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Biologische Korrelate von Wohlbefinden: Lebensqualität bei unterschiedlicher Ausprägung des Non-Hodgkin Lymphoms und Verbesserung kognitiver Prozesse durch Neurofeedback

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Health-related quality of life in patients with indolent and aggressive non-Hodgkin lymphoma

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Abstract: Indolent and aggressive non-Hodgkin lymphomas (NHL) are common types of hematologic malignancies but their effect on quality of life (QoL) is under-studied. In particular, the relation between different aspects of QoL and cognitive impairments and coping styles is relevant for individualized physical and mental health care. We studied emotional, physical, and subjective well-being in relation to cognitive capacities and coping style in 100 patients with NHL (44 females, age 61.3 ± 13.6). Questionnaires assessed health-related QoL (Functional Assessment of Cancer Therapy (FACT)), affect (Hospital Anxiety and Depression Scale, Positive and Negative Affective Schedule), distress (Distress Thermometer), and locus of control; semi-structured interviews targeted subjective QoL (Schedule for Evaluating the Individual Quality of Life) and cognitive impairments (Test for Early Detection of Dementia with Differentiation from Depression). Indolent NHL (n = 44) yielded better health-related QOL and positive affect and less anxiety than the aggressive type (n = 55; FACT: $t(97) = 1.90$, $p = .028$, anxiety: $t(97) = -1.9$, $p = .030$; positive affect: $t(96) = 2.01$, $p = .023$). In a factor analysis, physical and affective scales loaded on an emotional and physical well-being factor, which differed between the groups. Further, cognitive capacities and locus of control contributed to subjective QoL and reported distress. Emotional and physical scales assess QoL in NHL. However,

ABOUT THE AUTHORS

The behavioral psychobiology group of the RWTH Aachen University seeks to unravel systemic biological factors underlying and influencing human well-being. The principal method is functional imaging in addition to psychometric approaches. Psychosomatic effects on emotions and cognitions are studied as well as regulation strategies to improve well-being using behavioral, pharmacological, and neurofeedback approaches.

PUBLIC INTEREST STATEMENT

Non-Hodgkin lymphoma (NHL) is the most common blood cancer. The indolent and aggressive subtypes differ in survival time and treatment options but little of their impacts on quality of life (QoL) is known. Physical, affective, and cognitive factors influence QoL in cancer. In 100 NHL patients, we measured emotional, physical, and subjective well-being as well as cognitive capacities and coping style. Physical and emotional well-being was higher in the group with indolent cancer. In a factor analysis, the measures of physical well-being, depression, anxiety, and affect loaded on one main factor, which clearly differed between the groups. However, other factors suggested an influence of coping strategies and cognitive abilities on other QoL instruments, in particular subjective QoL and distress. Psycho-physical QoL appears a valid construct in NHL, but coping strategies influence subjective evaluation and help-seeking behavior, which may be hampered in patients with cognitive impairments.

cognitive impairments or external locus of control may hamper reporting of distress. Psychosocial support should specifically target at-risk patients.

Subjects: Anxiety & Mood Disorders; Anxiety in Adults; Behavioral Medicine; Hematologic Oncology; Mood Disorders in Adults - Depression, Mania, Bi-polar; Quality of Life

Keywords: psychooncology; cancer; locus of control; coping

1. Introduction

Non-Hodgkin lymphoma (NHL) is the sixth most common form of cancer, accounting for about 4% of all malignancies (Howlader et al., 2014). With respect to clinical outcome and impact on the patients, NHL can broadly be classified into two groups, indolent and aggressive lymphomas (Evans & Hancock, 2003). Generally, indolent lymphomas grow slowly, are often long asymptomatic; but the therapy is difficult and in the advanced stages, they are usually not curable. The faster growing aggressive lymphomas have poor survival outcome when not treated, but a rapid systemic chemotherapy in conjunction with antibodies such as rituximab can be curative (Shankland, Armitage, & Hancock, 2012). Such aggressive immune-chemotherapeutic regimes, however, can often produce significant acute and chronic adverse effects, with significant impact on the patients' well-being (Bellizzi et al., 2009).

The incidence of NHL is increasing worldwide, but also the survival has improved substantially, reaching about 69% (Howlader et al., 2014). The longer survival can be attributed to two factors: improved treatment regimens and a slower tumor growth in the aging population (Shankland et al., 2012). Consequently, an increasing number of NHL survivors, reaching in the United States over half a million, have to deal with the long-term and late effects of this chronic disease (Howlader et al., 2014; Naughton & Weaver, 2014). This includes not only the lymphoma-specific symptoms such as fever, night sweats, and weight loss, but also co-occurring emotional distress, which can be challenging for the patients and diminish their quality of life (QoL; for a review see Leak, Mayer, & Smith, 2011).

In addition to survival times, health-related QoL has become a widely accepted outcome measure in cancer research, constituting one of the most important treatment goals (Wedding, Pientka, & Höffken, 2007). It is a multi-dimensional construct influenced by physical functioning (e.g. fatigue and/or pain), mental health (e.g. anxiety and/or depression), cognitive abilities, and social factors (Naughton & Weaver, 2014). While many studies addressed QoL in breast, prostate, colorectal, and lung cancer, NHL is an understudied patient group (Kent et al., 2015; Smith et al., 2013).

The first systematic review of QoL in Hodgkin and NHL demonstrated worse physical but comparable mental QoL in patients as compared to the general population (Arden-Close, Pacey, & Eiser, 2010). Two studies demonstrated lower general health and more problems with work and finances as well as higher rates of anxiety and depression in NHL survivors compared to their peers in the general population (Jensen et al., 2013; Mols et al., 2007). Moreover, active treatment was associated with impaired physical functioning and worse psychological and social well-being (Mols et al., 2007; Smith, Zimmerman, Williams, & Zebrack, 2009).

Although the research of QoL in NHL survivors is growing, the heterogeneity of this disease is rarely taken into account. Studies focused mostly on QoL associations with socio-demographic and clinical characteristics, while limited research has been dedicated to the impact of differing clinical characteristics of aggressive and indolent forms on patients' well-being (Jensen et al., 2013). QoL has been studied in indolent (Webster & Cella, 1998) and aggressive forms of NHL (Doorduijn et al., 2005; Jensen et al., 2013) but, to our knowledge, only one study made a direct comparison so far, finding no differences except for better physical function within the indolent patient group (Blaes, Ma, Zhang, & Peterson, 2011).

In addition to biological factors, cognitive variables such as control beliefs are important predictors for the adjustments to chronic disorders. For instance, in other types of cancer, locus of control is the most frequently assessed control beliefs (see review in Neipp, Lopez-Roig, & Pastor, 2007). Indeed, locus of control is associated with QoL in hematological cancer as well (Allart, Soubeyran, & Cousson-Gélie, 2013). Further, cognitive impairments may interfere with reappraisal and thus reduce QoL (Sarkheil et al., 2014). In a sample of cancer patients after whole-brain radiation therapy, cognitive impairments predicted a decrease of QoL over time (Li, Bentzen, Li, Renschler, & Mehta, 2008). Conceivably, cognitive factors such as control beliefs (locus of control) and cognitive functions (impairments and intelligence) may contribute to QoL in NHL.

To better understand factors influencing QoL in NHL, we examined multi-dimensional QoL in 100 patients with aggressive and indolent forms of NHL. We applied selected scales, based on the existing literature on NHL, to assess cancer—as well as lymphoma-specific QoL, emotional and cognitive functions, subjectively valued QoL, and physical functions. Patients with the aggressive form of NHL were hypothesized to demonstrate lower health-related QoL as well as higher depression and anxiety than those with the indolent form. Exploratory analyses of differences in cognitive strategies of coping with the chronic disease should shed light on the factors underlying the different measures for QoL in NHL.

2. Methods

2.1. Participants

One hundred patients with NHL were recruited from the in and outpatient services of the Department of Oncology, Hematology, Hemostaseology and Stem Cell Transplantation at the University Hospital Aachen. The patients age ranged from 23 to 85 years (M = 61.32, SD = 13.6, 44 females; for demographics and basic clinical data see Tables 1 and 2). One patient withdrew informed consent and was excluded from the analysis. No exclusion criteria were applied. All participants were right-handed, fluent German speakers, and gave written informed consent before participation. Inclusion criteria were the histological diagnosis of a NHL according to the 2008 WHO classification (Swerdlow et al., 2008). Eligible patients were asked by the treating physician whether they might be interested in participating in a study on QoL in NHL patients and if they agree to be contacted by the study personal. Based on the WHO classification of lymphoma, the patients were classified into either an indolent (low grade B-cell or T-cell NHL; n = 46) or an aggressive NHL group (high or intermediate grade B-cell or T-cell NHL; n = 53). The Ethics Committee of the Medical Faculty of the RWTH Aachen University, Germany, approved the study protocol (EK123/11) in accordance to the Declaration of Helsinki.

2.2. Procedure

After being contacted by the treating physician, a trained rater explained the study procedure and aims to the patients. After the agreement to participate in the study, an appointment was made. The testing took place in the patient's room or the doctor's office of the outpatient services without other persons present except the rater and the patient. Standard instructions for each questionnaire and its items were read out loud to each patient. The participants could choose whether either they marked their response themselves or had the examiner do it for them. Two of the questionnaires—the Schedule for Evaluating the Individual Quality of Life (SeiQoL) as a semi-structured interview and the Test for Early Detection of Dementia with Differentiation from Depression (TFDD) —were always completed by the examiner. At the end of the testing session, a debriefing took place ensuring that the patient was feeling well, after discussing sensitive issues of their personal experiences. The testing session lasted about 60–90 min depending on the pace of the patient and their comprehension of the questions and tasks. It took place in the clinical environment without any other person present in the room. The order of the questionnaires were randomized and balanced. The patients received compensation for their time in the amount of 10€ per hour. Further, the treating physicians provided information about demographics such as age, gender, education, and about the clinical status and medical history by filling in a basic documentation (Knight et al., 2015).

Table 1. Socio-demographic information for indolent and aggressive NHL groups

	All patients (n = 99)	Indolent NHL (n = 46)	Aggressive NHL (n = 53)	Group comparison
	n (%)	*n* (%)	*n* (%)	*p*-value*
Gender				.106
Male	56 (56.6)	30 (65.2)	26 (49.1)	
Female	43 (43.4)	16 (34.8)	27 (50.9)	
Education				.910
Hauptschule (secondary general school)	20 (20.2)	9 (19.6)	11 (20.8)	
Realschule (secondary school)	17 (17.2)	7 (15.2)	10 (18.9)	
Gymnasium (high school)	29 (29.3)	14 (30.4)	15 (28.3)	
Other school	31 (31.3)	16 (34.8)	15 (28.3)	
Steady relationship				.667
Yes	83 (83.8)	39 (84.8)	44 (83.0)	
No	12 (12.1)	6 (13.0)	6 (11.3)	
Unknown	4 (4.0)	1 (2.2)	3 (5.7)	
Children				.968
Yes	76 (76.8)	36 (78.3)	40 (75.5)	
No	9 (9.1)	3 (6.5)	6 (11.3)	
Unknown	14 (14.1)	7 (15.2)	7 (13.2)	
Employment status				.402
Employed	14 (14.1)	7 (15.2)	7 (13.2)	
Sick leave	33 (33.3)	13 (28.3)	20 (37.7)	
Retired	49 (49.5)	25 (54.3)	24 (45.3)	
Home duties	1 (1.0)	1 (2.2)	0 (.0)	
Other	2 (2.0)	0 (.0)	2 (3.8)	

*Statistics with χ^2 or two-sample *t*-tests.

2.3. Measures

We applied a battery of instruments to assess patients' emotional, social, cognitive, and physical functions in a multi-dimensional fashion. Three instruments assessed QoL directly as a construct: Functional Assessment of Cancer Therapy: General (FACT-G; second version), Functional Assessment of Cancer Therapy: Lymphoma (FACT-Lym), and SeiQoL:

The FACT-G (second version) is a cancer-specific instrument investigating the health-related QoL in four domains: physical, social/family, emotional, and functional well-being (Cella et al., 1993). It was generated in several steps: first, items were generated based on semi-structured interviews with patients and oncology specialists; items were reduced before finally the scale was constructed. These items are presented on the scale as statements which are rated by the participants on a Likert scale from 0 (not at all) to 4 (very much) indicating how true it has been in the past week. The responses are summed up, with reverse coding for negative items, so that a high score indicates a better health-related QoL. As an example item, the first statement on the subscale physical well-being is "I have a lack of energy"; another example item from the subscale social/family well-being is "My family has accepted my illness". The FACT-G has a high test–retest of .92 as measured in 60 outpatients with cancer diagnoses. In our sample, Cronbach's α measured reliability of the total score and the subscales between .75 and .89 (6–7 or 20 items, n = 97–99). There is evidence for high convergent validity by comparing it to similar measures such as the Functional Living Index-Cancer (FLIC; $r = .79$) and to measures of mood such as the Profile of Mood States-Brief (briefPOMS; $r = .68$). A high divergent validity was confirmed by low correlations between the FACT-G and measures of social desirability as the Marlowe Crowne Social Desirability Scale (M-CSDS; $r = .22$; Cella et al., 1993).

The instrument FACT-Lym (Hlubocky, Webster, Cashy, Beaumont, & Cella, 2013) complements the FACT-G with a list of symptoms specific for lymphoma. It was also developed in three steps: item generation, item reduction, and construction of the measurement. A high score on this scale also indicates a higher health-related QoL. An example of its 15 statements is "I am bothered by lumps or swelling in certain parts of my body (e.g. neck, armpits, or groin)". A good internal consistency reliability was proven at three time points (T1 = .79, T2 = .85, and T3 = .84) and with a test–retest correlation coefficient of $r = .84$. In our sample, Cronbach's α measured reliability as .89 (15 items, $n = 94$). Convergent validity was tested comparing the FACT-Lym to validated measures such as the Physical Component Summary (PCS) and the Profile of Moods States Fatigue subscale (POMS-F), each with $r = .62$ ($p = .0001$). A high divergent validity was confirmed by low correlations between the FACT-Lym and the M-CSDS ($r = -.15$; Hlubocky et al., 2013).

The SeiQoL (O'Boyle, Browne, Hickey, McGee, & Joyce, 1993) is a semi-structured interview exploring individual QoL for subjective areas of values and to subsequently quantify them in a weighted sum score (Waldron, O'Boyle, Kearney, Moriarty, & Carney, 1999). The participants freely named their five most important areas in life, which were labeled as "*cues*". Then, for each of these cues, the current status was rated on a visual analog scale from 0 to 100. Further, a weighting of the relevance for each cue was determined, enabling the calculation of an allover SeiQoL index as weighted mean (range: 0–100). Patel, Veenstra, and Patrick (2003) reviewed studies comparing the reliability and validity of different instruments designed to measure individual health-related quality of life. The SeIQoL had adequate test–retest reliability with $r = .88$. In contrast to the Patient-Generated Index (PGI), SeiQoL showed a high internal reliability ranging from $r = .6$ to .9 and a high content validity $r = .72$–.88.

Two instruments assessed emotional state and distress:

The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) is a self-assessment two-dimensional scale reflecting the current state of depression and anxiety of patients in a hospitalized setting. It was validated—among others—in cancer populations and has good psychometric properties (Annunziata, Muzzatti, & Altoe, 2011). A study by Helvik, Engedal, Skancke, and Selbæk (2011) found an internal consistency reliability of .82 for the complete scale as well as .79 and .78 for the subscales, anxiety and depression, respectively. In our sample, Cronbach's α measured reliability as .81 and .83 (7 items, $n = 98$). The concurrent validity of .6 ($p < .01$) resulted from comparing the HADS to the emotional items of the Montgomery–Aasberg depression rating scale (MADRS). The authors concluded that the HADS distinguishes well between depression and anxiety and it can be used with medically hospitalized elderly.

The Distress Thermometer is a single visual analog scale, which was developed by the National Comprehensive Cancer National Comprehensive Cancer Network (2003) to measure the psychosocial distress in patient groups. The patients indicate the level of distress they have experienced over the past week on a visual scale (range: 0–10), where 0 indicates no distress, 5 moderate distress, and 10 extreme distress. A review by Donovan, Grassi, McGinty, and Jacobsen (2014) assessed the sensitivity of the instrument in a group of prostate cancer patients, compared it to the HADS, and evaluated its validity over 12 months using ROC analysis to identify cut-off values. The Distress Thermometer was found to be sensitive against the anxiety and depression subscales of the HADS with AUCs of .84 (95% CI = .78–.90) and .82 (95% CI = .68–.97) and the AUC to the total HADS of .83 (95% CI = .77–.90) using a cut-off of ≥ 3. A cut-off of ≥ 4 was shown to remain fairly sensitive after 12 months for the subscale depression (AUC = .73, 95%-CI = .58–.87) and the total HADS (AUC = .80, 95%-CI = .70–.89); the cut-off score of ≥ 6 applied to the subscale anxiety (AUC = .83, 95%-CI .73–.93). Their review confirmed its validity to identify distress, anxiety, and depression in a cancer population.

The Positive and Negative Affective Schedule (PANAS; Watson, Clark, & Tellegen, 1988) measures positive and negative mood. This instrument includes a list of 20 adjectives and a five-point Likert scale to indicate the experienced status of each adjective over a specific period. The two independent outcome variables—positive affect and negative affect—are calculated by summing up the 10 items on each subscale. Positive affect relates to enthusiasm, alertness, and the level of activity; the higher the score, the higher the person's energy. A high score on the negative affect subscale reflects distress and aversive mood state, whereas a low score indicates calmness and serenity. Its reliability was tested for different time instructions, such as "today" and "in the past few weeks". The internal consistency reliabilities are high for the positive affect as well as for the negative affect subscale, ranging from .86 to .90 and from .84 to .87, respectively. In our sample, Cronbach's α measured reliability as .86 and .88 (10 items, n = 91). The comparison of the two subscales confirmed a high divergent validity with low correlations ranging from $r = -.12$ to $-.23$, depending on the time of instruction (Watson et al., 1988).

Three more instruments quantified cognitive strategies and resources:

The standardized German instrument to health locus of control (KKG, Kontrollüberzeugungen zu Krankheit und Gesundheit) is operationalized with three outcome variables of control beliefs: internality, externality powerful others (POs), and externality chance (Lohaus & Schmitt, 1989). Internal control is high if patients believe their own behavior and their own personality are the source of their health control. The remaining variables reflect the belief that external sources have control over patient, i.e. someone else, e.g. a doctor (POs) or fortune/luck (chance). The internal consistency reliability for the subscales ranges from $r = .66$ to .76, and their test–retest reliability between $r = .72$ and .77 (Lohaus & Schmitt, 1989). In our sample, Cronbach's α measured reliability as .77, .62, and .72 (7 items, n = 92). The internal dimension and the external ones (POs and chance) are independent (Luszczynska & Schwarzer, 2005).

The German multiple selection vocabulary test (MSVT-B; Merz, Lehr, Galster, & Erzigkeit, 1975) characterizes premorbid verbal intelligence. It consists of a list with five words in each line; out of these five words, only one is found in a dictionary and the others are imaginary. The task is to identify the correct word. An example could be "nesa - naso - nose - neso - nosa". The review by Lehrl, Triebig, and Fischer (1995) finds a fair convergent validity between the MSVT-B and different IQ tests (median r = .72 in 22 samples), with the highest correlation of r = .81 in comparison to the WAIS-Full-IQ.

The TFDD (Ihl et al., 2000) detects early dementia symptoms and attempts to differentiate them from depression. The questions address immediate and delayed memory functions, praxis, verbal fluency, and orientation in time and space. The outcome score for cognitive impairments ranges from 0 to 50. A cut-off value of < 35 indicates a case of dementia. A separate score averages the level of depression from a self- and a rater-scale. A cut-off of > 8 refers to depression. A high inter-rater reliability of $r = .99$ ($p < .001$) was found for the dementia symptoms; for the depression symptoms r = .75 ($p < .001$). The test–retest reliability was $r = .87$ ($p < .001$) for the dementia items and $r = .70$ ($p < .05$) for the depression items. There is evidence for high convergent validity of the dementia items compared to similar measures such as the Mini-mental-status-test (MMST; $r = -.84$, $p < .001$), the cognitive subscale of the Alzheimer's disease assessment scale (ADAS; $r = -.89$, $p < .001$), and the sum score of the short cognitive performance test ($r = .86$, $p < .001$; Ihl et al., 2000).

2.4. Statistical analyses

Demographic information and test scores were compared between the groups (indolent vs. aggressive) using two-sample t-tests for continuous variables and χ^2 tests for categorical data. Factor analysis investigated the data structure. Therefore, a principal component analysis (PCA) was conducted on all 14 outcome scores of the questionnaires. Only factors with eigenvalues of at least 1 were considered. A high intercorrelation between the scales was expected and thus no factor rotation performed. Factor loadings of .4 and higher reflected relevant contribution from the respective test score. Factor scores were compared between the groups in two-sample *t*-tests. All statistical analyses were performed with SPSS 20 for Windows (SPSS Inc., Chicago, USA); the level of significance was set at $p = .05$ for the hypothesized direction.

3. Results

3.1. Demographic information

There were no significant differences between the groups concerning age, demographic data, disease duration, or clinical status (see Tables 1 and 2). We expected the diagnosis to influence the clinical treatment. In particular, a significant relationship between chemotherapeutic treatment and the malignancy of the lymphoma emerged ($\chi^2(1) = 6.22$, $p < .006$), with higher rate of chemotherapy in the aggressive subgroup. In a similar vein, a significant association was found between radiation therapy and the NHL type ($\chi^2(1) = 4.80$, $p < .014$) due to the use of radiation therapy in the indolent subgroup only. In 77.8% of the sample, other relevant physical diseases were recorded; 12.1% were currently given psychoactive medications/opiates and 4% of the patients had previous psychological or psychiatric treatments.

3.2. Group comparison of scales

The indolent group demonstrated significantly higher quality of life as measured with FACT-G ($M = 78.85$, $SE = 2.43$) than the aggressive group ($M = 72.34$, $SE = 2.33$; $t(97) = 1.93$, $p = .028$). The disease-specific FACT-Lym scale did not differ significantly between the indolent ($M = 43.93$, $SE = 1.41$) and the aggressive groups ($M = 41.05$, $SE = 1.44$; $t(97) = 1.41$, $p > .2$; Figure 1(a). No significant difference emerged for the SeiQoL index between the indolent ($M = 73.01$, $SE = 2.1$) and the aggressive NHL groups ($M = 71.05$, $SE = 2.47$; $t(95) = .59$, $p > .2$).

Concerning the affective symptoms on the HADS, patients with indolent NHL reported significantly less anxiety ($M = 4.46$, $SE = .49$) than patients with aggressive NHL ($M = 5.91$, $SE = .57$; $t(97) = -1.89$, $p = .03$). No difference between the groups was found in the HADS depression scores between patients with indolent NHL ($M = 4.57$, $SE = .64$) and those with aggressive NHL ($M = 5.64$, $SE = .59$; $t(97)=-.55$, $p = .112$; Figure 1(b). Further, the Distress Thermometer failed to document differences between the two groups ($t(96)=-.98$, $p = .160$). In regard to mood ratings on the PANAS, positive affect was higher in the indolent ($M = 33.85$, $SE = 1.06$) than in the aggressive lymphoma group ($M = 30.58$, $SE = 1.20$; $t(96) = 2.01$, $p = .023$; Figure 1(c). Negative affect did not differ between the indolent ($M = 18.46$, $SE = .92$) and aggressive lymphoma groups ($M = 19.65$, $SE = 1.12$; $t(96)=-.60$, $p > .2$).

No difference was found for the locus of control between the groups on any of the three subscales of the KKG: internality ($t(96)=-.23$, $p > .2$), externality powerful others ($t(96)=-.27$, $p > .2$), and externality chance ($t(96) = .09$, $p > .2$). Further, patients with indolent NHL did not differ in the TFDD dementia score ($M = 42.18$, $SE = .73$) from patients with aggressive NHL ($M = 41.98$, $SE = .81$; $t(92) = .18$, $p > .2$). Finally, no difference emerged on the depression scale of the TFDD between the indolent ($M = 5.54$, $SE = .53$) and the aggressive groups ($M = 5.88$, $SE = .54$; $t(92)=-.84$, $p > .2$).

3.3. Factor analysis

A factor analysis without rotation was conducted on the 14 outcome scores of the applied instruments. The Kaiser–Meyer–Olkin score was .75 indicating satisfactory sample size (84 subjects completed all scales; in the others, one or more was missing mostly due to exhaustion over the course of the interview) (Kaiser, 1974). The Bartlett's test for sphericity was significant (χ^2 (91) = 451.07, $p < .001$) implying that the variables correlated with each other. Four components yielded eigenvalues of at least 1.0 and explained 64.7% of variance in total. The other factors were not considered. Table 3 lists the factor loadings of each variable. Based on this factor structure, the factors were

Table 2. Clinical information for indolent and aggressive NHL groups

	All patients (n = 99)	Indolent NHL (n = 46)	Aggressive NHL (n = 53)	Group comparison
	n (%)	*n* (%)	*n* (%)	*p*-value
Current NHL status				.339
First illness	72 (72.7)	30 (65.2)	42 (79.2)	
Second tumor	1 (1.0)	1 (2.2)	0 (.0)	
Recurrence/Progression	20 (20.2)	12 (26.1)	8 (15.1)	
Remission	5 (5.1)	3 (6.5)	2 (3.8)	
Unknown	1 (1.0)	0 (.0)	1 (1.9)	
Treatments				
Operation	11 (11.1)	5 (10.9)	6 (11.3)	
Chemotherapy	88 (88.9)	37 (80.4)	51 (96.2)	
Radiation	4 (4.0)	4 (8.7)	0 (.0)	
Stem cell transplantation	9 (9.1)	6 (13.0)	3 (5.7)	
Other	6 (6.1)	4 (8.7)	2 (3.8)	
Other physical diseases				.914
Yes	77 (77.8)	36 (78.3)	41 (77.4)	
No	22 (22.2)	10 (21.7)	12 (22.6)	
Psychoactive medication/opiates				.291
Yes	12 (12.1)	6 (13.0)	6 (11.3)	
No	85 (85.9)	44 (95.7)	41 (77.4)	
Unknown	2 (2.0)	2 (4.3)	0 (.0)	
Previous psychological treatment				.64
Yes	4 (4.0)	2 (4.3)	2 (3.8)	
No	94 (94.9)	44 (95.7)	50 (94.3)	
Unknown	1 (1.0)	0 (.0)	1 (1.9)	
Current level of functioning (ECOG)				.818
Normal activity	22 (22.2)	10 (21.7)	12 (22.6)	
Symptoms, but nearly fully ambulatory	55 (55.6)	29 (63.0)	26 (49.1)	
Some bed time, but needs to be in bed less than 50% of the waking hours	14 (14.1)	8 (17.4)	6 (11.3)	
Needs to be in bed more than 50% of normal waking hours	8 (8.1)	5 (10.9)	3 (5.7)	

labeled “emotional and physical wellbeing”, “cognitive capacities”, “dependence on others”, and “help-seeking”.

The factor emotional and physical well-being explained 32.3% of variance with positive correlation with the QoL questionnaires and positive affect and negative association with anxiety,

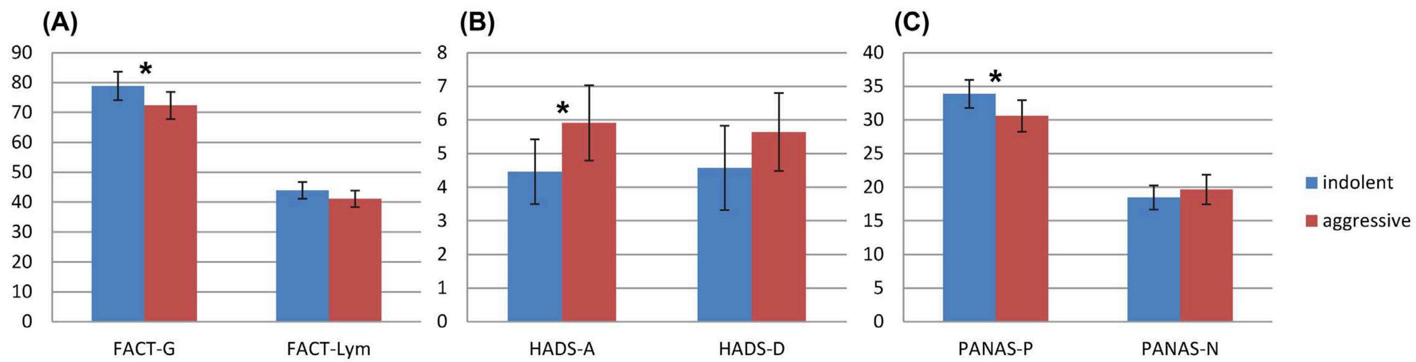

Figure 1. Group comparison (indolent vs. aggressive NHL) of quality of life.

Notes: The panels represent FACT-G and FACT-Lym (A), HADS (B), and PANAS (C); bar plots of group mean with 95% confidence interval. The general FACT scale, anxiety, and positive affect were significantly better in the indolent as compared to the aggressive NHL group (*: $p < .05$).

Table 3. Principal component analysis of the QoL-related outcome variables

	Factor loadings			
	Emotional and physical well-being	**Cognitive capacities**	**Dependence on others**	**Help-seeking**
FACT-G	**.818**	.225	.056	−.126
FACT-LYM	**.752**	.145	.179	−.030
SeiQoL index	**.457**	**−.406**	.107	−.201
Anxiety (HADS)	**−.810**	.170	.149	−.178
Depression (HADS)	**−.813**	−.318	.092	.026
Distress Thermometer	**−.554**	−.016	−.327	**.496**
Negative affect (PANAS)	**−.722**	.157	−.008	−.190
Positive affect (PANAS)	**.560**	**.417**	−.140	.143
Internal LOC (KKG)	−.105	**.668**	.140	**.535**
Powerful others LOC (KKG)	−.132	**.566**	**.416**	**−.455**
Chance LOC (KKG)	−.174	**.536**	**.529**	.177
MWT-B (verbal intelligence)	−.110	**.513**	**−.535**	−.205
Cognitive performance (TFDD)	−.014	**.427**	**−.655**	−.249
Depression (TFDD)	**−.746**	.075	.063	−.204
Eigenvalues	4.53	2.06	1.39	1.06
% of variance	32.4	14.8	10.0	7.6

Note: Factor loadings with contributions larger than .4 are set in bold.

depression, and negative affect. Cognitive capacities explained 14.8% of the variance and predicted higher cognitive scores and positive affect, whereas the SeiQoL was negatively correlated. Dependence on others explained 10.0% of the variance reflecting higher external control scores (POs, chance) and lower intelligence (verbal intelligence and TFDD score). Low verbal IQ and cognitive impairments seem to result in attribution of external factors to control. The factor help-seeking explained 7.6% of the variance; high internal LOC and low POs seem to lead to higher ratings on the visual analog scale for distress.

Only the first factor scores between the groups yielded significant difference between the groups, i.e. emotional and physical well-being was significantly higher in the indolent (M = .21, SE = .14) as compared to the aggressive group (M = −.20, SE = .15; $t(82) = −1.98$, p = .025). The higher well-being in the indolent group was mainly reflected by a better mood and a lower symptom load. The other three factors failed to show a significant difference between the groups (cognitive capacities: $t(82)$ = .52, p = .301, dependence on others: $t(82)$ = .31, $p > .2$, and help-seeking: $t(82)$ = .02, $p > .2$).

4. Discussion

In line with our hypothesis, patients with the aggressive form of NHL demonstrated a somewhat lower QoL, including physical, social/family, emotional, and functional well-being, as well as higher anxiety and lower positive affect than patients with indolent NHL. The group difference was, however, rather small. The factor analysis revealed four main components contributing to patients' functioning: emotional and physical well-being, cognitive capacities, dependence on others, and help-seeking. Coping styles and cognitive capacity seem to influence the subjective evaluation and the reporting of QoL and distress.

One previous study compared the QoL in patients with aggressive and indolent NHL but found no differences between the groups (Blaes et al., 2011). Similarly, we found no differences between NHL groups using the more general SeiQoL measure, but did find a difference using the FACT-G measure. This lack of differences might depend on the choice of questionnaires: the study applied a generic QoL scale and a fatigue scale. A number of studies support the use of disease-specific scales rather than generic ones to assess the subtle differences within the patient population since they are more sensitive to detect certain aspects of the disease and treatment that are relevant to a specific patient group (Mathiak, Mathiak, Karzel, Wola, & Ostaszewski, 2010; Oerlemans, Mols, & Nijziel, 2011). We found, however, no differences between the groups on the lymphoma-specific scale (FACT-Lym). The FACT-Lym assesses, in fact, the clinical symptomatic characteristic for lymphoma; the lack of differences on this scale confirms that both groups were similar with respect to their clinical status.

Significant differences between indolent and aggressive NHL groups emerged for anxiety (HADS) and positive affect (PANAS) but not for depression, negative affect, or cognitive measures. Aggressive NHL may acutely deter health or lead to death; therefore, this subtype may directly induce anxiety. In a similar vein, positive affect has been suggested to reflect rather interoceptive mechanisms and emotions directly in contrast to negative affect being influenced by cognitive processing (Mathiak, Klasen, Zvyagintsev, Weber, & Mathiak, 2013). Thus, the lack of significant group differences for negative affect (PANAS), depression (HADS and TFDD), and distress (Distress Thermometer) may reflect that the latter factors are influenced by cognitive processes such as coping (see Chiou, Potempa, & Buschmann, 1997). Cognitive functions such as locus of control (KKG), cognitive impairments (TFDD), and verbal intelligence (MWT-B) did not differ between the groups. Depression and positive affect may be directly affected by the disease process and cognitive processes may influence the other affective measures leading to a lack of group differences in addition to unsystematic effects.

Four components were identified within a factor analysis conducted with the above-mentioned measures. In summary, physical and affective scales loaded on an emotional and physical well-being factor, which differed between the groups. Within the remaining factors, associations between cognitive impairments, LOC, QOL, and distress were identified. Cognitive impairments and external locus of control may hamper NHL patients' reporting of distress.

Factor emotional and physical well-being: The applied factor analysis has to be treated as explorative method but it confirmed the discriminative profile of the *t*-tests and segregated the scales in a meaningful way. A high collinearity between QoL measures must be expected and thus the first factor should have particular high relevance. The first factor, accordingly, reflected general QoL and a third of the variance of the data. In this factor, very high loadings emerged for both scales each in FACT, HADS, and PANAS as well as for the TFDD depression scale. The observation that this factor differed between the indolent and the aggressive groups is an indicative that the disease-related psycho-physical distress mostly maps on one general QoL dimension.

Factor cognitive capacities: Cognitive coping strategies and adaptation mechanisms seem to influence aspects of QoL independent from disease factors. In our study, subjective QoL, the Distress Thermometer, and positive affect from the PANAS exhibited a somewhat smaller loading on the general QoL factor but showed relevant contributions to the other factors. In particular, the latter measure and health-related locus of control loaded on cognitive impairments and health-related locus of control. Higher cognitive capacities may enhance cognitive reappraisal and thereby increase positive affect (Sarkheil et al., 2014). Such search for coping strategies, however, may interfere with subjective QoL since different cues (life areas and values) contribute to the global SeiQoL scale.

Factor dependence on others: Cognitive impairments were associated with higher external locus of control. Thus, patients with reduced intellectual abilities may be at risk of developing dependent behavior and reduced functional status (see Repetto et al., 2002). Indeed, cognitive impairments predicted lower QoL in patients after whole-brain radiation (Li et al., 2008). Notably, hematological disorders may directly lead to cognitive impairments and thereby reduce QoL (Meyers, Albitar, & Estey, 2005).

Factor help-seeking: Locus of control and coping strategies are associated with QoL in hematological cancer (see review in Allart et al., 2013). In our factor analysis, patients with high internal and low external (powerful others) locus of control were more likely to indicate the wish for support in the Distress Thermometer. Indeed, help-seeking behavior is known to be influenced by the expected benefit (Ryan & Pintrich, 1997) and, thus, may be associated with an active coping style as observed with internal locus of control (Petrosky & Birkimer, 1991). Interestingly, the latter three factors involving cognitive capacities and styles did not differ between patients with indolent and aggressive NHL and, thus, may act as an independent factor on QoL. In general, a direct coping style was associated with internal locus of control, predicting more direct coping (Petrosky & Birkimer, 1991), better treatment outcomes, e.g. in lower back pain (Härkäpää, Järvikoski, Mellin, Hurri, & Luoma, 1991) or aggressive NHL (Jensen et al., 2013), and can be associated with more active help-seeking. In our NHL group, internal rather than external locus of control was associated with help-seeking and higher reported distress on the Distress Thermometer. In line with a previous study (Broers, Kaptein, Le Cessie, Fibbe, & Hengeveld, 2000), the group with external locus of control may be particularly accessible to support, despite the less active coping style and personalized pharmacological treatment of impaired mood may be considered (Laoutidis & Mathiak, 2013).

4.1. Implications for clinical practice and research

FACT-G and HADS are well-established instruments to study QoL and well-being in cancer patients (Annunziata et al., 2011; Cella et al., 1993; Helvik et al., 2011) Our data confirmed that these instruments are also well-suited to assess psycho-physical well-being in NHL patients. Interestingly, the physical-dominated measures in the FACT-G and the mood measures in the HADS loaded on the same factor, suggesting a high interdependence of affective state and physical well-being in this patient group. The HADS may be the most widely applied screening tool in oncology to detect distress (Mehnert, Lehmann, Cao, & Koch, 2006) and it can be assumed to capture significant contributions to psycho-physical well-being. In a similar vein, the Distress Thermometer has been developed as one-dimensional indicator for distress (National Comprehensive Cancer, 2003); however, in our sample, the reported distress seems to be influenced significantly by cognitive factors as well. For instance, patients with reduced intellectual abilities may be at risk of developing dependent behavior and should be provided with support for coping, to improve the functional status (Extermann & Hurria, 2007; Repetto et al., 2002; Rodin & Mohile, 2007). We suggest that screening instruments for distress in hematological cancer—in particular, the Distress Thermometer—should be better evaluated for their efficacy rather than only their psychometric properties.

A previous study suggested that the SeiQoL does not only measure QoL but reflects other cognitive factors as well (Moons, Marquet, Budts, & De Geest, 2004). In our study, the factor cognitive capacities showed a similar loading as the main emotional and physical well-being factor. Indeed, the SeiQoL test procedure may be too complex for the cognitively impaired (Moons et al., 2004). Additionally, this relation may reflect a lesser adaptive capacity to develop effective coping strategies. Moons et al. (2005) suggested that QoL research should rather focus on wants rather than needs. The SeiQoL may be a suitable instrument to extend the view on patients' values and personalize the treatment targets.

4.2. Limitations

Recruitment at a center for specialized care may have led to an overrepresentation of acutely sick patients with chronic, indolent forms of NHL. This is reflected in the relatively small difference between both subtypes in our population. Nevertheless, in contrast to a previous study (Blaes et al., 2011), the group difference validated QoL measures in NHL. As an advantage of the restricted recruitment strategy, all the patients were undergoing congruent diagnostic and therapy procedures throughout the groups. Further, it resulted in a relatively small number of this rather frequent disease. However, we did not rely on surveys but could address the patients directly with trained raters and even study patients with advanced age or low functioning.

The factor and mediation analyses were explorative methods to better describe the data. To keep the analysis transparent, despite a high collinearity between the different measures associated with QoL, we did not conduct a factor rotation, which may have led to more pronounced loading in the smaller factors. Despite its explorative nature, the factor analysis was able to identify more specific research questions for future research: (1) cognitive impairments do not only reduce QoL but may interfere with the ability to address and cope with distress, (2) mapping of complex QoL measures on single scales (e.g. Distress Thermometer and SeiQoL) may lead to confounds with cognitive factors, and (3) measures of health-related psycho-physical well-being (e.g. FACT and HADS) are valid measures for distress in NHL.

6. Conclusions

In patients with NHLs, health-related QoL is lower in the patient group with aggressive than in those with indolent type. The group difference is mainly driven by a factor of interdependent emotional and physical well-being. Cognitive impairments as well as coping styles influence the reported distress and subjective QoL. Conceivably, patients with cognitive impairments or externalized locus of control are at risk for requesting and receiving less psychosocial and medical support.

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Competing interests
The authors declare no competing interest.

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Social reward improves the voluntary control over localized brain activity in fMRI-based neurofeedback training

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Neurofeedback (NF) based on real-time functional magnetic resonance imaging (rt-fMRI) allows voluntary regulation of the activity in a selected brain region. For the training of this regulation, a well-designed feedback system is required. Social reward may serve as an effective incentive in NF paradigms, but its efficiency has not yet been tested. Therefore, we developed a social reward NF paradigm and assessed it in comparison with a typical visual NF paradigm (moving bar). We trained twenty-four healthy participants, on three consecutive days, to control activation in dorsal anterior cingulate cortex (ACC) with fMRI-based NF. In the social feedback group, an avatar gradually smiled when ACC activity increased, whereas in the standard feedback group, a moving bar indicated the activation level. In order to assess a transfer of the NF training both groups were asked to up-regulate their brain activity without receiving feedback immediately before and after the NF training (pre- and post-test). Finally, the effect of the acquired NF training on ACC function was evaluated in a cognitive interference task (Simon task) during the pre- and post-test. Social reward led to stronger activity in the ACC and reward-related areas during the NF training when compared to standard feedback. After the training, both groups were able to regulate ACC without receiving feedback, with a trend for stronger responses in the social feedback group. Moreover, despite a lack of behavioral differences, significant higher ACC activations emerged in the cognitive interference task, reflecting a stronger generalization of the NF training on cognitive interference processing after social feedback. Social reward can increase self-regulation in fMRI-based NF and strengthen its effects on neural processing in related tasks, such as cognitive interference. A particular advantage of social feedback is that a direct external reward is provided as in natural social interactions, opening perspectives for implicit learning paradigms.

Keywords: neurofeedback, real-time fMRI, social communication, reward, smile, avatar, Simon task, cognitive interference

Introduction

People constantly control their brain activity by engaging in voluntary actions that are linked to activation of specific brain regions (deCharms et al., 2005; deCharms, 2007). This does not always work well: to excel in difficult skills, to suppress unwanted emotions or to override automatic actions requires a long and difficult learning process or even sometimes fails altogether. Although we do control the brain activity indirectly via our actions, typically we cannot exert direct control over specific brain regions. Brain imaging techniques, such as functional magnetic resonance imaging (fMRI), help to understand the link between the physiological processes taking place within the brain and our subjective awareness (deCharms, 2007, 2008). Neurofeedback (NF) based on real-time fMRI (rt-fMRI) takes us even a step further: Subjects can voluntarily change the activity in a selected brain region and directly see the effect of the evoked brain activation. Although this particular method is still relatively new and subject to certain limitations, its potential implications are vast.

NF based on electroencephalography (EEG) is well-established for the treatment of attention-deficit/hyperactivity disorder (Monastra, 2005) and epilepsy (Sterman and Egner, 2006) for over 4 decades now. fMRI-based NF, enabling the regulation of a precisely selected brain region, became available much later with the development of brain-computer interfaces (BCIs) based on rt-fMRI (for a review, see Weiskopf et al., 2004b, 2007). rt-fMRI NF proved to have a good anatomical resolution and to elicit behavioral changes (for a review, see Birbaumer et al., 2009). However, its use as a clinical method is still limited. One of the limitations is that only about two thirds of the people subjected to this particular method succeed in controlling computerized devices with brain signals, while the remaining one third fails to do so (Friedrich et al., 2014). A number of factors determine how well this control can be achieved, including the training protocol, instructions, tasks, mode of feedback as well as psychological traits such as motivation and expected reward, mood, locus of control, and empathy. Indeed, according to Goebel et al. (2004), the social component of the study paradigm, that is the willingness to compete and win against a real opponent, may lead to very fast and effective learning. In accordance with these observations, deCharms (2008) proposed to develop new types of task paradigms for rt-fMRI NF, where participants would be trained without engaging in a deliberate cognitive process.

In a standard fMRI NF paradigm, participants are presented with a visual display of a color bar moving up-and-down or a fluctuating thermometer that reflect brain activity in a region of interest (ROI). Their task is to raise the level on such a bar display by regulating the brain activity in the selected ROI. It is proposed that successful learning follows the principles of operant conditioning, involving a reward when the required threshold is achieved (McCarthy-Jones, 2012).

Abbreviations: ACC, anterior cingulate cortex; BCI, brain-computer interface; EEG, electroencephalography; EPI, echo planar imaging; FWE, family-wise error (correction); NF, neurofeedback; ROI, region of interest; rt-fMRI, real-time functional magnetic resonance imaging; SPM, Statistical Parametric Mapping.

In EEG-based NF, the reward is often explicit, involving appointing points or making a game character move on the screen (Egner and Sterman, 2006) or make a Lego robot move forward (Mirković et al., 2013). In published rt-fMRI NF studies, the reward is often less direct such as the subject's own satisfaction with successful control of the bar display (or receiving social reward from an experimenter at the end of the task). deCharms et al. (2005) used task-related feedback stimulus, namely images of a fire changing its size to reflect a successful regulation of a pain-related area (rACC). Sokunbi et al. (2014) extended this particular approach, introducing feedback-guided self-regulation based on changing size of appetitive food pictures to regulate brain circuits related to hunger and food craving. They argued that the stimuli mimic avoidance behaviors during successful down-regulation and approach behaviors during unsuccessful down-regulation, increasing the face validity of the used training. Two remarkable studies applied explicit rewards in fMRI NF: Bray et al. (2007) offered monetary rewards when subjects successfully modified their motor cortex activity, and Goebel et al. (2004) added a social rivalry aspect in a so-called Brain-Pong game, where subjects played virtual ping-pong against each other, using their brain activity to control a racket ("brain-pong"). Although all the above attempts were successful, none was shown to be superior to standard feedback signals.

In daily life, we control our brain activity to change our facial expression, prosody, body posture, and other behavior based on subtle feedback signals that we receive from our partners in social interactions. Social reward, such as smile, can activate reward-related areas of the brain, similarly to other reward types, e.g., money (Izuma et al., 2008). We demonstrated in a pilot study that social reward can directly reinforce localized brain activity (Mathiak et al., 2010). In contrast to monetary reward (Bray et al., 2007), social reward can even be provided in real-time, i.e., by displaying positive facial expressions. Similar to the Brain-Pong setup (Goebel et al., 2004), where the inclusion of motivating (but not directly rewarding) social competition improved performance, social reward in the present approach may improve NF training by enhancing the motivation. Here, we investigated the impact of the feedback mode—smiling avatar face vs. standard bar display—on regulation performance during fMRI NF of the anterior cingulate cortex (ACC).

The ACC has been the focus of many studies due to its key role in regulating emotions, goal-directed behaviors, attentional processes, response selection, motor functions (Bush et al., 2000; Carter and van Veen, 2007), and above all in conflict monitoring and error perception (Botvinick et al., 2004; Kerns et al., 2004). The ACC can be successfully controlled using fMRI-based NF with standard paradigms (Weiskopf et al., 2003; deCharms et al., 2005; Emmert et al., 2014; Rance et al., 2014). However, in contrast to some visual and motor areas, no evident strategy emerged that yields activity increases without feedback mechanisms, so that the ACC is a suitable ROI to study learning in rt-fMRI NF. The ACC is reliably activated in both the color-word Stroop and the Simon tasks, which are both based on introducing interfering task-irrelevant stimuli (Peterson et al., 2002). In the Simon task, reactions to a target stimulus are slowed when the location of the target and the response side do not correspond, even though this is task-irrelevant. Both, the Stroop and the Simon task involve the ACC. However, in a direct comparison the Simon task led to significantly stronger ACC activations (Liu et al., 2004). Thus, we applied the Simon task to test for altered activation in the ACC region after NF training (generalization).

Twenty-four healthy participants were randomly allocated to one of two groups: a social and a standard feedback group. As for social reward, an avatar started gradually smiling when ACC activity increased. A bar display indicated the activation levels in the standard feedback group. To control for non-specific effects of the NF procedure, the subjects attempted to up-regulate their brain activity without receiving any feedback directly before (pre-test) and after the NF training (post-test). Further during the pre- and post-test, a cognitive interference task (Simon task) investigated change of ACC activity in a novel setting, also without feedback. The ability to voluntarily activate the ACC in an identical paradigm with no feedback served as measure for transfer of the NF training; the impact of the NF training on the ACC activity in the novel setting without feedback assessed generalization of the NF training (after Poppen et al., 1988; Simon and Gluck, 2013).

Hypotheses

We expected successful NF training in both groups. In comparison with the control group, the social feedback group should demonstrate:

1. Stronger NF effect, i.e., higher activation in the ACC during NF sessions.
2. Higher activation of the reward system during NF sessions in response to the direct social reward.
3. Stronger transfer effects leading to higher activation during regulation without feedback; and
4. Enhanced generalization, i.e., a stronger effect on ACC activations during the post-test Simon task.

Materials and Methods

Participants

Twenty-four right-handed subjects (13 females; age 25.62 ± 4.79) participated in the study. They were allocated based on the order of their inclusion in the study either to the social (12 subjects, 6 females, age 24.75 ± 2.80) or the standard feedback group (12 subjects, 7 females, $\chi^2_{(1)} = 0.168$, $p > 0.682$; age 26.5 ± 6.1, $t_{(22)} = -0.891$, $p > 0.383$). The alternating strategy did not exclude selection bias but minimized chronological bias (see Tamm and Hilgers, 2014). All participants were naïve to NF and reported the absence of any acute or history of major neurological or psychiatric disorder, any current use of psychoactive drugs as well as any contraindication for MRI. Written informed consent was obtained prior to participation. Afterwards, demographic information about age, gender, and education was collected. In addition, the participants were asked to complete The Positive and Negative Affect Schedule (PANAS; Watson et al., 1998) before and after NF training on each day. The study protocol was approved by the Ethics Committee of the Medical Faculty of the RWTH Aachen University, Germany, and the study was carried out in accordance with the Declaration of Helsinki.

Experimental Stimuli and Task

Training

All subjects underwent standardized instructions for mental strategies to obtain voluntary control of localized brain activation (based on a written instruction set, see Supplementary Material). The instructions suggested to either recall positive emotional autobiographic memories, to imagine performing their hobby (like engaging in sportive or musical exercise), or to concentrate on a specific perception (like the temperature in one of their feet) in order to increase the activity in the ROI. The NF procedure was explained in detail, including the delay of the NF signal, and they were instructed to try each regulation strategy for at least 10 s. These instructions were delivered by the experimenter in a personal contact before the first measurement, and on the other days, participants received reminder of the task. Additionally, after each session the participants were asked which strategies they used in order to control their brain activity.

Design Specification

All participants were trained to control their ACC activity by means of rt-fMRI NF on three separate days within 1 week. On each day, they performed three NF training sessions and two test sessions. We investigated neural correlates of three different conditions: (A) *NF*, i.e., up-regulation of the localized ACC activation with online feedback from the ROI signal (calculated over all nine NF sessions). The feedback signal here was either the bar or the avatar display; (B) *transfer*, i.e., up-regulation of the ACC ROI without feedback; and (C) *generalization* to a cognitive interference task, i.e., activity during the Simon task after NF.

Neurofeedback

In the social feedback group, 12 participants received social feedback in which a male avatar (created with Poser Pro, Smith Micro Inc.), with either dark or fair hair (alternating and counterbalanced among subjects) provided a rewarding smile when subjects succeeded to increase ACC activity. The avatar became neutral when ACC activity decreased. The facial expression changed gradually within 100 frames. The second avatar was presented motionless and created a baseline (**Figure 1A**; see also Mathiak et al., 2010).

In the standard feedback group (control group), twelve further participants underwent the same ACC NF training. For this particular group, the change of ACC activity was indicated by either increase or decrease of a green moving bar. A blue motionless bar indicated the baseline condition in this group (**Figure 1B**; see also Gröne et al., 2014). Each NF session consisted of eight NF blocks and nine baseline blocks (30 s each; see exemplary session in **Figure 1**). The feedback was updated every repetition time (TR; 1 s). During baseline blocks, participants' instructions were to count backwards from 100.

Transfer

In order to test for the transfer of the NF training, subjects were instructed to regulate their localized brain activity without receiving feedback directly before (pre-test) and after (post-test)

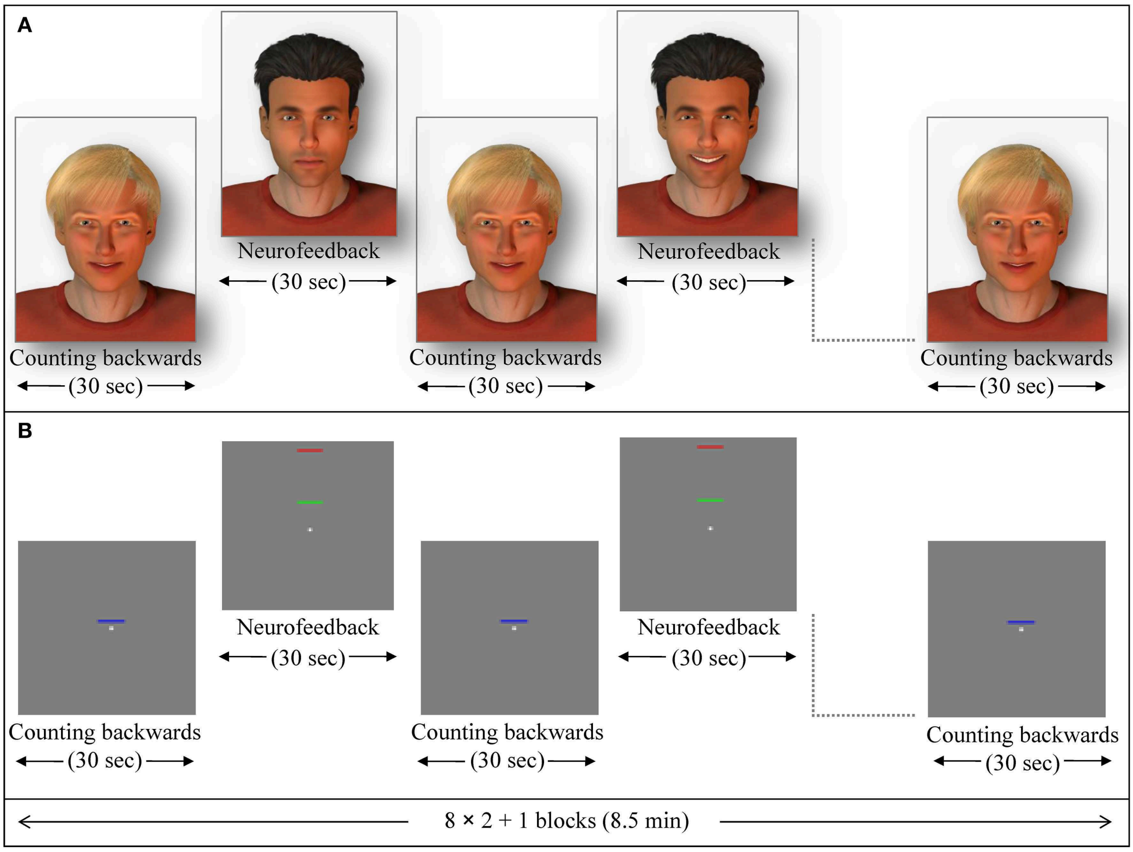

FIGURE 1 | Exemplary NF session. Feedback blocks alternated with baseline blocks (backwards counting) of 30 s duration each. **(A)** In the social feedback condition, a dynamic avatar (here the one with dark hair) rewarded successful up-regulation with a smile while the other avatar (blond) indicated the baseline. From the completed datasets, 5 participants were studied in this configuration, whereas in the 7 other participants the blond one provided the feedback. **(B)** During the standard feedback condition, green bars moved toward the red one to indicate increase of activity while blue bars provided a cue to count backwards (baseline).

the NF sessions. The static stimuli from the NF training—the avatar or the green bar respectively—were presented in four blocks indicating to use a mental strategy to regulate ACC activity. As in the NF sessions, the baseline stimuli indicated to count-backwards (five blocks).

Generalization

In order to test for behavioral effects of the ACC NF and for a generalization effect of the training, a cognitive visuo-spatial interference task, an adapted version of a Simon task, was conducted in the pre- and post-test. A fixation cross was presented in the middle of the screen and accompanied by arrows pointing up or down on either the left or the right side of the cross (**Figure 2**). The participants responded with the button press (right or left) to the direction of the arrow (up or down). Thus, when the subject had to press the button on the opposite side of the arrow, a conflict occurred (incongruent trials). The Simon task was presented in eight blocks of 42 s each. The response buttons were counterbalanced between subjects and the events were presented in a pseudo-randomized order. Reaction time and accuracy of each trial were collected as behavioral measures during the Simon task. The stimulation for the transfer and generalization task was programmed with Presentation software (Version 16.3, www.neurobs.com).

Data Acquisition and Analyses

fMRI scanning was conducted using a three Tesla whole body scanner (Magnetom TIM TRIO, Siemens, Erlangen, Germany). Echo planar imaging (EPI) covered 16 transverse slices parallel to the AC-PC line at a repetition time TR of 1 s (echo time TE = 28 ms; 64 × 64 matrix with 3 × 3 mm^2 resolution; 3 mm slice thickness plus 0.75 mm gap). We obtained 520 volumes for each NF training run (about 8.5 min) and 760 volumes for each pre- and post-test (12.5 min). A custom made anatomical template of the ACC defined the ROI (Mathiak et al., 2010).

Online spatial preprocessing of the acquired brain volumes was conducted using a custom toolbox based on standard SPM procedures (Koush et al., 2012). In short, motion correction used spline interpolation with co-registration to the preselected template. The NF signal was extracted from each voxel in the ROI during the NF conditions, averaged for each volume and calculated as percentage of signal change relative to the preceding

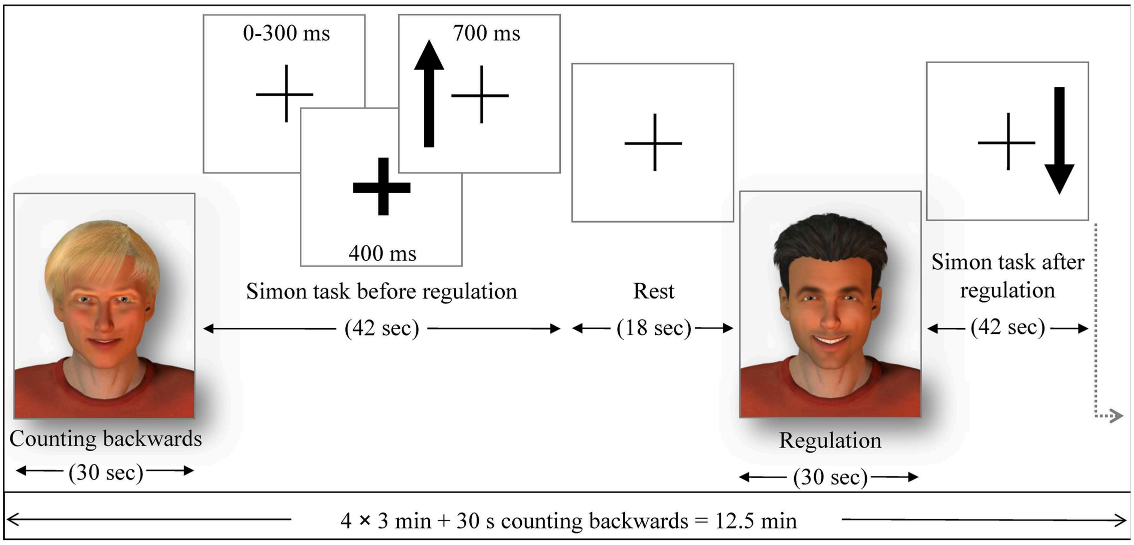

FIGURE 2 | The pre- and post-test runs. Similarly as in the NF run, either the avatars or the bar display indicated the regulation without feedback (transfer) or baseline condition. Each regulation/baseline condition was followed by a Simon task (generalization), where participants had to indicate with left or right button press (within 700 ms response time) if the arrow presented on a screen pointed up or down The side where the arrow was presented constituted congruent and incongruent trials. The occurrence of an arrow was announced 400 ms in advance by a thickening of the continuously presented fixation cross. The average trial duration was 1250 ms (with 300 ms jitter), yielding 32 trials in 42 s and followed by a 18 s rest period, where subjects passively viewed the fixation cross.

baseline block. Low frequency drifts were removed with an exponential moving average algorithm to improve the signal-to-noise ratio. A modified Kalman filter reduced outliers and high-frequency fluctuations. For feedback, the signal was rescaled in a fixed ratio such that about 1% signal change represented the full scale from neutral to maximally smiling face or from lowest bar position to the high target. Real-time analysis was performed on a separate PC using a custom Matlab toolbox for online fMRI preprocessing, analysis, and online feedback (for details on the online processing, see Koush et al., 2012).

Offline analysis of the imaging data comprised standard preprocessing and first level analysis in a block design. For the main effect, all runs and days were averaged since no specific time course of learning could be predicted. Group analysis was implemented as second-level two-sample t-test using the rather conservative family-wise error (FWE) correction for whole brain analysis and confirmative ROI analyses. In detail, the mapping analysis consisted of standard preprocessing steps with realignment, normalization, resampling with 2 mm isometric voxels, and smoothing (8-mm full-width at half-maximum Gaussian kernel) with SPM8 (FIL, http://www.fil.ion.ucl.ac.uk/spm/). The first 10 volumes of each run were excluded from the analyses to account for T1-saturation effects. For the NF runs, the regulation was modeled in a block design applying a generic hemodynamic response function. Transfer and generalization conditions were modeled in a block design as well. T-maps for contrasts of interest in the second-level group analyses were corrected for multiple comparisons across the volume using FWE correction and are shown at corrected threshold ($p < 0.05$). For data exploration, interaction of transfer and learning in the social reward condition are presented for a voxel-wise uncorrected threshold ($p < 0.001$). Threshold for cluster extend was always 15 voxels. Anatomical labeling was conducted in accordance with the Anatomy toolbox for SPM8 (Eickhoff et al., 2005).

In addition to the whole brain analyses, we conducted ROI analyses using small volume correction focusing on the ACC and on the reward system, respectively. Thereby we could specifically address the hypotheses 1–4 and ensure that signal changes encompassed the ACC or reward system ROI. The definition of the ACC was based on three-dimensional probability cytoarchitectonical maps, which offer a precise tool for the localization of brain functions as obtained from functional imaging studies (Amunts et al., 2007; Zilles and Amunts, 2010). The mask for the reward system comprised putamen and caudate nucleus as well as globus pallidus and was created using WFU PickAtlas toolbox for SPM8 Maldjian et al., 2003). Activation clusters were displayed at a threshold according to $p < 0.05$ FWE-corrected for the small volumes with cluster size bigger than 15 voxels.

For data exploration, we extracted average hemodynamic responses from ROIs for ACC and the reward system and—as baseline control—from bilateral parieto-occipital clusters (MarsBaR toolbox; Brett et al., 2002). Correlation between ACC regulation and reward responses were calculated. To study learning effects over the runs and sessions, the baseline-corrected ACC ROI signal entered into a repeated-measures ANOVA using linear predictors for *run* and *day* and the inter-subject variable *group*. All calculations were performed using Matlab 2010b (The Math Works, Natick, MA).

Results

Behavioral Data

Social and the standard feedback group did not differ with respect to the demographic variables age [$t_{(22)} = -0.891, p > 0.383$] or education [$t_{(22)} = -0.266, p > 0.792$]. For the positive affect subscale of the PANAS, repeated-measures ANOVA revealed significant main effects of days [$F_{(2, 42)} = 11.829, p < 0.0001$; day 1: 27.2 ± 0.9, d2: 24.0 ± 1.3, d3: 23.7 ± 1.3] and session [before vs. after fMRI measurement; $F_{(1, 21)} = 5.801, p < 0.025$; before: 26.0 ± 1.0, after: 23.9 ± 1.3]. Neither group [$F_{(2, 42)} = 1.709, p > 0.521$] nor the interactions between group and days [$F_{(2, 42)} = 1.709, p > 0.193$] and session [$F_{(1, 21)} = 0.329, p > 0.572$] yielded a significant effect. The negative affect exhibited the same pattern [days: $F_{(2, 42)} = 11.829$, $p < 0.0001$, d1: 11.9.3, d2: 11.0 ± 0.2, d3: 10.7 ± 0.2; session: $F_{(1, 21)} = 16.774, p < 0.025$; before: 11.7 ± 0.3, after: 10.7 ± 0.2; group or interaction with group: all $p > 0.09$]. In summary, the random allocation yielded comparable groups and general blunting over time but no effect of the feedback strategy on the reported mood emerged.

Reaction times and accuracies of responses collected during the Simon task were assessed with ANOVAs for repeated measures. One participant was excluded from this analysis due to missing data (from the standard feedback group). Since the sphericity assumption was violated for days [Mauchley's test $\chi^2_{(2)} = 15.88, p < 0.0001$] and for the interaction of days with congruency [$\chi^2_{(2)} = 6.2, p < 0.045$], the Greenhouse-Geisser correction was applied. Days [$F_{(1.29, 27.13)} = 15.065$, $p < 0.0001$], session [pre- vs. post-test, $F_{(1, 21)} = 11.731$, $p < 0.003$] and the Simon effect [$F_{(1, 21)} = 43.301, p < 0.0001$] yielded significant effects on the reaction time. Subjects responded faster over the 3 days (day 1: 535.8 ± 12.4; day 2: 501.4 ± 11.2: day 3: 491.8 ± 14.0 ms) faster during post- than pre-tests (pre: 520.1 ± 13.2; post: 499.2 ± 10.7 ms), and faster during congruent than incongruent trials (congruent: 490.7 ± 10.8, incongruent: 528.6 ± 13.1 ms). Accuracy was only affected by congruency [$F_{(1, 21)} = 26.318, p < 0.0001$; congruent: 97.4 ± 0.8%, incongruent: 94.6 ± 0.8%]. In summary, a clear effect of stimulus congruency on performance in the Simon task was replicated and training speeded the responses, but no effect of the specific NF training on behavior emerged.

Neurofeedback

In the feedback runs, a distributed network was more active during NF as compared to the counting backward baseline (**Figure 3A**). In addition to the ACC, this network comprised bilateral lateral occipital complex, striatum, and dorsolateral prefrontal cortex. In contrast, activation decreased in bilateral posterior insula, postcentral gyrus, and the posterior cingulum (**Table 1A**). Masking with the anatomically defined ACC and reward system confirmed the localization of this activation pattern to encompass the ACC (MNI = [−4, 28, 36], $t_{peak} = 10.02$, $p_{FWE} < 0.0001$) and the reward system with peaks in bilateral caudate nucleus (left: [−12, 6, 14], $t_{peak} = 11.94$, $p_{FWE} < 0.0001$; right: [14, 2, 18], $t_{peak} = 13.13$, $p_{FWE} < 0.0001$).

The group comparison revealed a higher effectiveness of the social NF over the standard feedback, as demonstrated by a significantly higher bilateral ACC activity ($t_{peak} = 10.67$, $p_{FWE} < 0.0001$; **Figure 3B**). Furthermore, an extended activation cluster emerged encompassing bilateral inferior frontal gyrus, the left occipital gyrus, and the left middle temporal gyrus (**Table 1B**). Anatomical ACC and reward system masks confirmed the localization of higher activation during social feedback in the ACC ([−10, 34, 10], $t_{peak} = 9.00$, $p_{FWE} < 0.0001$) and the reward system bilaterally with peaks in bilateral putamen (left:

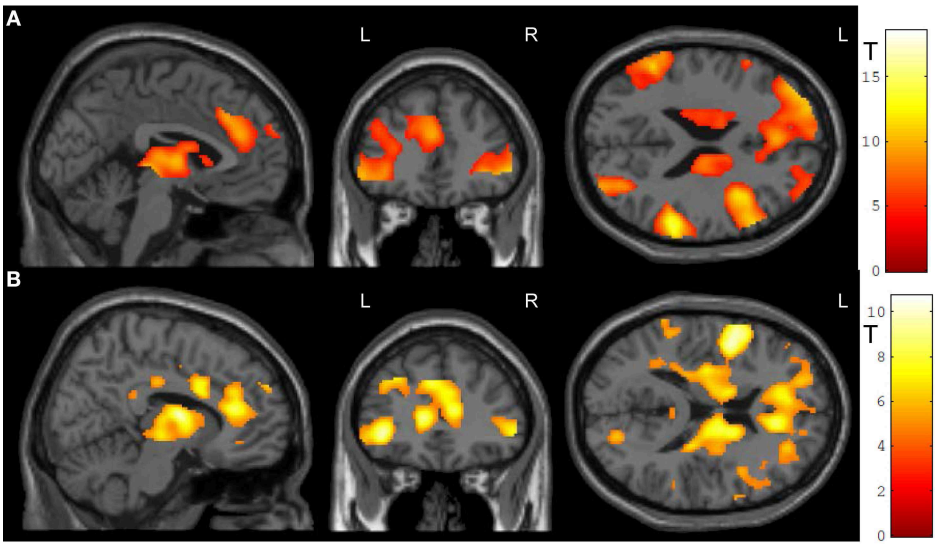

FIGURE 3 | NF training. **(A)** Both modes of neurofeedback led to increased activity in ACC and in reward-related brain areas. **(B)** In the social feedback group, activity was higher in bilateral ACC and in the reward system as compared to the standard feedback group. Moreover, clusters in prefrontal, occipital, and temporal lobe emerged in this group comparison as well (see **Table 1** for details). All maps are displayed at a threshold according to $p < 0.05$, FWE-corrected.

TABLE 1 | Activation clusters during NF training.

Region	Peak MNI coordinates			Cluster size	*T*-value	*p*-value (FWE)
	x	y	z			
(1A) Neurofeedback						
Right inferior temporal gyrus	48	−58	0	4545	18.47	0.0001
Right inferior frontal gyrus pars orbitalis	42	26	2	19418	17.49	0.0001
Left superior temporal gyrus	−54	−50	28	3462	11.59	0.0001
Left middle frontal gyrus	−40	12	42	206	7.10	0.0001
ACC	−8	−20	34	41	6.19	0.0001
(1B) Neurofeedback: social > standard feedback						
Left inferior frontal gyrus	−48	4	10	24583	10.67	0.0001
Dorsal ACC	−2	−18	38	2721*	10.67	0.0001
Rostral ACC	10	34	16	2144*	8.46	0.0001
Right primary visual cortex	20	−76	12	178	6.40	0.0001
Right inferior parietal cortex	46	−54	42	530	7.82	0.0001
Left lingual gyrus	−18	−70	2	152	6.45	0.0001
Right primary visual cortex	20	−76	12	178	6.40	0.0001
Right rolandic operculum	−54	−18	22	186	6.34	0.0001
Left middle occipital gyrus	−18	−70	2	152	6.45	0.0001
Left inferior occipital gyrus	−46	−72	2	184	6.21	0.001
Left middle temporal gyrus	−58	−32	−4	49	5.38	0.002

The cluster sizes for the ACC were calculated in a mask based on three-dimensional probabilistic cytoarchitectonic maps.

[−32, −10, 2], $t_{peak} = 9.51$, $p_{FWE} < 0.0001$; right: [36, 0, −4], $t_{peak} = 9.06$, $p_{FWE} < 0.0001$). Thus, hypotheses 1 and 2 were confirmed with higher ACC and reward system activity during social feedback. Notably, the average responses in the ACC ROI correlated with the one from the reward system [$r_{(24)} = 0.535$, $p = 0.0071$], suggesting a direct relationship of reward processing and learning success.

Learning of NF related regulatory control may be associated with increase of signal change over time. After baseline correction for the bilateral parieto-occipital junction clusters, average signal change in the ACC ROIs revealed a complex learning pattern influenced by the repetition over three runs on 3 days each (see **Figure 4**). Learning curves in NF may be complex and highly non-linear (Sarkheil et al., 2015), but frequently are approximated by linear curves. Therefore, repeated-measures ANOVA included runs and days as separate linear predictors and revealed a clear *days* × *group* interaction [$F_{(1, 23)} = 8.239$, $p < 0.0089$] but no main effect or other interaction [all $F_{(1, 23)} < 1.8$, $p > 0.19$, except a trend for *days*, $F_{(1, 23)} = 3.022$, $p = 0.0961$]. Further, the probability that individuals achieved control over the signal was estimated on their run-wise success rate and varied across subjects but not between the groups (mean ± SD: 69.4 ± 32.3%). In summary, the differential signal increase observed in the ACC seemed stronger in the social feedback group across runs as well as days, which was statistically confirmed for a stronger linear increase across days only.

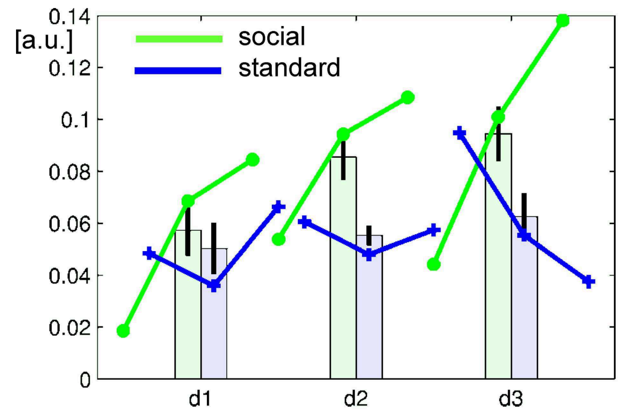

FIGURE 4 | Learning curve over runs (lines) and days (bars). In the baseline-corrected ACC ROI, the average signal increased in the social feedback group (green), but less so with standard feedback (blue). Repeated-measures ANOVA revealed a significant *group* × *days* interaction confirming a significantly stronger increase over days after feedback display with faces than with bars. Error bars represent the 95%-confidence interval for the repeated-measures estimator.

Transfer

Transfer conditions revealed significantly higher ACC activity during the post-test regulation blocks without feedback compared to baseline blocks; in addition to ACC activity, distributed activation clusters emerged in bilateral inferior frontal gyrus and occipital gyrus, in the right middle occipital and middle temporal gyrus, left posterior cingulate cortex as well as thalamus (**Figure 5A**, **Table 2A**). ROI masks confirmed localization of activity in the ACC ([−10, 32, 24], $T_{peak} = 5.23$, $p_{FWE} < 0.0001$).

To test the prediction that transfer may differ between the two learning conditions, the interaction of transfer and learning groups was calculated. Indeed, during regulation blocks higher

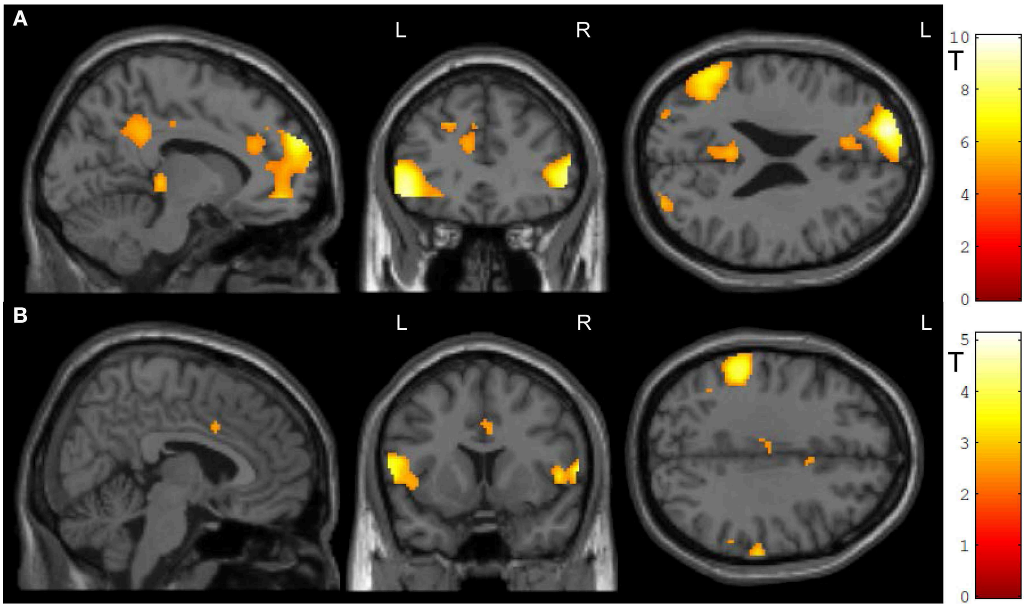

FIGURE 5 | Transfer. (A) In both groups, ACC activity increased during transfer condition i.e., regulation without feedback ($p < 0.05$, FWE-corr.). **(B)** Social feedback led to higher transfer than standard feedback, although this activation did not survive the correction ($p < 0.005$, uncorr.). Further, the social learning group yielded higher activity in the left inferior frontal gyrus and the left inferior parietal cortex (see **Table 2**).

ACC activity was found in the social feedback group as compared to standard feedback (**Figure 5B**, **Table 2B**) but this interaction survived only an uncorrected threshold ($p < 0.005$) with an cluster-extend threshold of 15 voxels. Only peaks at the left inferior frontal gyrus and inferior parietal cortex survived the FWE-correction (**Table 2B**). The ROI analysis indicated higher regulation increase of the ACC in the social feedback group, but the peak did not survive the FWE-correction (MNI = [6, 10, 34], $T_{peak} = 2.58$, $p_{uncorr} < 0.005$). Lacking a higher activation in the social transfer condition after FWE-correction, we could not confirm Hypothesis 3.

Generalization

Generalization was tested as the effect of the transfer (regulation without feedback) on a subsequent block with the cognitive interference task, i.e., the group-by-task interaction during the Simon task. We found that ACC activation during cognitive interference processing was reduced after social reward compared to standard feedback. Higher ACC activity emerged in the non-social feedback group compared to social feedback group ($T_{peak} = 5.34$, $p_{FWE} < 0.001$; **Table 3**; **Figure 6**). ROI analysis confirmed the localization in the ACC (MNI = [−8, 34,−6], $T_{peak} = 4.63$, $p_{FWE} < 0.001$). Hypothesis 4 stated stronger effects on ACC activity during the generalization task after social NF training and this was corroborated by the data.

Discussion

The present study investigated the effectiveness of social reward in rt-fMRI NF training of the ACC and compared it to a standard-type feedback in form of a moving bar. As predicted, social reward led to stronger ACC activity during NF training. After the training, both groups were able to regulate ACC activity without receiving feedback, with a trend for better performance in the social feedback group. Furthermore, during a cognitive interference task a significant difference for ACC activation emerged suggesting stronger generalization of the social feedback training on cognitive processing.

We extended previous studies using monetary reward (Bray et al., 2007) and created an innovative NF training based on a real-time social reward. In operant conditioning, a desired response is repeatedly paired with reward, resulting in increasing probability that the response occurs again. A conscious process is not necessary for the learning to take place. Although NF is believed to be based on principles of operant conditioning, no reward is delivered for a correct response in typical fMRI NF paradigms. The learning requires instead the explicit knowledge of the task in order to perform it correctly. Although changing the size of the color bar according to instruction can be satisfying as it signals success (the own satisfaction serves as a reward in this case), in a different context, e.g., during watching a movie with a color bar changing, it would not represent a rewarding value. Bray et al. (2007) made a first step in implementing an implicit feedback in a behavioral shaping paradigm; subject's responses were gradually changed by reinforcing small changes leading to a desired target behavior (Dinsmoor, 2004). The subjects did not need to have explicit knowledge of the task, but learned it gradually via receiving or missing a financial reward, depending on their performance. Although monetary reward constitutes a strong reinforcer, it is difficult to deliver in a real-time feedback in order to gradually shape the behavior.

TABLE 2 | Activation clusters during transfer.

Region	Peak MNI coordinates			Cluster size	*T*-value	*p*-value (FWE)
	x	y	z			
(2A) Transfer						
Left inferior frontal gyrus extending in ACC and others	−52	24	8	5138	10.02	0.0001
Right V5	36	−78	10	975	8.40	0.0001
Right inferior frontal gyrus pars triangularis	54	34	6	540	8.31	0.0001
Left middle occipital gyrus	−36	−80	14	3627	7.61	0.0001
Right middle temporal gyrus	46	−54	4	460	6.21	0.0001
Posterior cingulate cortex	−4	−40	34	995	6.06	0.0001
Left thalamus	−12	−30	0	164	5.64	0.0001
Right superior temporal gyrus	66	−40	18	19	4.66	0.018
(2B) Transfer: social > standard feedback						
Left inferior frontal gyrus pars opercularis	−50	2	12	1294	5.11	0.003
Left inferior parietal cortex	−54	−36	42	1001	4.57	0.026
Right inferior frontal gyrus pars opercularis	50	16	4	713	4.24	0.0001 (uc.)
Right inferior parietal cortex	66	−24	36	436	3.30	0.001 (uc.)
Right inferior parietal cortex	48	−42	46	78	2.97	0.002 (uc.)
Left middle cingulate cortex	−6	−22	40	100	2.96	0.002 (uc.)
Right Insula	42	−18	−6	23	2.75	0.003 (uc.)
Right middle frontal gyrus	30	42	20	28	2.60	0.005 (uc.)
ACC	6	10	34	25	2.58	0.005 (uc.)

uc.: uncorrected p-value

TABLE 3 | Group comparison of generalization (Simon task).

Simon task (transfer*group)	Peak MNI coordinates			Clustersize	*T*-value	*p*-value (FWE)
Region	**x**	**y**	**z**			
ACC	−12	34	−8	168	5.34	0.001
Precuneus	−4	−60	22	2225	7.06	0.0001
Left inferior parietal cortex	−34	−64	20	691	6.28	0.0001
Right middle temporal gyrus	48	−58	22	241	5.92	0.0001
Left middle frontal gyrus	−28	16	42	24	5.08	0.003
Right fusiform gyrus	34	−58	0	22	4.93	0.007

Emotional expressions aim to communicate our experiences and to influence the behavior of others (Horstmann, 2003). Social reward offers therefore a more ecologically valid paradigm to shape the behavior of subjects in real-time as compared to monetary reward. This common social learning mechanism can directly influence the level of localized brain activity using a BCI. Indeed, the social reward led to stronger localized brain activity than the standard feedback. Subjects learned to differentially regulate brain activity depending on the avatar faces. The use of differential stimuli to shape behavior opens new perspectives for developing social feedback paradigms with implicit learning, circumventing explicit cognitive control.

The presence of social reward led to bilateral activation of an anatomically-defined ROI in the corpus striatum (putamen, caudate nucleus, and globus pallidus). These structures belong to a network activated by pleasant and rewarding events (Haber and Knutson, 2010). They are involved in driving incentive-based learning and choosing appropriate responses to stimuli, thereby helping to achieve rewards and avoid punishments, and consequently allow the development of goal-directed behavior (Robbins and Everitt, 1996; Delgado, 2007; Liljeholm and O'Doherty, 2012). Social reward was demonstrated to share comparable neural pathways with monetary reward (Izuma et al., 2008). A number of fMRI and neurophysiology studies confirmed that neural activity in the striatum is modulated by social rewards and by learning in a social context (for a review see Báez-Mendoza and Schultz, 2013; Ruff and Fehr, 2014). Our results are compatible with these studies; moreover we demonstrated that the learning of control over the brain activation improves due to the direct reward.

During the generalization condition, activation in the ACC decreased more in the social feedback group. Although cerebral activation typically increases with higher task load, it is well established that in the course of skill training one can observe the decrease of brain activation (Chein and Schneider, 2005). The effects of training on brain plasticity have been studied in the

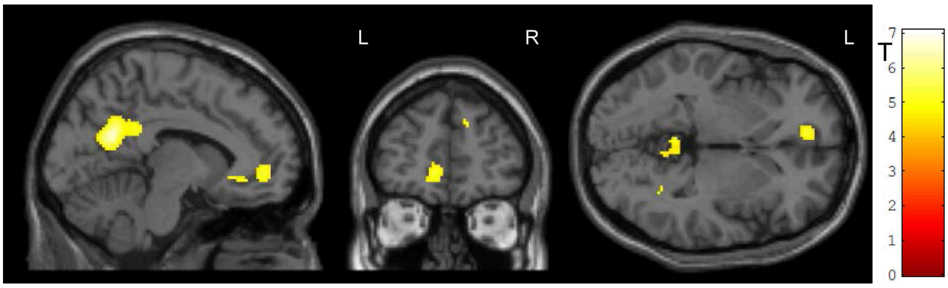

FIGURE 6 | Generalization. The social feedback led to lesser ACC activity during interference processing in the Simon task ($p < 0.05$, FWE-corr.). The same comparison revealed a prominent cluster at the precuneus as well (see **Table 3**).

sensorimotor system, demonstrating a systematic decrease in the motor and somatosensory cortex (Ikegami and Taga, 2008; Kwon et al., 2013; Walz et al., 2014). In trained musicians, gray matter density decreased with expertise in bilateral perirolandic and striatal areas that are related to sensorimotor function, possibly reflecting high automation of motor skills (James et al., 2013). In a similar vein, in a working memory task, the activation in the right inferior frontal gyrus and the right intraparietal sulcus initially increased with improved performance, but decreased when performance consolidated after the prolonged training (Hempel et al., 2004). Moreover, low-performance led to large and load-dependent activation increases in distributed cortical areas when exposed to excessive task requirements, suggesting a recruitment of additional attentional and strategy-related resources by low- as compared to high-performing participants (Jaeggi et al., 2007). In general, the recruitment of a large-scale neural network decreases in the automatic phase, as stimulus-response associations become better and task performance progresses from a consciously controlled manner in the early learning phase to an unconscious form in the late automatic phase (Toni et al., 1998; Müller et al., 2002; Dobbins et al., 2004). Kozasa et al. (2012) compared the performance of trained meditators with non-meditators in a Word-Color-Stroop task, i.e., a cognitive interference task based on a similar principle as the Simon task. Although there were no group differences for the behavioral interference effect, non-meditators activated attention and motor control higher than meditators. The authors suggested that the meditation training improved efficiency via enhanced sustained attention and impulse control. Similarly, in our study, after up to 2 weeks of NF-training, subjects who received social reward could maintain the similar behavioral results in Simon task while engaging less ACC activity than subjects who received standard feedback. The behavioral effects in our study demonstrated an increase of the performance in the Simon task over the training time, reflecting the accompanying decrease in ACC activation due to learning and the corresponding shift from a large network to more specialized regions. In combination with the lack of effects on the behavioral level, we conclude that the social reward led to a reduced neural recruitment to achieve a similar behavioral performance in the Simon task.

Rapid technological advance in fMRI and BCI extends the range of NF applications leading to its increasing popularity. Within the last 2 decades, a number of brain regions were controlled with rt-fMRI NF, including motor areas (deCharms et al., 2004; Yoo et al., 2008), anterior cingulate cortex (Weiskopf et al., 2003; deCharms et al., 2005), supplementary motor and parahippocampal areas (Weiskopf et al., 2004a), anterior insula (Caria et al., 2007; Berman et al., 2013), right inferior frontal gyrus (Rota et al., 2009), amygdala (Zotev et al., 2011; Brühl et al., 2014; Young et al., 2014), nucleus accumbens (Greer et al., 2014), dopaminergic neurons in the substantia nigra/ventral tegmental area complex (Sulzer et al., 2013) or networks of regions, such as individually localized emotion networks (Johnston et al., 2010), the interhemispheric balance between left and right visual cortices (Robineau et al., 2014), or a distributed ensemble of brain regions related to feelings of tenderness/affection (Schoenberg and David, 2014). The first applications of NF in patient groups suggest its potential in the treatment of several disorders, including chronic pain (deCharms et al., 2005), chronic tinnitus (Haller et al., 2010), Parkinson's disease (Subramanian et al., 2011), depression (Linden et al., 2012; Young et al., 2014), obesity (Frank et al., 2012), nicotine addiction (Canterberry et al., 2013; Li et al., 2013), or schizophrenia (Ruiz et al., 2013).

A well-designed feedback system is crucial in order to achieve a successful training of regional brain activation (Sitaram et al., 2008; Sokunbi et al., 2014) and allow its further development into an effective and accurate clinical intervention. Social feedback, offering direct reward for successful regulation, increased the effectiveness of the NF training. We applied a social smile of a changing intensity, which is a very simplified form of social reward. Indeed, more complex social stimulation (including social gestures, prosody, and complex emotional expression) could serve as an even stronger reinforcer and further improve performance. Sokunbi et al. (2014) propose to choose the visual stimuli that relate to the function of the target brain area. In accordance with this view, social feedback could be particularly well fitted to train impaired social interactions in psychiatric patients in implicit learning tasks.

Limitations

Although we studied a relatively large group of participants for such a complex paradigm, the group size is a limitation. Possibly due to the small group size, we failed to demonstrate stronger ACC regulation during the transfer sessions (regulation without feedback) and behavioral effects on the Simon task in the social feedback group. Despite the high variability of learning success, subgroup analyses with the focus on learners and non-learners are not feasible at this stage. It would be of particular importance to determine the variability between subjects in learning and reward sensitivity during NF and determine predictors for this (Scheinost et al., 2014). In particular, we did not consider the individual learning processes over the three session in 3 days each. Moreover, the test for difference in transfer effects between the social and standard NF might not be optimally selected. Although the test was identical with the learning procedure, it could have a different meaning for both groups. While in the standard feedback the bar in itself presented no rewarding value, it was not the case with the smiling faces. During social NF, subjects received social reward. In the transfer task, they were presented with slightly smiling facial expressions that might have had negative emotional value relative to smiling faces they viewed while regulating successfully. Showing subjects a neutral stimulus while trying to regulate their ACC activation without feedback might improve those results.

The reward system is typically associated with the basal ganglia, but many other brain regions respond to reward as well, including the ACC, the orbital prefrontal cortex, the midbrain dopamine neurons, the dorsal prefrontal cortex, amygdala, hippocampus, thalamus, lateral habenular nucleus, and specific brainstem structures such as the pedunculopontine nucleus and the raphe nucleus (Haber and Knutson, 2010). The exact role of ACC in reward processing is however not fully understood. It has been hypothesized to play a role in sustaining effective choice behavior based on the previous experience (Chudasama et al., 2013) and particularly in anticipation of loss by risky decisions (for a review, see Liu et al., 2011). A recent meta-analysis of brain imaging studies on social decision making in the ultimatum game suggested that the ACC controls and monitors conflicts between emotional and cognitive motivation, in line with its postulated role in general conflict monitoring (Gabay et al., 2014). In this respect, replacing the moving bar with an explicit social reward should not lead to additional ACC involvement, among others, because both tasks require similar involvement to obtain the desired outcome and only the rewarding value of this outcome differs. Although introducing social reward in the NF paradigm improved learning, we cannot rule out a direct impact on reward on the ACC activation, e.g., via increasing the net value of the expected reward (Apps and Ramnani, 2014). Future research may focus on other brain regions to examine if the effect of social reward is universal for all brain structures, or if it specifically facilitates learning in reward-sensitive regions.

Finally, the sequential group allocation based on the order of inclusion does not preclude observer biases. This should be addressed by using random allocation. This in turn, however, may introduce time effects depending on the block size for random allocation (see Tamm and Hilgers, 2014). Another problem in this study design, like in many other feedback trials, is the limited possibility to blind the conditions to the participant as well as the experimenter. In particular for therapeutic trails, this remains a challenge to blind control conditions in fMRI neurofeedback.

Conclusions

We suggest that social reinforcers can lead to improved learning of self-regulation and improve effects of fMRI-based NF on underlying neural processes such as cognitive interference processing. The advantage of social feedback over standard visual feedback or over monetary rewards is the online provision of a direct external reward that we can experience every day in social interactions. Further research is needed to evaluate if social feedback training has the potential to make the learning process more implicit (deCharms et al., 2005; Sulzer et al., 2013).

Author Contributions

KAM: Development of study paradigm and data analysis. Supervision over data analysis and interpretation. Manuscript revision. EA: Data acquisition, data analysis and interpretation. Manuscript writing. YK: Implementation of toolbox for real-time fMRI and technical support by data acquisition. Revising the manuscript. MD: Contribution to design and data analysis. Revising the manuscript. JC: Contributions to data collection and statistical analysis. Revising the manuscript. TG: Contribution to design and data collection. Revising the manuscript. FZ: Contribution to design. Revising the manuscript. NP: Contribution to development of ACC masks and data analysis. Revising the manuscript. PS: Contribution to data acquisition. Revising the manuscript. SB: Contribution to analysis of behavioral data. Revising the manuscript. MZ: MRI support and technical support by data acquisition. Revising the manuscript. KM: Supervision of and conceptual contributions to study. Data analysis and interpretation. Manuscript revision. All the authors read and approved the final version of the manuscript. All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary Material

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnbeh.2015.00136/abstract

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Erklärung § 5 Abs. 1 zur Datenaufbewahrung

Hiermit erkläre ich, dass die dieser Dissertation zu Grunde liegenden Originaldaten bei meinem Betreuer, ***Univ.-Prof. Dr. med. Dr. rer. nat. Klaus Mathiak, Klinik für Psychiatrie, Psychotherapie und Psychosomatik***, des Universitätsklinikums Aachen, hinterlegt sind.

Aachen, den 18.06.2016 Eliza Maysun Alawi

Erklärung gemäß § 5 Abs. (1) und (2), und § 11 Abs. (3) 12. der Promotionsordnung

Hiermit erkläre ich, **Eliza Maysun Alawi,** an Eides statt, dass ich den wesentlichen Anteil an der Publikation:

Alawi, E.M., Mathiak, K.A., Panse, J., & Mathiak, K. (2016). Health-related quality of life in patients with indolent and aggressive non-Hodgkin lymphoma. Cogent Psychology, 3: 1169582

geleistet habe.

Die Anteile an der Arbeit waren wie folgt:

A) E. M. Alawi: Durchführung sämtlicher dargestellter Experimente, Datenanalyse, Interpretation der Daten und Erstellung des Manuskriptes.
B) K. A. Mathiak: Beratung und Verbesserungsvorschläge des Manuskripts.
C) J. Panse: Unterstützung bei der Rekrutierung der Probanden, Verbesserungsvorschläge des Manuskripts.
D) K. Mathiak: Allgemeine Beratung und Supervision bei allen Schritten der Studie.

Aus diesem wesentlichen Anteil ergibt sich selbstverständlich die Stellung als Erstautorin.

Eliza Maysun Alawi, M.Sc.

Als Doktorvater und korrespondierender Autor bestätige ich die Angaben von Eliza M. Alawi.

Univ.-Prof. Dr. med. Dr. rer. nat. Klaus Mathiak

Ich schließe mich der Erklärung von Prof. Mathiak als Koautor(in) an:

Krystyna A. Mathiak

Jens Panse

Erklärung gemäß § 5 Abs. (1) und (2), und § 11 Abs. (3) 12. der Promotionsordnung

Hiermit erkläre ich, **Eliza Maysun Alawi,** an Eides statt, dass ich den wesentlichen Anteil an der Publikation:

Mathiak, K.A.*, **Alawi, E.M**.*, Koush, Y., Dyck, M., Cordes, J.S., Gaber, T.J., Zepf, F.D., Palomero-Gallagher, N., Sarkheil, P., Bergert, S., Zvyagintsev, M., & Mathiak, K. (2015). Social reward improves the voluntary control over localized brain activity in fMRI-based neurofeedback training. *Frontiers in behavioral neuroscience, 9,* 136
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Die Anteile an der Arbeit waren wie folgt:
A) E. M. Alawi: Durchführung sämtlicher dargestellter Experimente, Implementierung der Simon Aufgabe im Paradigma, Datenerhebung, Datenanalyse und Interpretation, Zwischenanalysen für Konferenzen und Erstellung des Manuskriptes.
B) K. A. Mathiak: Paradigma entworfen, implementiert, Entwicklung der Avatare, Durchführung von Pilotmessungen und der Pilotauswertung, Beratung bei Analyse, Beratung und Verbesserungsvorschläge des Manuskripts.
C) Y. Koush: Erstellung der Toolbox und technische Unterstützung bei den Echtzeit Messungen. Verbesserungsvorschläge des Manuskripts.
D) M. Dyck: Supervision der Datenanalysen, Feedback bei der Paradigmaentwicklung. Verbesserungsvorschläge des Manuskripts.
E) J. Cordes: Unterstützung bei der Datenerhebung, Feedback bei der SPM Analyse. Verbesserungsvorschläge des Manuskripts.
F) T. Gaber: Unterstützung bei der Datenerhebung (6 Wochen), Beitrag bei Paradigma-implementierung. Verbesserungsvorschläge des Manuskripts.
G) F. Zepf: Beratung zu Untersuchungsprotokoll. Verbesserungsvorschläge des Manuskripts
H) N. Palomero-Gallagher: Entwicklung der ACC Masken in Jülich für die ROI Analysen. Verbesserungsvorschläge des Manuskripts.
I) P. Sarkheil: Unterstützung während der Datenerhebung, Feedback bei der Paradigmaentwicklung. Verbesserungsvorschläge des Manuskripts
J) S. Bergert: Analyse der Simon Verhaltensdaten. Verbesserungsvorschläge des Manuskripts.
K) M. Zvyagintsev: MR und technische Unterstützung bei den Echtzeit Messungen. Verbesserungsvorschläge des Manuskripts.
L) K. Mathiak: Allgemeine Beratung und Supervision bei allen Schritten der Studie. Verbesserungsvorschläge des Manuskripts.

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Als Doktorvater und korrespondierender Autor bestätige ich die Angaben von Eliza M. Alawi.

Univ.-Prof. Dr. med. Dr. rer. nat. Klaus Mathiak

Ich schließe mich der Erklärung von Prof. Dr. Dr. Klaus Mathiak als gleichberechtigte Erstautorin an.

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