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How to determine whether conceptual endophenotypes can improve clinical outcomes in patients suffering from major depression: an exploratory approach

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Abstract

Depression is a complex mental health disorder, resulting in a high degree of disability. Since symptom constellation, course, and outcome are heterogeneous in these patients, current research initiatives are striving to establish stratified diagnostic and treatment approaches. In the past two decades, Dirk Hellhammer and his team introduced Neuropattern, a new diagnostic concept, which is based on conceptual endophenotypes of the stress response network. We explore how to use this concept in clinical practice in order to ultimately determine whether it brings any value over standard care. In view of the novelty of the concept and the difficulties dealing with such a concept at a practical level, it was necessary to initiate an exploratory study to determine key factors for planning future clinical trials.

We report results and learning from an exploratory single-site study investigating the use and potential benefits of Neuropattern in standard care. Inpatients (ICD-10 diagnosis F32, F33; N=178) were allocated to either treatment as usual (standard group, SG) or a novel Neuropattern oriented exploratory treatment (intervention group, IG). Symptom severity was assessed with psychometric tests at admission to hospital, during the first six weeks, and upon discharge from the hospital. In addition, direct and indirect costs were assessed for the 3-month-intervals prior to and after the hospital stay.

Compared to the SG, depression scores of patients in the IG showed a faster decline once psychotherapeutic and pharmacological treatment were based on an individualized explanatory model. The patients in the IG with an F33 diagnosis showed a more pronounced reduction of depression severity during the stay in the hospital and a stronger and quicker reduction of general symptom severity. Comparing the average depression scores at the start of the study and after six weeks, a decline in symptoms was observed for all Neuropatterns.

Some limitations of the study have to be mentioned: The study was not blinded, was single-site, included highly depressed inpatients only, and was conducted for no longer than 8 months. The results highlight some important points regarding taking the Neuropattern approach to the bedside and researching its efficacy and effectiveness to support personalized treatments in clinical care.

Key words: Neuropattern, endophenotypes, depression, precision medicine

1. Introduction

Depression is one of the most common mental health problems with a 12-month prevalence in the adult German population estimated at 8.2% (Jacobi et al., 2015) and the lifetime prevalence at about 17% (Jacobi et al., 2004). Depression occurs more frequently in women than in men and can begin at any age, but is most prevalent between ages 18 and 29 (Busch et al., 2013). The World Health Organization (WHO) estimated that major depression caused more disability worldwide than ischemic heart disease or cerebrovascular disease and may soon represent the most severe illness worldwide (WHO, 2008). In addition to the symptoms, depression causes significant loss of health-related quality of life (Williams et al., 2016) and entails high direct costs (e.g., cost of physicians, drug treatment, and psychotherapy) and indirect costs (e.g., sick leave; Andlin-Sobocki and Wittchen, 2005; Cuijpers et al., 2007, 2010; Layard, 2006; Thomas and Morris, 2000; Luppa et al., 2007; Olesen et al., 2012).

However, it is not simple to diagnose and treat depression, given the complexity and heterogeneity of symptoms: A variety of different symptoms (Fried, 2017) range along a continuum without clear-cut points (Melzer et al., 2002), and complex comorbidity with somatic and psychological disorders as well as different etiologies make the diagnostic process and individualized treatment difficult and time-consuming.

Different strategies have been developed to improve personalized diagnostic and therapeutic treatments. The National Institute of Mental Health (NIHM) of the United States launched the “Research Domain Criteria” (RDoC): “RDoC´s ultimate goal is precision medicine for psychiatry – a diagnostic system based on a deeper understanding of the biological and psychosocial basis of a group of disorders that is unambiguously among the most disabling disorders in medicine“ (Insel, 2014, p. 396). In the long run, RDoC intends to establish a brain-based classification of mental illness, by detecting and discriminating types of pathogenetic dysregulation which would improve personalized treatments. It is currently a framework for organizing research, starting with five domains of functioning (negative valence systems, positive valence systems, cognitive systems, systems for social processes, and arousal/regulatory systems). The RDoC matrix documents information for each psychopathological construct and sub-construct with respect to genes, molecules, cells, circuits, physiology, behavior, and self-reports (Casey et al., 2013; Cuthbert and Kozak, 2013).

Another strategy towards personalized medicine was proposed by the National Research Council of the US National Academies of Sciences, entitled “A Framework for Developing a New Taxonomy of Disease” (NRC, 2011), which assumes that the successful translation of basic research to clinical care requires a knowledge network that provides a fruitful exchange between basic and clinical research. This knowledge network generates subgroups mainly from individual characteristics of the genome, epigenome, microbiome, and exposome and the patient´s signs and symptoms. Thus, the knowledge network has its main focus on the physiological and environmental functions that are relevant for pathology. Both kinds of data mining may ultimately generate valid endophenotypes that can predict the prognosis or treatment response for an individual patient and which may replace inadequate symptom-oriented descriptive procedures (Miller and Rockstroh, 2013).

1.1 Neuropattern

For mood disorders, it is not yet foreseeable, if, when, and to which extent such strategies will become applicable for clinical routine (Maj, 2016a). Maj (2016b) recently addressed the need for a conceptual framework, which takes the tremendous complexity and heterogeneity of a multiplicity of biological, intrapsychic, interpersonal and sociocultural factors into account. Such a strategy, called Neuropattern, was developed by Hellhammer and his group since 1999 (Hellhammer et al., 2018).

Briefly, Neuropattern focuses on dysregulations of three subsystems of the stress response network in the brain: the (1) ergotropic systems, which facilitate task-directed mental and physical activities, mainly represented by adrenergic functions, (2) trophotropic systems, which promote rest, regeneration, and reconstitution of energy stores, primarily including brain serotonergic and parasympathetic functions, and (3) glandotropic systems, which organize the behavioral adaptation to stress and support the energy supply for the brain, essentially represented by the hypothalamic-pituitary-adrenal (HPA) axis (for details see Hellhammer et al., 2018; Hellhammer et al., 2012; Hellhammer and Hellhammer, 2008).

Each dysregulation of these subsystems is conceptualized by a characteristic pattern of psychological, biological, and symptom measures.

So far 13 patterns have been operationalized: CRF(corticotropin releasing factor)-hypoactivity, CRF-hyperactivity, CRF-hyperreactivity, NA(noradrenaline)-hypoactivity,

NA-hyperactivity, NA-hyperreactivity, sympathetic hypoactivity, sympathetic hyperreactivity, serotonin-hypoactivity, serotonin-hyperreactivity, cortisol-hypoactivity, cortisol-hyperactivity, and GR(glucocorticoid receptor)-resistance. For example, CRF-hypoactivity is expected to be associated with lowered cortisol levels upon awakening, lethargy as a psychological characteristic, and hypersomnia as the symptomatic variable. Evidence for the psychopathological relevance of a Neuropattern is fulfilled, once a patient presents a sufficient amount of priori defined criteria of each of these three categories (Contreras et al., 2018). Table 1 gives an overview of the number of psychological, biological, and symptomatic variables and the corresponding examples for each Neuropattern (Contreras, 2018).

Table 1

The combination of measures of individual differences reflect the current knowledge on the biological, psychological, and symptom concomitants of such dysregulations, as well as on relevant modulators such as early adversity, genetic and epigenetic determinants (Hellhammer and Hellhammer, 2008). Hypotheses on such dysregulations are considered “conceptual endophenotypes”. In contrast to empirically endophenotypes, conceptual endophenotypes are hypothetical and are of heuristic value. Their reliability and validity is continuously elaborated in an iterative process between basic and clinical research. It is expected that such kind of information would already help to improve the competence of the physician to individualize treatments. This new research strategy has recently been published in detail by Hellhammer, Meinlschmidt and Pruessner (2018).

1.2 Aim of the study

The aim of the following study was to explore possible benefits of applying Neuropattern diagnostics in a hospital for behavioral medicine in depressed patients, as previously shown in a comparable study in inpatients with various mental disorders and high somatization (Hero et al., 2012). In a practice-based exploratory approach, therapeutic success was compared between a group of depressed patients who received Neuropattern diagnostics (intervention group, IG) in addition to the hospital’s standard treatment, and a group which received the hospital’s standard treatment only (standard group, SG). We were interested to explore if the application of Neuropattern

results in (1) a quicker reduction in unspecific and specific symptom severity during the first six weeks of the hospital stay (longitudinal assessment); (2) a stronger decrease in unspecific and specific symptom severity in the time between admission to the hospital and discharge from hospital (pre-post assessment); and (3) a stronger decrease in the number of consultations with the doctor and days of sick leave (indicative of lower direct and indirect costs) in the 3-month follow-up period.

We further explored whether and which conceptual endophenotypes contribute to the therapeutic success of the treatment. We were interested in understanding whether the Neuropattern concept would add any value in clinical practice compared to the treatment as usual. The novelty of such a concept and the difficulties in dealing with it at a practical level required initiating an exploratory study in order to determine the key factors to take into account in future clinical trials. The study protocol was approved by the ethical committee of the respective Chamber of Physicians (*Landesärztekammer Hessen*, Reg. Nr. FF 99/2010).

2. Materials and methods

2.1 Study design, location and subjects

We conducted an open-label, non-registered naturalistic exploratory study. The study was implemented within the daily routine of a hospital for behavioral medicine in central Germany (North Hesse). Here, all patients (privately insured) were screened on arrival. Inclusion criteria were a diagnosis of ‘depression’ (ICD-10 F32, F33; including comorbidity) and age 18-70 years. Of these, n=56 did not fulfill diagnostic criteria, n=2 were too old, and n=47 refused to apply Neuropattern diagnostics based on personal reasons (see Fig. 1). After admission to the hospital, written informed consent was obtained from 178 German-speaking patients.

The patients were allocated to either Neuropattern diagnostics (IG) or the standard treatment provided by the hospital (SG). A list with alternating treatment assignments was held in the hospital administration. When a patient met the inclusion criteria, the clinical investigator called the hospital administration and was provided with the allocation for his patient. The administrator was blind to the characteristics of the patient and the clinical investigator was blind to the state of the list.

Both groups received a complex therapy program consisting of diagnosis-specific as well as unspecific group therapy and individual psychotherapy based on behaviour therapy, progressive muscle relaxation, art therapy, vocational therapy, sports and exercise therapy, psychoeducation, and regular ward rounds. In addition, psychopharmacological treatment was delivered, based on either the clinician's preferred medication or the medication that the patient had been prescribed previously. The IG additionally received Neuropattern diagnostics. Changes to the treatment are described separately below. The psychoeducation for the SG followed a general diathesis (vulnerability) stress model (Ingram and Luxton, 2005).

No patient was free of medication at the beginning of the evaluation. Two patients dropped out before the intervention started, and 23 patients did not return questionnaires at the follow-up 3 months after the intervention. No further drop-outs were documented at the second follow-up 6 months after the intervention (see Fig. 1 for flow chart).

Figure 1

After applying the exclusion criteria and drop-out occurring during the study, the study population comprised 131 inpatients diagnosed with depression (ICD-10 F32, F33), who were treated for a period of at least 6 weeks. In total, 69 women and 62 men took part in the study. Sociodemographic data are reported in Table 2. Patients in this study were largely in their late forties, had a better than general economic status, and stayed in the hospital for about 2 months. Although patients had to fulfil the criteria for either ICD-10 F32 or F33, about half of the patients (48%) fulfilled the criteria for at least one additional diagnosis. At the start of the study period, the two groups of patients did not differ significantly on any of the analyzed variables.

Table 2

2.2 Assessment

The Brief Symptom Inventory (BSI; Derogatis, 1992; Franke, 2002) was used to assess the general symptom severity at the time of a patient´s admission to the hospital and at

discharge from hospital. The Beck Depression Inventory (BDI; Beck et al., 1961; Hautzinger et al., 1995) was used to assess the symptom specific severity of depression at these time points as well. The Symptom Check List, Short Version 9 (SCL-K9; Klaghofer and Brähler, 2001; Prinz et al., 2013), a short version of the Symptom Check List SCL-90-R, and the German version of the Hamilton Rating Scale for Depression (HAMD; Hamilton, 1960) were administered weekly by trained research assistants during the first six weeks of the hospital stay. An evaluation questionnaire was used to assess the direct and indirect costs (days of sick leave and visits to physicians during the past three months) at admission to the hospital and at three months after discharge from hospital.

The following questionnaires and assessments were administered to the patients of the IG only: The Neuropattern Questionnaire (NPQ) – Anamnesis (NPQ-A; Hellhammer, 2009a) is an anamnestic questionnaire for the physician to collect information about physiological diseases and anthropometric data. The NPQ – Symptom List (NPQ-S; Hellhammer, 2009b) collates stressful life events, emotional and cognitive stress responses, and exhaustion states. The NPQ – Patient Questionnaire (NPQ-P; Hellhammer, 2009c) collects perceived psychological and symptomatic traits associated with dysregulation of the stress response network. The NPQ – Pre-/Post-natal Stress Questionnaire (NPQ-PSQ; Hellhammer, 2009d) is a questionnaire to inquire pre-, peri- and postnatal adverse events during early development that are considered relevant for the pathogenesis of health disorders. Finally, the Patient Health Questionnaire (PHQ; Löwe et al., 2002; Spitzer et al., 1999) is a valid screening test of psychiatric disorders.

The information obtained with these questionnaires and biomarkers (salivary cortisol levels at 0, 30, 45 and 60 min after awakening and at 15:00 hrs and 20:00 hrs; low-dose (0.25 mg) dexamethasone suppression test (DST); measures of heart rate variability before sleep, overnight, and after awakening) was used to assign patients in the IG to the 13 conceptual endophenotypes in accordance with the procedures described by Hellhammer and Hellhammer (2008).

2.3 Neuropattern diagnostic and treatment recommendations

For an overview of Neuropattern's diagnostic components, see Table 3.

Table 3

As described in more detail in Hellhammer et al. (2018), each of the 13 Neuropatterns is a priori defined by biological, psychological, and symptom measures. To qualify for a Neuropattern, a patient has to fulfill a given number of criteria from these three categories.

Thus, a patient can qualify for one or more Neuropatterns. A computerized analysis results in a report. For each possible constellation, the automatic report comes with a disease model ("stress triangle") and suited psychological and pharmacological treatment recommendations.

After the diagnostic phase, patients of the IG received an individualized explanatory model of the dysfunctions from which psychotherapeutic and pharmacological recommendations were derived. The procedure explaining the Neuropattern diagnostics as well as the Neuropattern-based disease model was standardized and documented in the study protocol. For the explanatory model, we used a picture to illustrate dysregulations of the trophotropic serotonergic and parasympathetic systems, the ergotropic noradrenergic and sympathetic systems, and the glandotropic systems, respectively. In easy words and illustrations, the patients were informed about dysfunctions of the stress response network by a trained research assistant: advice was provided about what can be done to rebalance the three systems.

2.4 Data analysis

Statistical analyses were performed using the SPSS statistical software package (PASW 17, Chicago, Illinois, USA). Data are presented according to the intent-to-treat principle with means ± standard error (SE) and 95% confidence intervals (95% CI). Variables for intangible costs were measured either two (BDI, BSI) or six times (SCL-K9, HAMD). We performed two 2 × 2 × 2 and two 2 × 2 × 6 repeated-measures analyses of variance (ANOVA) to account for differences in intangible costs over time (BDI, BSI, SCL-K9, HAMD) between treatment and control group as well as patients with diagnoses for a depressive episode (ICD-10 F32) or a recurrent depressive disorder (ICD-10 F33). For each repeated-measures ANOVA, we estimated group ×

time, diagnoses F32/33 × time and group × diagnoses F32/33 × time interaction effects to evaluate potential differences in change over time with respect to group affiliation and diagnosis F32/33.

In case of significant interaction effects between time and group (or ICD-10 diagnoses F32/33), we performed contrast analyses for repeated-measures to determine the specific time span, in which SCL-K9 or HAMD scores developed differently between groups (or diagnoses F32/F33). In case of significant interaction effects between time, group and diagnoses F32/F33, we performed repeated-measures ANOVAs post-hoc for both ICD-10 F32 and F33 patients separately to estimate potential differences in the ICD-10 F32 and the F33 subsamples.

Greenhouse-Geisser corrected degrees of freedom (df) are reported for F-statistics whenever sphericity of repeated measurements was violated. Potential relationships with the Neuropattern diagnostic were explored with descriptive analyses.

The variables 'consultations with the doctor' (direct costs) and 'days of sick leave' (indirect costs) did not meet the necessary assumptions to perform parametric testing. Thus, difference values were calculated (baseline value minus follow-up assessment). As the assumptions for parametric testing were also violated for these difference variables, Mann Whitney U-tests were used on difference values to test for group differences in direct and indirect costs.

3. Results

3.1 Comparison of intervention and standard group

Repeated-measures ANOVAs showed significant changes over time in the direction of significant lower values for BDI, BSI, HAMD, and SCL-K9 (all $p<.001$). We found no significant main effect for group (IG/Neuropattern vs. SG), or ICD-10 diagnosis F32/33 (all $p\geq.05$). Furthermore, repeated-measures ANOVAs revealed a significant time × group interaction for HAMD scores indicating faster decreases in HAMD scores in the IG (Neuropattern) as compared to the SG (Fig. 2). Contrast analyses for repeated measures showed these decreases to be significant in the time span between t1 and t2 ($F(1, 95)=6.08$, $p=.015$, partial-$\eta^2=0.06$). Moreover, we found significant time × group × diagnosis F32/33 interactions for BDI, BSI, and SCL-K9 scores (Fig. 3). Test statistics

of these results are summarized in Table 4. Contrast analyses for repeated measures of SCL-K9 scores show these decreases to be significant in the time span between t2 and t3 (F (1, 97)=4.55, p=.035, partial-η^2=0.045). Post-hoc repeated-measures ANOVAs for either ICD-10 F32 or F33 patients revealed significant time × group interactions only in the F33 (BDI: F (1, 57)=3.57, p=.064, partial-η^2=0.059; BSI: F (1, 57)=5.09, p=.028, partial-η^2=0.082; SCL-K9: F (3.16, 142.06)=2.66, p=.047, partial-η^2=0.056) but not in the F32 subsample (BDI: F (1, 61)=2.02, p=.160; BSI: F (1, 61)=1.59, p=.213; SCL-K9: F (3.26, 169.57)=0.72, p=.551).

Fig. 2 and 3

Table 4

With respect to 'consultations with the doctor' and 'days of sick leave', Mann-Whitney U tests revealed no significant differences between IG (Neuropattern) and SG neither for baseline ('consultations with the doctor': U=1778, Z=−0.84, p=.399; 'days of sick leave': U=1846.5, Z=−0.66, p=.513) nor for difference values for baseline minus the three month catamnesis after discharge from the hospital ('consultations with the doctor': U=1332.5, Z=−0.81, p=.419; 'days of sick leave': U=1204.5, Z=−1.59, p=.112).

3.2 Results of the exploratory analyses

As we found a positive effect of Neuropattern for the whole IG with regard to the reduction of HAMD-scores, it was explored which of the Neuropatterns contributes most to this therapeutic effect.

Table 5 shows the total scores for the HAMD t0 and t5 for the various Neuropattern. The different Neuropatterns occur in varying numbers: the most frequent Neuropatterns are serotonin-hyperreactivity and serotonin-hypoactivity, no patient qualified for cortisol-hyperactivity.

Table 5

Comparing the mean scores of the HAMD at t0 and at t5 a decline can be observed across all the various Neuropatterns. This result is true for the whole group of patients (Table 5) as well as for the subgroups diagnosed ICD-10 F32 and/or F33; the results calculated separately for these two groups are not shown here as they were essentially the same as for the total group.

4. Discussion

In this practice-based exploratory study, we set out to evaluate the effect of providing a cohort of inpatients (ICD-10 F32, F33) with an individualized explanatory model of dysfunction based on Neuropattern (Hellhammer et al., 2012).

4.1 Primary results

The results of this study show that depression scores declined more rapidly in the whole IG compared to the SG during the hospital stay. The results are in line with a previous Neuropattern study in inpatients with various mental disorders and high somatization which also showed a significantly greater improvement for the intervention group in self-rating assessments on symptom severity (Hero et al., 2012). For the F33 subgroup of patients of the IG, we found a more pronounced reduction of depression severity during the stay in the hospital, and a stronger and quicker reduction of general symptom severity. However, our analyses revealed no effect of Neuropattern on the reduction of ‘days of sick leave’ and ‘consultations with the doctor’ after discharge from hospital.

Future studies should explore in more detail the causal pathways leading to this finding. Our results suggest a role of the individualized explanatory model of dysfunction from which treatment recommendations were derived. Potential pathways that might lead to such a finding are (1) a more targeted application of evidence-based intervention techniques during the hospital stay as outlined above; (2) a shift to a more active engagement and empowerment of individual patients to tackle their daily lives more effectively and with a feeling of control (Tew et al., 2012); (3) other pathways that have been suggested to be relevant in interventions targeting lifestyle and behavioral changes (Clarke et al., 2015; Serrano-Ripoll et al., 2015; Pampallona et al., 2002); and (4) pharmacological treatment recommendations, which should best be monitored in single case studies (Smith, 2012). The particular challenge here is to have administered

a substance recommended by Neuropattern diagnostics that may be breaking with clinical routine (Boyle, 2013). In clinical routine, the selection of medication is rather oriented on patients' psychopathology and the medication's side effects.

Krishnan (2015) recently compared the approach of the National Research Council (NRC) with common taxonomies, the Diagnostic and Statistical Manual of Mental Disorders, and the Research Domain Criteria of the National Institute of Mental Health. The NRC considers a knowledge network necessary to understand the biology and underlying causes of psychiatric diseases, and to successfully discriminate subgroups for a new taxonomy. Studies applying conceptual endophenotypes are likely to add relevant data to such a knowledge network. An obvious advantage of Neuropattern is the utility of this system. Once validated, some conceptual endophenotypes may prove predictive value of individualized treatments and eventually become endophenotypes, which can contribute to a new taxonomy of mood disorders (Hellhammer and Hellhammer, 2008).

4.2 Exploratory analyses and considerations for future studies

Our exploratory analyses showed positive change for patients across all observed Neuropatterns: A decrease in the total score could be observed in the HAMD. A more striking finding for future studies of treatment efficacy and/or effectiveness as well as treatment selection are the differing frequencies with which these patterns were observed in our naturalistic patient sample. The allocation frequencies ranged from zero (0%) to 36 (71%) of IG patients. Methods and concepts underpinning treatment selection research have made progress (e.g., Cohen and DeRubeis, 2018). Methods to plan such studies with appropriate sample sizes, both with view to confirmatory trials (sample size calculation/power analysis: Artman et al., 2018) as well as studies in naturalistic settings or secondary data analyses (Riley et al., in press a, b) are increasingly available. And due to the high number of potential confounding variables including social-psychological aspects such as expectations on clinicians' and patients' side, and non-specific treatment factors (Lambert, 2013), planning such studies is a particular challenge. Understanding the epidemiology of potential moderators and mediators of treatment outcomes is therefore crucial for planning (especially confirmatory) studies which aim to evaluate the impact of conceptual endophenotypes.

Another key aspect for future studies is the economic viability of the approach. The quicker reduction of symptoms of depression in the IG might be an economic argument

of using Neuropattern in clinical practice. Since introducing novel diagnostic routines and interventions is usually accompanied by additional costs (e.g., materials and staff time, for more detail see Hellhammer et al. 2018), the current study suggests that there might be scope for recovering (at least some of) the costs of the Neuropattern intervention through savings made by insurance companies and employers. Follow-up studies should use more detailed instruments to assess the tangible costs of depression and shed more light on this aspect. But, this is again an aspect that pertains to the field of personalized approaches more generally and has only recently received more attention (e.g., Snooks et al., 2018).

4.3 Limitations

Several limitations of this pilot study should be mentioned. Although independently allocated, the patients and the treating clinicians were not blinded. The patients knew whether they had been included in the treatment as usual (SG) or IG/Neuropattern group with the expected better response, expected by both the patients and the clinicians. Therefore, we cannot exclude a Hawthorne, Rosenthal and other effect related to non-blinding as possible explanation for the between-group effects (Jakovljevic, 2014; McCambridge et al., 2014). Such effects nevertheless cannot account for the potential specific findings presented in our analysis. Further, the patients of both groups shared all therapeutic activities apart from the Neuropattern diagnostic and since the time available for patient consultation and ward rounds was not changed, the same amount of time was spent in therapeutic activities and consultations.

In addition, the study was single-site, it included highly depressed inpatients only (see Table 1), and was conducted for no longer than 8 months. Any of these factors might have affected the results. Besides replication in different psychiatric settings, studies exploring longer time frames or settings with therapies of lower intensity (e.g., outpatient psychotherapy) would be instrumental to identify an optimal target population for Neuropattern.

All patients received medication at the time of their admission. For patients of the IG, Neuropattern led to pharmacological treatment recommendations which might be better suited to rebalance potential dysregulations. The physician was free to consider such recommendations, particularly if the patient did not respond well to his/her current medication, and if there were no other reasons (contraindications, side effects, drug

interactions) not to follow the recommendation. In many patients, the medication already met the recommendation of Neuropattern. After discharge, patients of both groups either continued on these medications, or stopped or replaced pharmacological treatments. However, this data set did not provide a sufficiently large size of subgroups to run statistical analyses of the effects of treatment recommendations on outcome measures. Single case studies may be the best way to learn which patients may eventually profit from such recommendations (Smith, 2012).

As with most practice-based studies, it was difficult to pin down exactly the extent to which medical personnel adhered to the recommendations, read the individual information about the patients, or which recommendations were implemented. Although this aspect is commonly encountered in practice-based research (Strauss et al., 2015), Neuropattern was mainly devised for primary care settings and focuses on stress-related pathology. To introduce it into a clinical setting such as a psychiatric hospital where acute diseases are treated and which has its own routines made it even more important to work towards smoothly integrating the Neuropattern diagnostics in clinical practice.

This also constitutes one of the reasons behind the third limitation of this study: The Neuropattern system also has a component that assesses biomarkers as part of the diagnostic routine (Dallman and Hellhammer, 2011; Hellhammer et al., 2012). Previous studies have established that genetic or epigenetic effects play a role in the stress system (Cai et al., 2015; Klengel et al., 2014), particularly as related to our measures of early adversity. In this study, we were not yet able to test how far Neuropattern diagnostic can integrate these biomarkers to optimize the treatment effect. However, this has been investigated in two other consecutive studies, which are currently being prepared for publication.

4.4 Conclusion

Subtyping depression represents a promising attempt to overcome the lack of specificity of many diagnostic constructs and help by optimizing the healing process. The results of our study are encouraging, yet we must continue to increase efforts in this research domain so that we can move towards evidence-based assessment and treatment of depression (Cuijpers et al., 2012).

Author contributions

Niels Bergemann, Katrin Bruhn, and Karen Loscheider designed the study and wrote the protocol. Katrin Bruhn and Karen Loscheider participated in patient recruitment and screening, conducted the clinical assessments and collected the data. Friedemann Gerhards, Dominic Vogt, and Jan R. Böhnke performed the statistical analyses; Niels Bergemann, Katrin Bruhn, Dominic Vogt, and Friedemann Gerhards drafted the manuscript. All authors contributed to and have approved the final manuscript.

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Conflicts of interest statement

The authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interests.

Compliance with ethical standards

All patients gave their informed consent prior to their inclusion in the study. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1964 and its later amendments. The study protocol was approved by the ethical committee of the respective Chamber of Physicians (*Landesärztekammer Hessen*, Reg. Nr. FF 99/2010).

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Figures

Fig. 1. Flow chart of the chronological steps of the study

Fig. 2. Comparison of the intervention group (IG; Neuropattern, N=67) and standard group (SG, N=64) with respect to mean changes in the HAMD scores (error bars represent standard errors; *indicates significance by contrast calculation; t0 = baseline, t1 – t5 = time points of weekly assessments)

Fig. 3. Comparison of the intervention group (IG; Neuropattern, N=67) and standard group (SG, N=64) with respect to mean changes in the Beck's Depression Inventory (BDI), Brief Symptom Inventory (BSI), and short version of the Symptom Check List (SCL-K9) for patients with ICD-10 F32 and F33 diagnosis at admission to hospital (pre) and discharge from hospital (post); (error bars represent standard errors; t0 = baseline, t1 – t5 = time points of weekly assessments)

Tables

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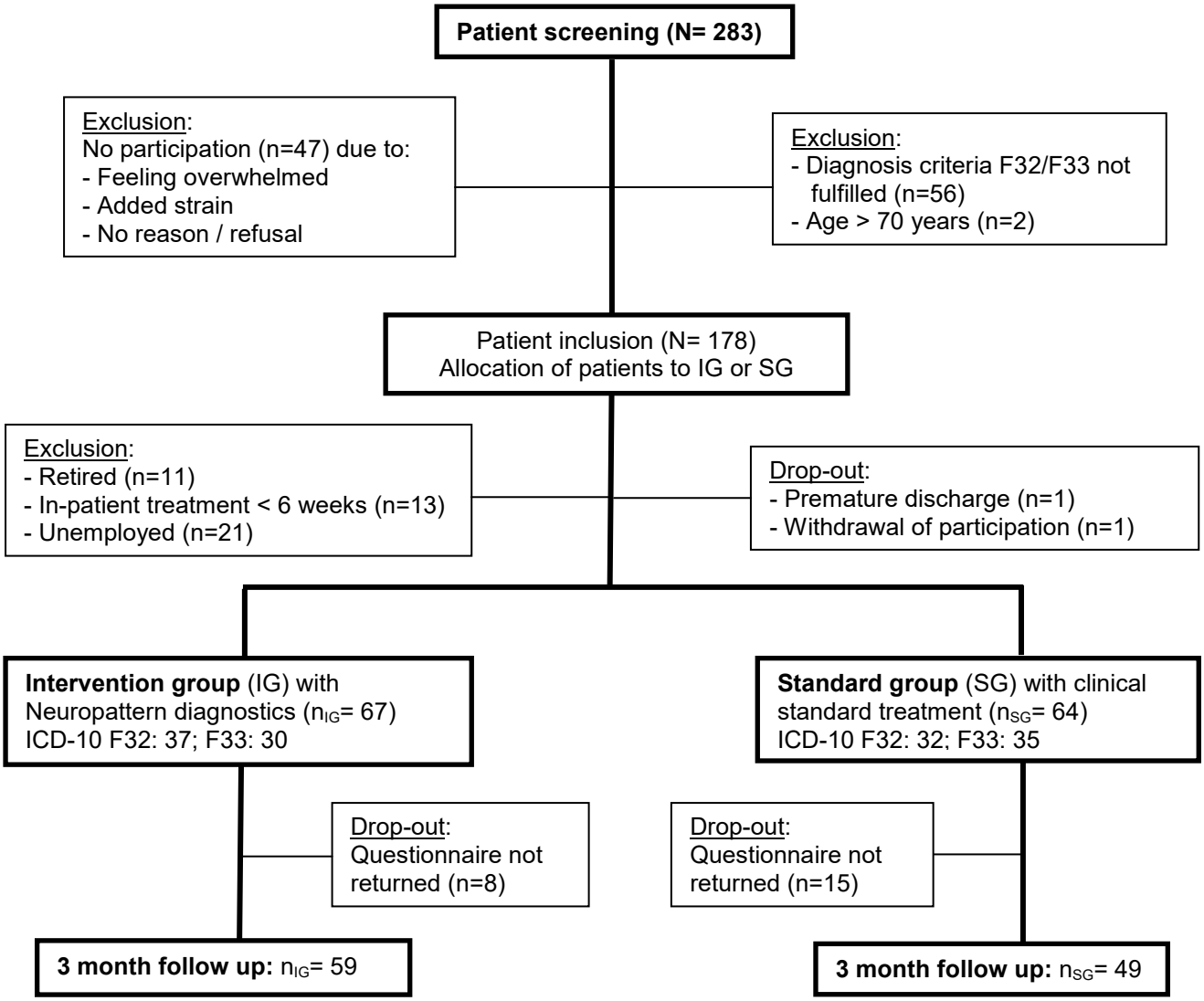

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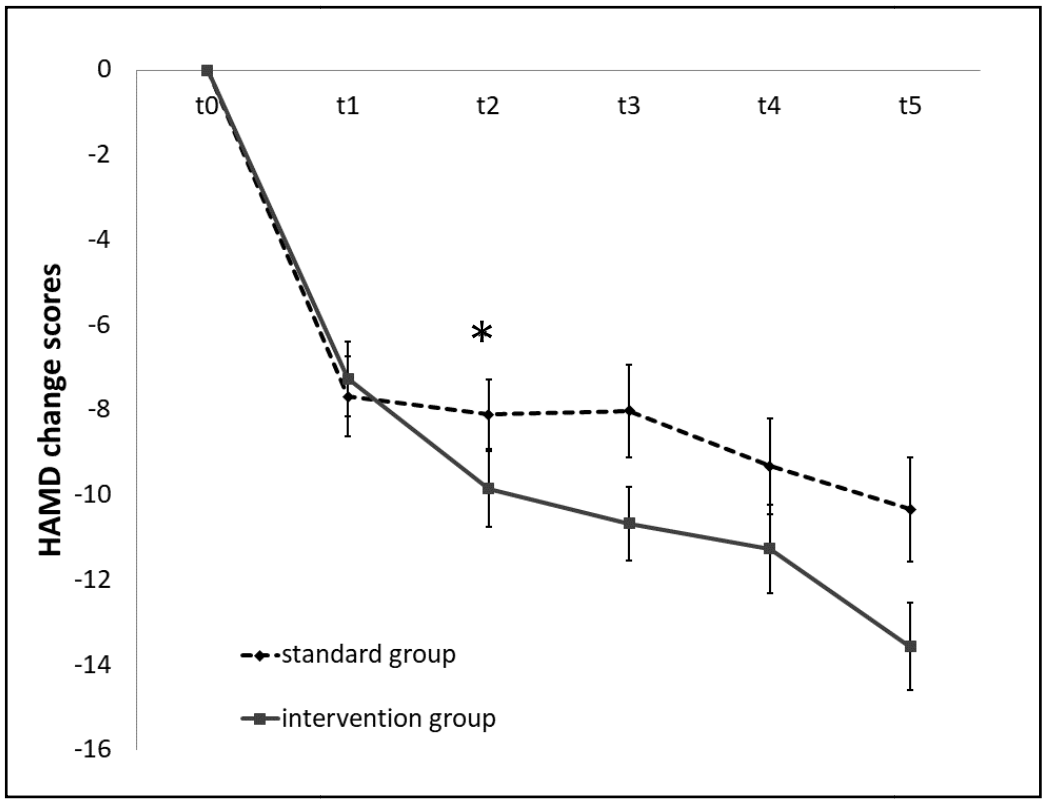

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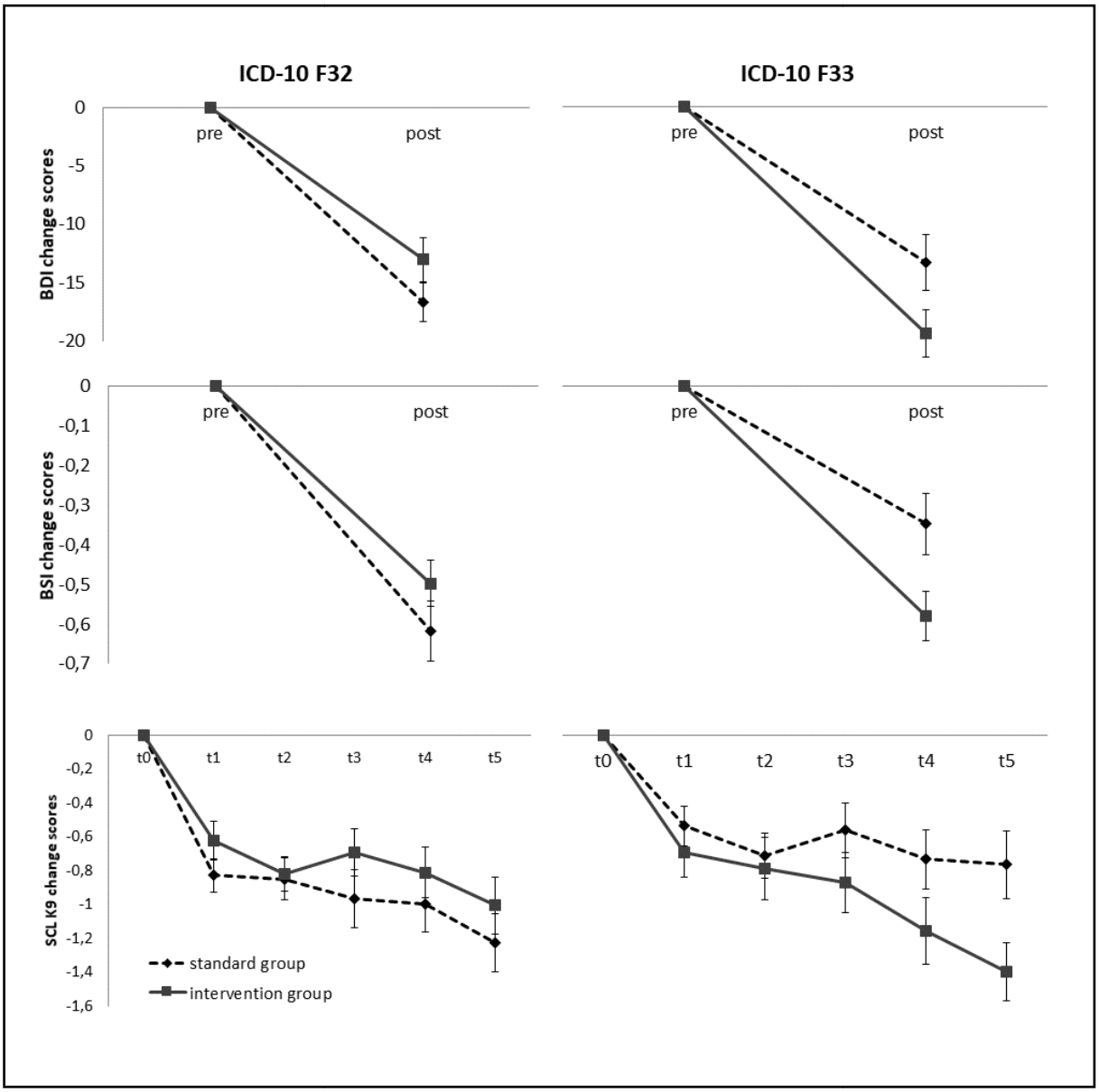

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Table 1. Neuropatterns, number of items, and examples of psychological, biological, and symptomatic criteria (adapted from Contreras, 2018)

Neuropattern	**Psychological Variables**	**Biological Variables**	**Symptomatic Variables**
CRF-hypoactivity	11; lethargy	3; lowered cortisol levels upon awakening	7; hypersomnia
CRF-hyperactivity	13; anhedonia	5; elevated cortisol levels upon awakening	13; generalized anxiety disorder, depression
CRF-hyperreactivity	7; worried, ruminating	10; strong increase of cortisol levels upon awakening	6; Anticipatory stomach complaints
NA-hypoactivity	10; burnout	5; high LF ms² in the evening ECG	7; migraine following stress
NA-hyperactivity	15; tension, drivenness	5; high LF ms² in the evening ECG	12; anxiety disorder
NA-hyperreactivity	18; irritability	6; high LF ms² in the ECG after awakening	8; emotional sweating
Serotonin-hypoactivity	14; impulsiveness	5; elevated LFms²/HFms² ratio	7; premenstrual syndrome
Serotonin-hyperreactivity	12; resignation	3; high HF ms² in the ECG	5; reaktive depression
Cortisol-hypoactivity	10; malaise	4; low levels of cortisol after dexamethasone	8; alternating pain
Cortisol-hyperactivity	7; fatigue	11; low suppression of cortisol after dexamethasone	13; muscle fatigue
Sympathetic hyperactivity	5; attributed nervousness	5; high LF ms² in the evening ECG	9; hypertension
Sympathetic hyperreactivity	6; stage fright	5; high LF ms² in the morning ECG	4; sweating under physical stress
GR-resistance	9; exhaustion	0; normal cortisol levels	8; pain

CRF = corticotropin releasing factor, NA = noradrenaline, GR = glucocorticoid receptor, HF = high frequency according to spectral analyses of the ECG); LF = low frequency according to spectral analyses of the ECG

Table 2. Sociodemographic data and descriptive statistics

	n_{IG}	n_{SG}	M_{IG}	M_{SG}	Test statistics
M age (*SE*)	67	64	47.64 (1.08)	47.53 (1.09)	$t_{129} = -0.07$, $p = .943$
Gender (m:f)	30:37	32:32	–	–	$\chi^2 = 0.37$, $p = .600$
Comorbidity:					$U = 2108.5$, $z = -0.18$, $p = .855$
one diagnosis	37	31	–	–	–
two diagnoses	16	25	–	–	–
three diagnoses	9	5	–	–	–
> three diagnoses	5	3	–	–	–
Diagnosis distribution (F32 : F33)	37:30	29:35	–	–	$\chi^2 = 1.29$, $p = .296$
M duration of stay in days (*SE*)	67	64	56.93 (2.10)	58.38 (1.96)	$t_{129} = 0.50$, $p = .615$
Socio-economic status (based on the social class index, Winkler et al., 1999)					$U = 2029$, $z = -0.55$, $p = .584$
lower class	0	1	–	–	–
lower middle class	3	4	–	–	–
middle class	7	8	–	–	–
upper middle class	26	22	–	–	–
upper class	13	14	–	–	–
Intangible costs					
BDI_{pre} (*SE*)	66	64	25.56 (1.32)	24.95 (0.99)	–
BDI_{post} (*SE*)	63	59	10.56 (1.40)	10.15 (1.31)	–
BSI_{pre} (*SE*)	66	64	0.99 (0.05)	0.97 (0.05)	–
BSI_{post} (*SE*)	63	59	0.46 (0.05)	0.47 (0.05)	–
HAMD	67	64			
$t_{0\ (1st\ week)}$ (*SE*)			23.42 (0.84)	22.33 (0.86)	–
$t_{1\ (2ndweek)}$ (*SE*)			16.04 (0.96)	14.59 (0.88)	–
$t_{2\ (3rd\ week)}$ (*SE*)			13.44 (0.82)	14.11 (0.84)	–
$t_{3\ (4th\ week)}$ (*SE*)			12.50 (0.94)	14.04 (0.96)	–
$t_{4\ (5th\ week)}$ (*SE*)			11.83 (0.89)	12.59 (0.91)	–
$t_{5\ (6th\ week)}$ (*SE*)			09.67 (0.89)	11.74 (0.91)	–

SCL-K9	52	49			
$t_{0\ (1st\ week)}$ (*SE*)			2.04 (0.12)	2.03 (0.11)	–
$t_{1\ (2ndweek)}$ (*SE*)			1.40 (0.11)	1.36 (0.10)	–
$t_{2\ (3rd\ week)}$ (*SE*)			1.25 (0.10)	1.26 (0.10)	–
$t_{3\ (4th\ week)}$ (*SE*)			1.29 (0.11)	1.28 (0.12)	–
$t_{4\ (5th\ week)}$ (*SE*)			1.10 (0.12)	1.18 (0.12)	–
$t_{5\ (6th\ week)}$ (*SE*)			0.89 (0.09)	1.05 (0.12)	–
Direct costs					
Consultations with the $doctor_{pre}$ *M* (*SE*)	50	38	2.76 (0.26)	3.92 (0.50)	–
Consultations with the $doctor_{3mth.post}$ *M* (*SE*)	50	38	2.04 (0.22)	2.29 (0.27)	–
Indirect costs					–
Days of sick leave $_{pre}$ *M* (*SE*); *Mdn*	50	36	31.12 (4.76); 25	28.86 (4.76); 23	–
Days of sick leave $_{3mth.post}$ *M* (*SE*); *Mdn*	50	36	28.72 (5.28); 10	30.19 (5.12); 31	–

M = mean; SE = standard error; Mdn = median; IG = intervention group; SG = standard group
BDI= Beck Depression Inventory; BSI = Brief Symptom Inventory; SCL-K9 = Symptom Check List, Short Version; HAMD = Hamilton Rating Scale for Depression

Table 3. Overview of the components of Neuropattern diagnostics

Methods		**Measures**
Questionnaires	Neuropattern Questionnaire (NPQ) – Anamnesis (NPQ-A; Hellhammer, 2009a)	• Medical history • Vital signs • Current diagnosis • Past treatment • Current medication
	Patient Questionnaire (NPQ-P; Hellhammer, 2009c)	Psychological and symptomatic variables
	Symptom Lists (NPQ-S; Hellhammer, 2009b)	• Stress-reactivity • Exhaustion quality • Adverse life events
	Pre-/Post-Natal Stress Questionnaire (NPQ-PSQ; Hellhammer, 2009d)	Pre- and post-natal adversity
	Patient Health Questionnaire (PHQ; Löwe et al., 2002; Spitzer et al., 1999)	Screening for ICD-10 diagnoses of mental disorders
Biomarkers	• 16 saliva samples • Low dose (0.25 mg) dexamethasone suppression test (DST) • Heart rate variability	Not reported

Table 4. Results of repeated-measures ANOVAs with group and depression diagnosis as factor and BDI, BSI, HAMD and SCL-K9 scores as outcome

	F	df	error f	p	partial-η^2
BDI					
Main effect					
Time	232.82	1	118	**<.001**	0.664
Group	0.42	1	118	.519	
ICD-10 diagnosis F32/F33	1.53	1	118	.219	
Interaction effect					
Time × Group	0.20	1	118	.656	
Time × ICD-10 diagnosis F32/F33	0.01	1	118	.934	
Time × Group × ICD-10 diagnosis F32/F33	5.57	1	118	**.020**	0.045
Group × ICD-10 diagnosis F32/F33	0.03	1	118	.865	
BSI					
Main effect					
Time	216.64	1	118	**<.001**	0.647
Group	0.13	1	118	.724	
ICD-10 diagnosis F32/F33	0.96	1	118	.330	
Interaction effect					
Time × Group	0.66	1	118	.418	
Time × ICD-10 diagnosis F32/F33	1.83	1	118	.179	
Time × Group × ICD-10 diagnosis F32/F33	6.34	1	118	**.013**	0.051
Group × ICD-10 diagnosis F32/F33	0.08	1	118	.773	
HAMD					
Main effect					
Time	96.01	3.69	351.77	**< .001**	0.503
Group	0.26	1	95	.609	
ICD-10 diagnosis F32/F33	3.93	1	95	.050	
Interaction effect					
Time × Group	3.14	3.69	351.77	**.017**	0.032
Time × ICD-10 diagnosis F32/F33	0.55	3.69	351.77	.688	
Time × Group × ICD-10 diagnosis F32/F33	1.17	3.69	351.77	.325	
Group × ICD-10 diagnosis F32/F33	1.77	1	95	.187	
SCL-K9					
Main effect					
Time	60.47	3.33	322.77	**<.001**	0.384
Group	0.06	1	97	.805	
ICD-10 diagnosis F32/F33	0.23	1	97	.635	
Interaction effect					
Time × Group	0.78	3.33	322.77	.517	
Time × ICD-10 diagnosis F32/F33	0.45	3.33	322.77	.735	
Time × Group × ICD-10 diagnosis F32/F33	2.74	3.33	322.77	**.038**	0.027
Group × ICD-10 diagnosis F32/F33	0.42	1	97	.519	

The effect size partial-η^2 is only reported for significant results; BDI = Beck's Depression Inventory, BSI = Brief Symptom Inventory, HAMD = Hamilton Rating Scale for Depression, SCL-K9 = short version of the Symptom Check List

Table 5. Hamilton Rating Scale for Depression (HAMD) in patients with ICD-10 F32 and F33 at t0 and t5 for the different Neuropatterns (total sample size N = 51, patients could qualify for more than one Neuropattern)

	HAMD		
		t0	*t5*
	n	*Mean (SD)*	*Mean (SD)*
CRF-hypoactivity	6	26.17 (5.23)	7.83 (3,13)
CRF-hyperactivity	11	22.00 (7.47)	12.36 (5.61)
CRF-hyperreactivity	15	22.93 (5.96)	9.13 (6.13)
NA-hypoactivity	11	25.27 (5.78)	13.91 (5.49)
NA-hyperactivity	18	24.11 (4.42)	10.06 (5.40)
NA-hyperreactivity	23	22.78 (7.20)	11.00 (5,74)
Serotonin-hypoactivity	33	25.12 (4.61)	11.76 (5,32)
Serotonin-hyperreactivity	36	24.72 (5.06)	11.28 (6.08)
Cortisol-hypoactivity	3	24.33 (5.13)	8.00 (6.08)
Cortisol-hyperactivity	0	---	---
Sympathetic hyperactivity	4	23.25 (5.68)	13.00 (7.66)
Sympathetic hyperreactivity	3	19.33 (2.08)	4.67 (2.08)
GR-resistance	4	23.00 (6.48)	17.00 (5.60)

CRF = corticotropin releasing factor, NA = noradrenaline, GR = glucocorticoid receptor

Highlights

- Neuropattern: Diagnostic tool applying conceptual endophenotypes of stress response network
- Facilitates the detection and treatment of stress-related disorders
- Faster decline of depression score under Neuropattern based treatment compared to standard care in inpatients suffering from major depression.