Some of the outcome measures in the current test battery overlapped with this neuropsychological assessment, which could have led to practice effects.

## Conclusion

In conclusion, this first social cognitive training for adult patients with NS, based on existing evidence-based and best-practice social cognition and alexithymia interventions, has proven to be a feasible training for this population. Moreover, encouraging results were found with regard to the enhancement of emotion recognition. Based on the process evaluation, some alterations in the training protocol and test

battery may be helpful in order to optimize the procedure. Future studies are needed using a larger sample and randomized controlled design, in order to evaluate further the effectiveness of the training.

## Disclosure

The authors report no conflicts of interest in this work.

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