Chapter 8

Increased psychopathology and maladaptive personality traits, but normal cognitive functioning, in patients after long-term cure of acromegaly

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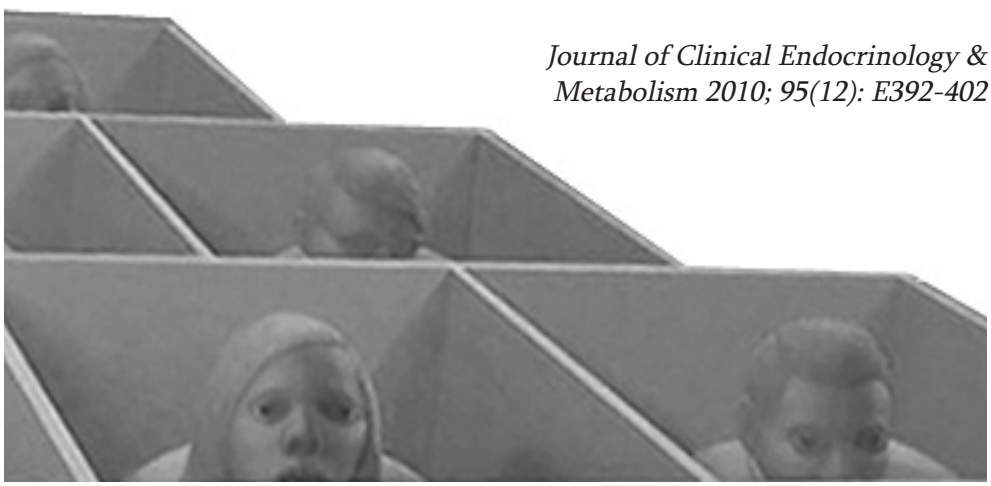
Journal of Clinical Endocrinology & Metabolism 2010; 95(12): E392-402



Abstract

Objective: Active acromegaly is associated with psychopathology, personality changes, and cognitive dysfunction. It is unknown whether, and to what extent, these effects are present after long-term cure of acromegaly.

Aim: The aim of the study was to assess psychopathology, personality traits, and cognitive function in patients after long-term cure of acromegaly.

Design: This was a cross-sectional study.

Patients and Methods: We studied 68 patients after long-term cure (13±1yr) of acromegaly and 68 matched controls. We compared these data with 60 patients treated for nonfunctioning pituitary macroadenomas (NFMAs) and 60 matched controls. Psychopathology was assessed using the Apathy Scale, Irritability Scale, Hospital Anxiety and Depression Scale, and Mood and Anxiety Symptoms Questionnaire short-form, and personality was assessed by the Dimensional Assessment of Personality Pathology short-form (DAPPs). Cognitive function was assessed by 11 tests.

Results: Compared with matched controls, patients cured from acromegaly scored significantly worse on virtually all psychopathology questionnaires and on several subscales of the DAPPs. Compared with NFMA patients, patients cured from acromegaly scored worse on negative affect ($P=0.050$) and somatic arousal ($P=0.009$) and seven of 18 subscales of the DAPPs ($P<0.05$). Cognitive function in patients cured from acromegaly did not differ from matched controls or patients treated for NFMA.

Conclusion: Patients with long-term cure of acromegaly show a higher prevalence of psychopathology and maladaptive personality traits but not cognitive dysfunction, compared with matched controls and patients treated for NFMA. These results suggest irreversible effects of previous GH excess, rather than effects of pituitary adenomas per se and/or their treatment, on the central nervous system.

Introduction

Acromegaly is associated with typical signs and symptoms caused by excess of GH and IGF-I. Almost 60yr ago, Bleuler (1, 2) reported that patients with active acromegaly and acromegalic patients after radiotherapy were often dull and apathetic and sometimes had an irritable mood. Subsequently other studies documented that patients with active acromegaly suffer from cognitive dysfunction, personality changes, and various forms of psychopathology (3–7). These observations suggest that the central nervous system is also involved in the clinical syndrome of active acromegaly. This notion is supported by the presence of GH receptors in various brain areas outside the classical pathways of the GH-IGF-I axis (8). Some of these structures are crucial for cognitive function and influence mental status and personality through connections with the limbic system and frontal lobe (9).

Many of the systemic changes induced by previous excess of GH and/or IGF-I are not completely reversed on successful biochemical treatment of active acromegaly (10), which may also be true for the effects of GH and/or IGF-I on the central nervous system. For instance, 36% of the patients with long-term cure of acromegaly showed elevated scores for anxiety and depression (11). We hypothesized that some of the effects of GH and/or IGF-I excess on the central nervous system might be irreversible. Therefore, the aim of the present study was to assess whether previous GH and/or IGF-I excess is associated with psychopathology, maladaptive personality traits, and cognitive dysfunction. We compared psychopathology, personality traits, and cognitive function between patients with long-term cure of acromegaly and gender-, age-, and education-matched controls. To assess to what extent treatment of pituitary adenomas per se affected our parameters, we additionally compared patients with long-term cure of acromegaly to patients treated for nonfunctioning pituitary macroadenomas (NFMAs).

Patients and Methods

Patients

We included four groups of subjects: 1) patients with long-term cure of acromegaly, and 2) age-, gender-, and education-matched control subjects for these patients with previous acromegaly, 3) patients previously treated for NFMA, and 4) age-, gender-, and education-matched control subjects for the patients previously treated for NFMA. The inclusion of two separate control groups was necessary because patients with acromegaly and patients treated for NFMA differ with respect to age and distribution of level of education.

Inclusion criteria were a history of acromegaly or NFMA, treatment by transsphenoidal surgery, age above 18yr, and remission of acromegaly defined by strict biochemical criteria (12). Exclusion criteria were a low Mini-Mental State Examination (MMSE) score, present or previous drug or alcohol abuse, and neurological disorders, not related to acromegaly or NFMA, because of potential interference with mental status, personality, and cognition.

We asked all eligible patients followed up in our institution to participate. Each patient was asked to provide a control subject of comparable gender, age, and educational level. When patients did not respond to our invitation within 3 wk, we encouraged them by phone to participate. The response rate was 93%. Of all patients (n=164) who were contacted to participate in this study, 92 patients were interested, of whom 68 completed all questionnaires and cognitive tests. Sixty patients preferred not to participate, and 12 patients did not respond. The clinical characteristics of the patients who did not participate were not different from those of the participating patients. Reasons for not participating were remote distance to our institution, participation in other studies, old age, and debilitating disease. None of the subjects stopped participation during the study at a later stage.

The diagnosis of acromegaly had been established by clinical signs and symptoms and biochemical tests, including impaired suppression of GH during glucose tolerance test and increased IGF-I levels for age. Cure of acromegaly was defined by normal serum IGF-I levels for age and serum GH levels less than 1.9μg/l for all patients and, in patients without somatostatin analog treatment, also by normal suppression of GH levels (<0.38μg/liter) during a glucose tolerance test (13). Remission was confirmed by repeating the tests at yearly intervals. Patients were followed up at our outpatient department, and pituitary hormone replacement was prescribed dependent on the results of the yearly evaluation of pituitary functions (see below).

In addition, we invited 133 patients previously treated by transsphenoidal surgery for nonfunctioning pituitary macroadenomas to participate. Each patient was asked to provide a control of comparable gender, age, and educational level, who was evaluated on the same day as the patient. The response rate was 96%. Eighty-four patients agreed to participate in this study, of whom 60 filled out all questionnaires and completed all cognitive tests. Forty-three patients preferred not to participate, and six patients did not respond. There were no differences in clinical characteristics between the patients who decided to participate and those who decided not to participate. None of the subjects stopped participation during the study at a later stage.

Pituitary function was assessed in patients treated for acromegaly or NFMA at yearly intervals by experienced clinical endocrinologists. This evaluation consisted of measurement of free T_4 and testosterone/SHBG (male patients) levels. If

these laboratory results were below the lower limit of the respective reference ranges, substitution with L-T_4 and/or testosterone was prescribed. In the case of amenorrhea and low estradiol levels in premenopausal women, estrogen replacement was prescribed. Corticotrope function was assessed by appropriate stimulation tests, including a CRH stimulation test or an insulin tolerance test. Normal cortisol reserve was defined by stimulated cortisol concentrations greater than 550nmol/l. In cortisol-deficient patients, the hydrocortisone dose was on average 20mg/d divided into two to three dosages. Evaluation of GH deficiency was performed by an insulin tolerance test and/or a GHRH-arginine test, only in patients under the age of 70yr and only after at least 2yr of remission. In NFMA patients with inadequate stimulation of GH levels by one of these tests, treatment with recombinant human (rh) GH was prescribed, aiming at IGF-I levels between 0 and +2 SD values. Patients previously treated for acromegaly were tested with the same tests (14), but in case of GH deficiency, these patients were treated with rhGH from 2005 onward during a controlled trial of rhGH replacement (15).
The protocol was approved by the Medical Ethics Committee of the Leiden University Medical Center, and written informed consent was obtained from all subjects.

Study design

The study consisted of a single study visit, during which each participant participated in a structured interview and performed the cognitive tests. Furthermore, patients and controls were asked to complete five questionnaires on psychopathology and personality traits at home and to return these in a prepaid envelope.

Questionnaires

Apathy Scale

Apathy was assessed by the Apathy Scale that consists of 14 questions on a 4-point scale measuring different features of apathy in the 2 previous weeks. The total score of this scale ranges from 0 to 42 points, with higher scores indicating greater apathy. Apathy is defined by a total score of 14 points or more (16, 17).

Irritability Scale

Irritability was assessed by the Irritability Scale that consists of 14 items on a 4-point scale, which assesses different features of irritability in the 2 previous weeks. The total score ranges from 0 to 42 points, with higher scores indicating greater irritability. Irritability is defined by a total score of 14 points or more (17).

Hospital Anxiety and Depression Scale (HADS)
Anxiety and depression were assessed by the HADS that consists of 14 items on a 4-point scale. Both anxiety and depression subscale scores range from 0 to 21 points. Higher scores indicate more severe anxiety and/or depression. Anxiety or depression is defined by total scores more than 13 points on the respective subscales (18, 19).

Mood and Anxiety Symptoms Questionnaire short-form (MASQ-30)
The MASQ-30 consists of 30 items to assess symptoms of mood and anxiety disorders subdivided into the three subscales: negative affect, lack of positive affect, and somatic arousal. The scores of each subscale range from 10 to 50, with higher scores indicating more severe negative affect, more positive affect, or more somatic arousal. There are no formal cutoff scores for these subscales (20, 21).

Dimensional Assessment of Personality Pathology short-form (DAPPs)
The DAPPs consists of 136 items assessing personality subdivided into 18 subscales: submissiveness, cognitive distortion, identity problems, affective lability, stimulus seeking, compulsivity, restricted expression, callousness, oppositionality, intimacy problems, rejection, anxiousness, conduct problems, suspiciousness, social avoidance, narcissism, insecure attachment, and self-harm. The score for each subscale differs with maxima of 30–40, and higher scores indicate more pronounced maladaptive personality traits. There are no formal cutoff scores for these subscales (22, 23).

Cognitive evaluation

Cognitive tests were used to assess the full spectrum of cognitive functioning. A functional classification was used to subdivide the 11 tests into the cognitive domains global cognitive functioning, memory, and executive functioning (24). The psychological evaluation took approximately 1.5handwasperformed in a predefined order. None of the patients required more than one session to complete all tests. The following tests were used: MMSE, Wechsler Memory Scale, Verbal Learning Test of Rey, Rey Complex Figure Test, Trail-Making Test, Stroop Color-Word Test, Letter-Digit Substitution Test, Digit-Deletion Test, Figure Fluency Test, FAS test, and the synonyms subtest of the Groninger Intelligence Test-2 (32–41).The description of these tests is included as an online supplement, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org.

Statistical analysis

Data were analyzed using PASW Statistics version 17.0.2 (SPSS Inc., Chicago, IL, USA). All data were presented as mean ± SD, unless mentioned otherwise. The primary analysis comprised the comparison of the results between patients cured of acromegaly and their matched controls and between the patients with NFMA and their matched controls. Groups were compared using a linear mixed model, with the matched patient-control pairs as random factor. For the clinical characteristics, a nonparametric χ^2 test was used in case of categorical data, and the Mann-Whitney test was used in case of continuous variables. Secondary analysis comprised the comparison of results in relation to patient and treatment characteristics. To compare patients treated for acromegaly and patients treated for NFMA, mean and SD scores for each questionnaire subscale were calculated for each control group, and subsequently Z-scores were calculated for each patient group in relation to their appropriate control group. The Z-scores were compared using a general linear model, with additional radiotherapy and hypopituitarism as fixed factors. Odds ratios were calculated using the (ad)/(bc) formula. The odds ratios represent the odds of a score above the cutoff score in a specific questionnaire in the acromegaly or NFMA group to the odds of a score above the cutoff score in the matched controls. Independent variables affecting psychopathology and personality in patients cured of acromegaly were explored by stepwise linear regression analysis. The standardized β-coefficients of this analysis were reported. The level of significance was set at $P \leq 0.05$.

Results

Patient characteristics

Patients with long-term cure of acromegaly

All patients (n=68) had been treated by transsphenoidal surgery and 15 patients (22%) had been treated by additional radiotherapy. Eleven patients (16%) were treated by somatostatin analogs, and two patients (3%) received pegvisomant therapy. All patients were in biochemical remission. Twenty-one percent of the patients had suffered from a microadenoma, 54% from a noninvasive macroadenoma, and 21% from an invasive macroadenoma. The mean duration of active disease before treatment was 7.4±0.7yr, whereas the mean duration of remission was 13.1±1.0yr. Mean GH levels before operation were 96±16μg/liter and mean IGF-I SD adjusted for gender and age was 8.5±0.8. The GH concentrations preoperatively are derived from the mean of four samples obtained with 30-min intervals during 2h (Table 1).

At the time of the current study, 29 patients (43%) required treatment for pitu-

Table 1 Clinical characteristics of patients with long term cure of acromegaly and of patients previously treated for NFMA

	Acromegaly patients (n=68)	NFMA patients (n=60)
Gender (male/female)	35/33	34/26
Age in years	59 (11)	62 (10)
Education (n)	Low: 34	Low: 20
	Medium: 8	Medium: 23
	High: 26	High: 17
Transsphenoidal surgery, n (%)	68 (100%)	60 (100%)
Additional radiotherapy, n (%)	15 (22%)	27 (45%)
Somatostatin analogue therapy, n (%)	11 (16%)	NA
Pegvisomant therapy, n (%)	2 (3%)	NA
Duration active disease, yr (se)	7.4 (0.7)	NA
Duration of remission/follow-up, yr (se)	13.1 (1.0)	13.5 (1.4)
Hypopituitarism, n (%)	Any axis: 29 (43%)	Any axis: 56 (93%)
	GH: 16 (24%)	GH: 46 (77%)
	LH/FSH: 13 (19%)	LH/FSH: 34 (57%)
	TSH: 17 (25%)	TSH: 40 (67%)
	ACTH: 21 (31%)	ACTH: 40 (67%)
GH level before operation (se)	96 µg/liter (16)	NA

Data are mean ± SD unless otherwise mentioned, NA; not applicable, se; standard error of the mean

itary insufficiency, and 16 patients (24%) were treated for GH deficiency with rhGH. There were no differences between patients and controls in gender, age, and education level. During the interview, 44% of the patients reported memory problems in daily life, and 25% reported problems in executive functioning.

Patients treated for nonfunctioning pituitary macroadenomas

All patients (n=60) had previously been treated by transsphenoidal surgery and 27 patients (45%) also by postoperative radiotherapy. Fifty-six patients (93%) required treatment for pituitary insufficiency, and 46 NFMA patients (77%) were on rhGH replacement therapy. There were no differences between patients and controls in gender, age, and education level (Table 1). During the interview, 37% of the patients reported memory problems in daily life, and 27% reported problems in executive functioning.

Psychopathology, personality traits, and cognitive function

Patients with long-term cure of acromegaly versus their matched controls

Patients with long-term cure of acromegaly scored worse compared with matched controls on the Apathy Scale (P=0.001), the Irritability Scale (P=0.006), the anxiety and depression subscales of the HADS (P=0.031, and P=0.003, respectively), and the somatic arousal subscale of the MASQ-30 (P=0.042). There were no differences on the negative and positive affect subscales of the MASQ-30 between pa-

tients and controls. Furthermore, patients with cured acromegaly scored worse on the affective lability (P=0.003), oppositionality (P=0.012), anxiousness (P=0.030), and self-harm (P=0.042) subscales of the DAPPs (see also Table 2).
On the Apathy Scale, 47% of the patients with acromegaly (odds ratio 3.3) had a score of 14 or more, indicative for the presence of clinically significant apathy, whereas 35% of the patients (odds ratio 2.0) had a score of 14 or more on the Irritability Scale, indicative for the presence of clinically significant irritability. On the HADS, 19% of the patients with cured acromegaly (odds ratio 2.1) scored greater than 13, indicative for the presence of clinically relevant depression or anxiety. There were significantly more patients than controls with clinically relevant scores on the Apathy Scale (P=0.001) but not on the other questionnaires.
The data on cognitive function are included as a supplemental table (Supplemental Table 1). There were a few significant differences between patients and controls in cognitive functioning. Patients with long-term cure of acromegaly scored significantly worse on only one verbal memory test, in which they remembered fewer words than controls in two of three trials (P=0.017 and P=0.012). Furthermore, patients performed worse on all aspects of a verbal fluency test (P=0.020).

Patients treated for NFMA versus their controls
Patients treated for NFMA scored worse only on the Apathy scale (P=0.001) and on the depression subscale of the HADS compared with their matched controls (P<0.001). On the DAPPs, NFMA patients scored worse on the trait affective lability (P=0.011), compared with controls (Table 3).
On the apathy scale, 40% of the NFMA patients (odds ratio 2.4) scored 14 or more and 27% of the patients (odds ratio 1.8) scored 14 or more on the Irritability Scale. Twenty-five percent of the patients (odds ratio 4.4) scored greater than 13 on the HADS. There were significantly more patients than controls with a clinically relevant score on the Apathy Scale and the HADS (P=0.034 and P=0.005, respectively).
The data on cognitive function are included as a supplemental table (Supplemental Table 2). There were hardly any differences between patients and controls in tests of cognitive function. Patients treated for NFMA scored better on the MMSE (P=0.013) but could remember fewer words on one of three trials measuring verbal memory (P=0.043). Furthermore, patients made more errors on one of two trials of the Trail-Making Test (P=0.007).

Table 2 Psychopathology and personality traits in patients with long term cure of acromegaly and their matched controls

	Acromgaly (n=68)	Matched controls (n=68)	P-value
Apathy Scale			
Total score	13.8 (6.1)	10.5 (4.8)	**0.001**
Score ≥14, n(%)	32 (47%)	14 (21%)	**0.001**
Irritability Scale			
Total score	12.7 (7.7)	9.5 (5.7)	**0.006**
Score ≥14, n(%)	24 (35%)	14 (21%)	0.056
HADS			
Anxiety	5.0 (3.7)	3.8 (3.1)	**0.031**
Depression	4.3 (4.2)	2.4 (2.8)	**0.003**
Score >13, n(%)	13 (19%)	7 (10%)	0.146
MASQ-30			
Negative Affect	16.6 (6.0)	15.1 (5.1)	0.126
Positive Affect	28.4 (8.8)	30.6 (8.2)	0.089
Somatic Arousal	14.6 (5.4)	12.9 (4.3)	**0.042**
DAPP			
Submissiveness	17.1 (6.2)	15.8 (5.0)	0.160
Cognitive distortion	9.9 (3.8)	8.8 (2.7)	0.055
Identity problems	11.0 (4.9)	9.8 (4.1)	0.128
Affective lability	19.2 (6.5)	16.0 (5.8)	**0.003**
Stimulus seeking	13.9 (4.0)	14.9 (5.0)	0.218
Compulsivity	22.3 (6.8)	21.8 (6.6)	0.653
Restricted expression	20.5 (6.3)	20.1 (5.7)	0.680
Callousness	16.5 (5.4)	16.0 (5.2)	0.558
Oppositionality	22.2 (7.4)	19.2 (6.4)	**0.012**
Intimacy problems	20.2 (7.4)	18.2 (5.6)	0.084
Rejection	18.9 (6.0)	18.7 (5.9)	0.776
Anxiousness	14.0 (5.3)	12.2 (4.3)	**0.030**
Conduct problems	9.8 (2.5)	9.6 (2.7)	0.616
Suspiciousness	11.2 (3.8)	12.1 (4.7)	0.206
Social avoidance	12.1 (5.3)	11.5 (4.5)	0.455
Narcissism	15.5 (5.8)	14.6 (4.9)	0.306
Insecure attachment	13.1 (6.0)	13.0 (5.6)	0.940
Self-harm	7.6 (3.8)	6.6 (2.0)	**0.042**

Data are mean (SD), unless otherwise mentioned

Supplementary Table 1 Cognitive outcomes: patients cured from acromegaly *vs* matched controls

		Acromegaly (n=68)	Matched Controls (n=68)	P-value
Global cognitive function				
MMSE	Score	28.3 (1.7)	28.2 (1.8)	0.722
Memory				
Wechsler Memory Scale	Memory Quotient	112.7 (17.2)	113.7 (15.8)	0.694
	Information	5.8 (0.4)	5.9 (0.3)	0.618
	Orientation	4.9 (0.3)	4.9 (0.3)	1.00
	Concentration	7.4 (1.7)	7.2 (1.8)	0.466
	Logical memory	6.8 (4.0)	6.8 (3.0)	
	Digit span	9.6 (1.9)	9.9 (1.9)	0.350
	Visual memory	8.6 (2.8)	8.5 (3.3)	0.744
	Associative learning	15.0 (3.6)	16.2 (2.8)	**0.017**
Verbal Learning Test of Rey	Imprinting, total	5.1 (1.9)	5.2 (2.2)	0.608
	Immediate, total	9.0 (2.6)	9.8 (2.5)	**0.027**
	Delayed, total	6.6 (3.1)	7.7 (3.2)	**0.012**
Rey Complex Figure test	Immediate	17.8 (5.4)	18.3 (6.9)	0.602
	Delayed	17.6 (5.5)	17.8 (7.0)	0.887
Executive functioning				
Trail making test	Trail A, time	0.4 (0.3)	0.4 (0.2)	0.537
	Trail A, errors	0.1 (0.4)	0.2 (0.4)	0.621
	Trail B , time	1.3 (0.8)	1.2 (0.9)	0.625
	Trail B, errors	0.6 (1.7)	0.8 (2.4)	0.649
Stroop color-word test	Interference, total	38.1 (10.0)	40.1 (10.0)	0.251
	Interference, mistakes	1.4 (5.7)	0.3 (0.7)	0.105
Letter-digit substitution test	# correct	31.2 (7.7)	31.7 (7.7)	0.657
	# errors	0.1 (0.3)	0.6 (3.9)	0.305
Digit-deletion test	# correct	376.1 (89.0)	395.0 (85.5)	0.188
	# missed	4.7 (4.2)	4.5 (5.5)	0.766
Figure Fluency	# patterns	58.0 (24.0)	57.6 (22.3)	0.906
	% repeats	11.3 (12.5)	8.3 (9.0)	0.120
	% errors	18.4 (15.2)	17.7 (14.8)	0.751
FAS	# correct	32.0 (13.3)	37.3 (13.9)	**0.019**
	% repeats	1.1 (1.9)	2.1 (3.1)	**0.015**
	% errors	4.0 (5.1)	1.7 (3.0)	**0.002**
Groninger Intelligence test	Synonyms score	4.5 (2.0)	4.9 (1.8)	0.132

Data are mean (SD)

Table 3 Psychopathology and personality traits in patients treated for NFMA and their matched controls

	NFMA patients (n=60)	Matched controls (n=60)	P-value
Apathy Scale			
Total score	13.1 (5.0)	10.4 (3.7)	**0.001**
Score ≥14, n(%)	24 (40%)	13 (22%)	**0.034**
Irritability Scale			
Total score	9.9 (5.7)	8.5 (5.3)	0.175
Score ≥14, n(%)	16 (27%)	10 (17%)	0.200
HADS			
Anxiety	4.5 (3.6)	3.6 (3.1)	0.131
Depression	4.1 (3.9)	1.9 (2.2)	**0.000**
Score >13, n(%)	15 (25%)	4 (7%)	**0.005**
MASQ-30			
Negative Affect	15.5 (5.7)	15.1 (5.6)	0.739
Positive Affect	29.6 (8.5)	30.5 (8.2)	0.562
Somatic Arousal	14.7 (5.2)	14.3 (4.8)	0.715
DAPP			
Submissiveness	16.7 (5.8)	16.9 (6.2)	0.832
Cognitive distortion	9.6 (4.0)	9.9 (4.8)	0.647
Identity problems	10.2 (4.9)	9.3 (4.3)	0.310
Affective lability	18.3 (5.7)	15.7 (5.7)	**0.011**
Stimulus seeking	14.6 (4.7)	14.7 (5.4)	0.861
Compulsivity	21.9 (6.8)	21.0 (5.8)	0.441
Restricted expression	21.6 (4.6)	20.5 (5.6)	0.227
Callousness	16.6 (4.6)	15.8 (4.3)	0.369
Oppositionality	20.6 (6.7)	19.2 (6.1)	0.242
Intimacy problems	20.0 (6.5)	20.3 (6.2)	0.810
Rejection	19.0 (11.1)	17.2 (5.7)	0.258
Anxiousness	12.8 (4.6)	12.3 (4.8)	0.542
Conduct problems	9.6 (2.7)	9.4 (2.3)	0.765
Suspiciousness	10.9 (3.4)	11.2 (4.0)	0.590
Social avoidance	11.1 (3.9)	10.3 (3.9)	0.232
Narcissism	15.5 (5.0)	14.7 (5.0)	0.378
Insecure attachment	12.9 (5.1)	12.6 (5.3)	0.827
Self-harm	6.9 (2.4)	6.4 (1.7)	0.199

Data are mean (SD), unless otherwise mentioned

Comparison of Z-scores between patients cured from acromegaly and patients treated for NFMA

Patients with long-term cure of acromegaly had higher scores on the negative affect subscale (P=0.05) and the somatic arousal subscale (P=0.009) of the HADS compared with treated NFMA patients. Furthermore, in comparison with NFMA

Supplementary Table 2 Cognitive outcomes: patients cured from NFMA *vs* matched controls

		NFMA (n=60)	Matched Controls (n=60)	P-value
Global cognitive function				
MMSE	Score	28.9 (1.1)	28.3 (.8)	**0.013**
Memory				
Wechsler Memory Scale	Memory Quotient	119.0 (16.7)	119.2 (14.2)	0.999
	Information	5.9 (0.3)	5.9 (0.3)	0.721
	Orientation	4.9 (0.3)	4.9 (0.2)	0.788
	Concentration	7.6 (1.8)	7.5 (1.4)	0.812
	Logical memory	7.4 (3.2)	7.5 (2.7)	
	Digit span	10.1 (1.6)	10.0 (1.6)	0.818
	Visual memory	8.9 (3.4)	8.7 (3.4)	0.686
	Associative learning	15.8 (2.9)	16.4 (3.2)	0.250
Verbal Learning Test of Rey	Imprinting, total	5.1 (1.8)	5.3 (1.9)	0.546
	Immediate, total	9.1 (2.9)	9.8 (2.1)	0.122
	Delayed, total	6.6 (3.4)	7.8 (2.8)	**0.043**
Rey Complex Figure test	Immediate	19.5 (6.8)	19.5 (6.1)	0.889
	Delayed	19.3 (6.4)	19.3 (6.3)	0.902
Executive functioning				
Trail making test	Trail A, time	0.6 (0.4)	0.5 (0.4)	0.109
	Trail A, errors	0.3 (0.5)	0.1 (0.3)	**0.007**
	Trail B , time	1.5 (0.7)	1.3 (0.7)	0.072
	Trail B, errors	0.6 (1.3)	0.5 (0.9)	0.641
Stroop color-word test	Interference, total	36.0 (8.4)	37.2 (8.0)	0.407
	Interference, mistakes	0.2 (0.4)	0.2 (0.5)	0.953
Letter-digit substitution test	# correct	30.7 (8.3)	31.1 (7.0)	0.721
	# errors	0.0 (0.2)	0.1 (0.4)	0.126
Digit-deletion test	# correct	358.4 (77.9)	382.2 (74.9)	0.054
	# missed	3.8 (4.2)	4.7 (4.6)	0.222
Figure Fluency	# patterns	48.1 (21.3)	54.6 (21.9)	0.083
	% repeats	8.9 (8.8)	6.6 (6.3)	0.107
	% errors	20.3 (11.3)	22.2 (15.4)	0.376
FAS	# correct	33.4 (12.9)	32.7 (11.4)	0.779
	% repeats	1.1 (2.0)	1.1 (2.0)	0.619
	% errors	2.2 (5.7)	1.8 (3.0)	0.873
Groninger Intelligence test	Synonyms score	5.2 (1.9)	4.9 (1.8)	0.395

Data are mean (SD)

patients, acromegaly patients scored worse on the submissiveness (P=0.049), cognitive distortion (P=0.001), identity problems (P=0.036), affective lability (P=0.044), oppositionality (P=0.025), anxiousness (P=0.005), and self-harm (P=0.008) subscales of the DAPPs. This is depicted in Figure 1 and Figure 2.
Patients with long-term cure of acromegaly scored worse on two aspects of executive functioning tests measuring attention, compared with NFMA patients, on which they worked more slowly (P=0.015) and made more mistakes (P=0.042). The memory tests were not different between the patient groups. The data on cognitive function are included as a supplemental table (Supplemental Table 3).

Comparison of psychopathology of patients with long-term cure of acromegaly and patients with NFMA by Z-scores, calculated for each patient group by comparison with their own matched control groups (i.e. Z-score of 0.0).

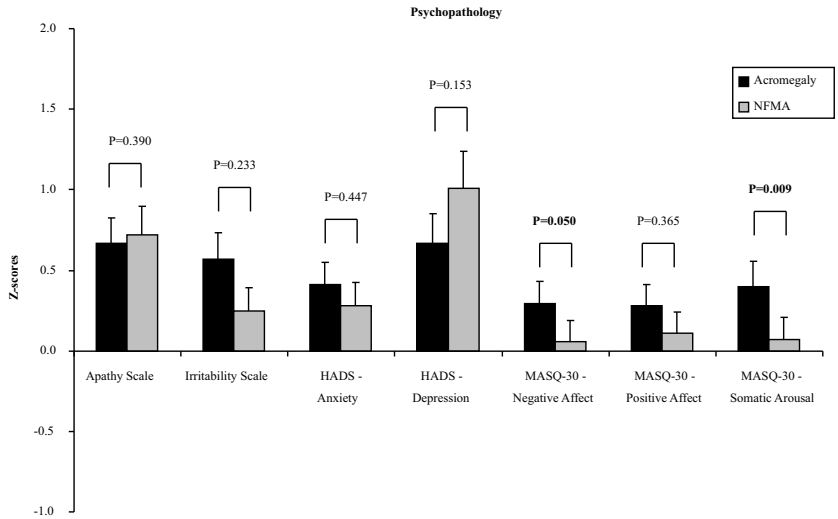


Figure 1: *Z-scores of patients cured of acromegaly and patients treated for NFMA, calculated for each patient group by comparison with their own matched control groups. Z-scores with standard errors are given in this figure. On the negative affect subscale and somatic arousal subscale of the MASQ-30 patients with long-term cured acromegaly scored worse when compared with patients with treated NFMA.*

Comparison of personality of patients treated for acromegaly and patients treated for NFMA by Z-scores, calculated for each patient group by comparison with their own matched control groups (i.e. Z-score of 0.0).

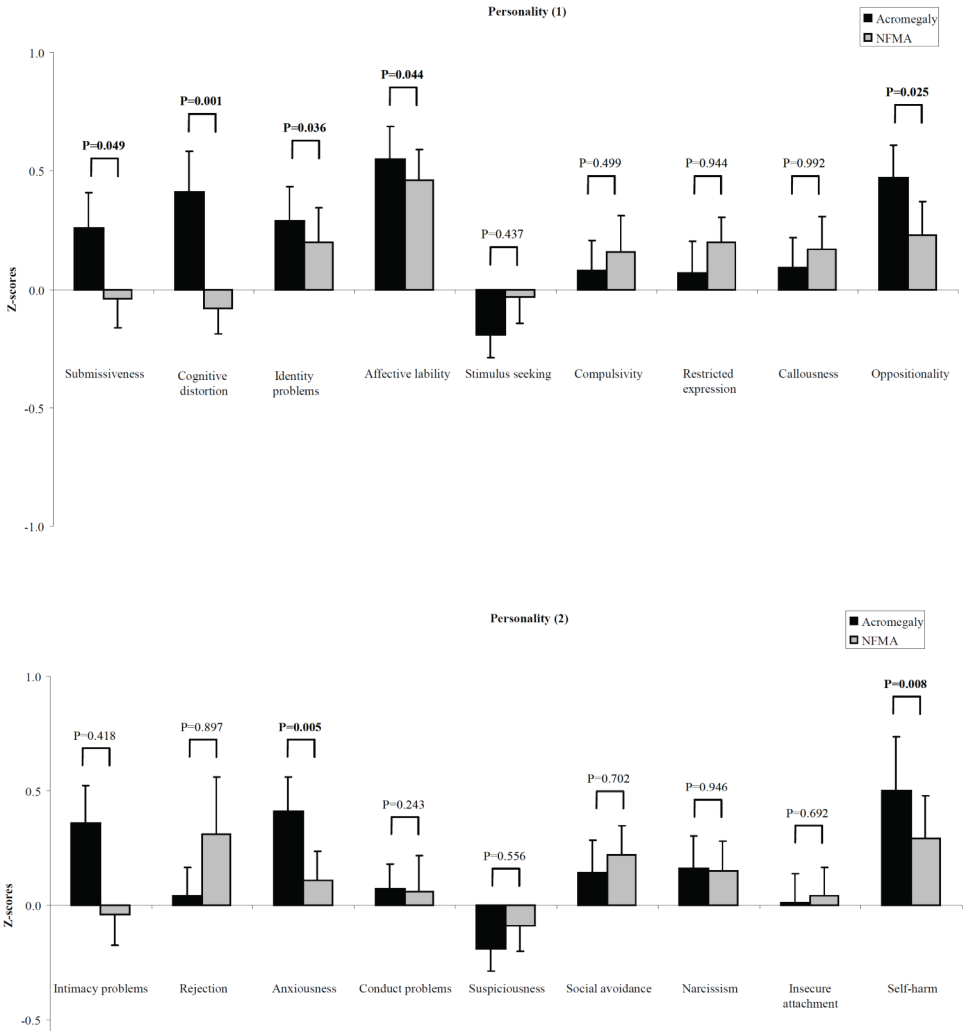


Figure 2: *Z-scores of patients cured of acromegaly and patients treated for NFMA, calculated for each patient group by comparison with their own matched control groups. Z-scores with standard errors are given in this figure. Patients with long-term cured acromegaly scored worse on the DAPP subscales submissiveness, cognitive distortion, identity problems, affective lability, oppositionality, anxiousness, and self-harm when compared with patients with treated NFMA.*

Supplementary Table 3. Cognitive function: comparison between patients with acromegaly and patients with NFMA by Z-scores, calculated for each patient group by comparison with their own matched controls

		Z-scores acromegaly (n=68)	Z-scores NFMA (n=60)	P-value
Global				
MMSE	Score	0.06 (-0.2 to 0.3)	0.35 (0.2 – 0.5)	0.236
Memory				
Wechsler Memory Scale	Memory Quotient	-0.06 (-0.3 to 0.2)	-0.01 (-0.3 to 0.3)	0.446
	Information	-0.09 (-0.4 to 0.2)	-0.04 (-0.4 to 0.3)	0.915
	Orientation	0.00 (-0.2 to 0.2)	-0.05 (-0.3 to 0.2)	0.794
	Concentration	0.11 (-0.1 to 0.3)	0.05 (-0.2 to 0.4)	0.652
	Logical memory	0.00 (-0.3 to 0.3)	-0.06 (-0.3 to 0.3)	0.828
	Digit span	-0.15 (-0.4 to 0.1)	0.04 (-0.2 to 0.3)	0.511
	Visual memory	0.05 (-0.2 to 0.2)	0.05 (-0.2 to 0.3)	0.417
	Associative learning	-0.41 (-0.7 to 0.1)	-0.19 (-0.4 to 0.1)	0.117
Verbal Learning Test of Rey	Imprinting, total	-0.07 (-0.3 to 0.1)	-0.11 (-0.4 to 0.2)	0.411
	Immediate, total	-0.34 (-0.6 to -0.1)	-0.34 (-0.7 to 0.1)	0.145
	Delayed, total	-0.36 (-0.6 to -0.1)	-0.41 (-0.7 to -0.1)	0.092
Rey Complex Figure test	Immediate	-0.07 (-0.3 to 0.1)	0.01 (-0.2 to 0.3)	0.051
	Delayed	-0.02 (-0.2 to 0.2)	0.00 (-0.2 to 0.3)	0.243
Executive function				
Trail making test	Trail A, time	0.09 (-0.2 to 0.4)	0.28 (0.0 – 0.5)	0.967
	Trail A, errors	-0.09 (-0.3 to 0.2)	0.75 (0.3 – 1.2)	0.406
	Trail B , time	0.07 (-0.2 to 0.3)	0.31 (0.0 – 0.6)	0.831
	Trail B, errors	-0.07 (-0.2 to 0.1)	0.11 (-0.3 to 0.5)	0.824
Stroop color-word test	Interference, total	-0.20 (-0.4 to 0.0)	-0.15 (-0.4 to 0.2)	0.345
	Interference, mistakes	1.55 (-0.3 to 3.5)	0.00 (-0.2 to 0.2)	0.355
Letter-digit substitution test	# correct	-0.07 (-0.3 to 0.2)	-0.06 (-0.3 to 0.3)	**0.018**
	# errors	-0.14 (-0.2 to -0.1)	-0.22 (-0.3 to -0.1)	0.325
Digit-deletion test	# correct	-0.22 (-0.5 to 0.0)	-0.32 (-0.6 to 0.0)	0.229
	# missed	0.05 (-0.1 to 0.2)	-0.19 (-0.4 to 0.0)	**0.042**
Figure Fluency	# patterns	0.02 (-0.2 to 0.3)	-0.30 (-0.5 to 0.0)	0.094
	% repeats	0.33 (0.0 – 0.7)	0.37 (0.0 – 0.6)	0.828
	% errors	0.05 (-0.2 to 0.3)	-0.13 (-0.3 to 0.0)	0.258
FAS	# correct	-0.38 (-0.6 to -0.1)	0.06 (-0.2 to 0.4)	0.148
	% repeats	-0.32 (-0.5 to -0.2)	0.03 (-0.2 to 0.3)	0.610
	% errors	0.77 (0.3 – 1.1)	0.14 (-0.4 to 0.4)	0.194
Groninger Intelligence test	Synonyms score	-0.22 (-0.5 to 0.0)	0.17 (0.0 – 0.5)	0.347

Data are Z-scores mean (95% CI)

Factors associated with psychopathology and personality traits in patients with cured acromegaly

Stepwise linear regression analysis was performed using the absolute test scores of the patients with long-term cure of acromegaly as dependent variables and pre-surgical GH level, pre-surgical IGF-I SD value, rhGH replacement therapy, somatostatin therapy, hypopituitarism, additional radiotherapy, duration of active disease, and duration of remission as independent variables.

The negative affect subscale of the MASQ-30 was negatively associated with hypopituitarism (β=-0.380, P=0.011), with hypopituitarism being associated with lower scores. The positive affect subscale of the MASQ-30 was negatively associated with radiotherapy (β=-0.348, P=0.022), which indicates that radiotherapy is associated with lower scores. However, only a small percentage of the patients received radiotherapy (22%, n=15), which makes it difficult to draw solid conclusions on the association between our parameters of interest and radiotherapy. Furthermore, the subscales compulsivity of the DAPPs (β=-0.334, P=0.027), restricted expression (β=-0.336, P=0.026), and insecure attachment (β=-0.307, P=0.043) were all negatively associated with rhGH replacement therapy, which means that patients who receive rhGH have a tendency to score lower on these subscales. The subscale oppositionality was positively associated with pre-surgical IGF-I SD value (β=0.323, P=0.033), which indicates that higher pre-surgical IGF-I SD values are associated with higher scores on oppositionality. The rejection subscale was negatively associated with pre-surgical GH level (β=-0.333, P=0.027), with higher preoperative GH levels being associated with a lower score. Anxiousness was negatively associated with duration of remission (β=-0.311,P=0.040), with longer duration of remission being associated with lower anxiousness.

Discussion

This study demonstrates that patients with long-term cure of acromegaly suffer from increased psychopathology and maladaptive personality traits, but hardly from increased cognitive dysfunction, compared with matched controls. Patients with long-term cure of acromegaly also showed more psychopathology, and especially more maladaptive personality traits, compared with patients treated for NFMA. These observations indicate that the increased psychopathology and maladaptive personality traits observed in patients with long-term cure of acromegaly are not merely caused by pituitary adenomas per se and/or their treatment, but rather by previous GH excess.

A direct comparison of parameters of interest between patients with long-term

cure of acromegaly and patients treated for NFMA is confounded by relevant differences in other clinical characteristics. Therefore, we included matched control subjects for each patient group. We calculated Z-scores for each patient group in comparison with their own matched controls. Subsequently we compared these Z-scores to detect possible differences between patients with acromegaly and NFMA patients. By using these Z-scores, we have carefully corrected for the differences in clinical characteristics between both groups of patients. We have used this approach for similar problems in the comparison of patients with Cushing's disease *versus* patients with NFMA (25, 26).

Table 4 summarizes the previous studies on psychopathology in patients with acromegaly. Previous studies on psychopathology in patients with active acromegaly reported affective disorders, fatigue, and loss of drive causing irritability and impatience (3). Most patients cured of acromegaly notice an increase in physical well-being (6), but they still have a high prevalence of psychological distress, especially anxiety disorders and major depression (27, 28), although another study found only increased prevalence of affective disorders (29). Limitations of those studies are the limited number of included patients, and heterogeneous clinical characteristics. Moreover, the effects of long-term cure of acromegaly have not been studied in detail.

Several previous studies assessed the effects of acromegaly on personality (Table 4). Patients with active acromegaly were characterized by industriousness, conscientiousness, and compulsiveness and sometimes lack of self-confidence (3). Furthermore, in patients with active acromegaly, a high need for sociability, high self-assuredness, and industry have been reported (4). After treatment, patients with acromegaly show a pattern of increased anxiety-related personality traits with reduced impulsivity and novelty-seeking behavior (30). Thus, those previous studies indicate that maladaptive personality traits are present in active and treated acromegaly patients.

Our study extends these results by indicating that maladaptive personality traits remain present after very long-term cure of acromegaly. Our study differs in several respects from previous studies. First, the number of patients included is relatively large in the present study compared with earlier studies. Second, the duration of cure was very long in our study compared with previous studies. Third, we compared patients with long-term cure of acromegaly both with matched controls and with patients previously treated for NFMA. From the current study, in addition to the studies summarized in Table 4, the notion emerges that patients with *active* acromegaly suffer from increased prevalence of psychopathology and maladaptive personality traits, and that long-term treatment of acromegaly results in some, but not complete, recovery of these parameters.

Patients with long-term cure of Cushing's disease suffer from impaired cognitive

functioning (25). This is in contrast to the current observations in patients with long-term cure of acromegaly. We speculate that these differences in cognitive function between patients with long-term cure of acromegaly and patients with long-term cure of Cushing's disease are explained by glucocorticoid specific irreversible effects on the central nervous system on structures involved in cognitive function, which are apparently not affected by previous GH and IGF-I excess.

In the present study, the outcomes of the questionnaires in patients with long-term cure of acromegaly were still well within the normal reference ranges of -2 SD and +2 SD (Figs. 1 and 2). Anecdotal reports have documented patients with pituitary disease and an apathy syndrome who had been incorrectly diagnosed as major depression and who had been treated accordingly with antidepressants for a long time (31). Our own subjective experiences in routine clinical practice suggest that there are subtle differences between the personalities of patients cured from acromegaly and those of patients with other pituitary diseases. However, clinical endocrinologists are not trained to detect subtle manifestations of psychopathology and maladaptive personality traits. We speculate that the results of our study confirm the clinical impression that patients cured from acromegaly have different and more serious complaints than patients with NFMA, even though patients treated for NFMA have a higher incidence of hypopituitarism.

In summary, patients with long-term cure of acromegaly have a high prevalence of psychopathology, compared with matched controls. Furthermore, patients with long-term cure of acromegaly have a greater degree of maladaptive personality traits, compared with both matched controls and patients treated for NFMA. These results suggest irreversible effects of previous GH excess on the brain, rather than effect of pituitary adenomas and/or their treatment in general.

Table 4 Overview of studies on psychopathology and personality in patients with acromegaly

Author, year	Number of subjects	Gender (m/f)	Age (yr), mean ± sd	Active/treated	Duration of disease control	Methods	Outcomes
Richert, 1983 (3)	Acromegaly: 20	4/16	uk	Controlled (10) Surgery (10) RT (0) SMS (0) Active (10)	6-9 months following transsphenoidal adenomectomy	H-W test, Luria test, Ravens test, D2-A test	Premorbid personality is very similar in all acromegalic patients. Psychopathological symptoms include fatigue and loss of drive. Postoperative: loss of drive and mental disorders improve. When GH is not normalized: more depression and anxiety.
Sablowski, 1986 (4)	Acromegaly: 9 Cushing's disease: 9 Prolactinoma: 6 CNS disease: 24	uk	uk	Active (9), measured again 1 week after surgery	Measured 2-4 days after hospitalisation and again 1 week post-surgery	FPI, Giessen test, STAI	Tendency to higher scores of trait-anxiety in adenoma patients compared to controls. Compared to other pituitary tumor patients; acromegaly patients show relatively little anxiety and depression, but show a high need for sociability, high self-assuredness, and industry.
Flitsch, 2000 (6)	Acromegaly:18 Cushing's disease: 19 NFMA: 11	12/6	46 ± 7	Active (18), measured again 6-8 months after surgery	Re-examined 6-8 months after surgery	Semi-structured interview, FPI, STAI, PFT, Bf-S, GBB	Fatigue and loss of energy were the most reported problems in acromegaly. After surgery, most patients noticed an increase in physical well-being.
Sonino, 2004 (27)	Acromegaly: 10 Other endocrine: 136	uk	39 ± 13 (all patients)	Controlled (10) Surgery (uk) RT (uk) SMS (uk)	Cured disease or in remission for at least 6 months	SCI DSM-IV, DCPR, PSI, MOS	81% of the total sample presented at least one psychiatric or psychological disorder. High prevalence of psychological distress in long-term follow-up endocrine patients. Most frequent findings: anxiety disorders and major depression.
Sonino, 2007 (28)	Acromegaly: 10 Other pituitary: 76 Non-pituitary: 60	uk	39 ± 12 (all patients)	Controlled (10) Surgery (4) RT (uk) SMS (7)	Cured disease or in remission for > 9 months < 3 years	SCI-DSM-IV, DCPR, PSI, MOS	Endocrine patients report more stressful life circumstances, psychological distress, abnormal illness behaviour and pain than controls. Endocrine patients show more psychopathology, psychological distress and impaired QoL after curation or remission when compared to controls.
Tanriverdi, 2008	Acromegaly: 18	7/11	40 ± 11	Active (18)	-	P300 auditory event	Mean P300 amplitude in acromegaly patients

(7)	GH deficiency: 19 Matched controls: 16					related potentials (ERPs)	significantly lower than in normal controls and GH deficiency patients. Negative correlation between IGF-I levels and P300 amplitudes. P300 amplitude is related to decision making and memory processing, which is lower in patients with acromegaly.
Sievers, 2009 (30)	Acromegaly: 70 NFMA: 58 Normal controls: 140	31/39	55 ± 11	Controlled (46) Surgery (65) RT (19) SMS (25) Active (24)	uk	EPQ-RK, TPQ	Compared to healthy controls, patients with acromegaly show a pattern of increased anxiety-related personality traits. Acromegaly seemed to be associated with reduced impulsivity and novelty-seeking behaviour.
Sievers, 2009 (29)	Acromegaly: 81 Controls with chronic somatic disorder: 3281 Controls without somatic disorder: 430	38/43	55	Controlled (47) Surgery (73) RT (20) Medical treatment (44) Active (34)	Mean time after surgery 10 yr	DIA-X/M-CIDI	Patients with acromegaly show increased prevalence of affective disorders (major depression and dysthymia), but not anxiety disorders.
Present study	Acromegaly: 68 Matched controls: 68 NFMA: 60 Matched controls: 60	35/33	59 ± 11	Controlled (68) Surgery (68) RT (15) SMS (11)	Duration of remission 13 ± 8 yr	Apathy Scale, Irritability Scale, HADS, MASQ-30, DAPP, MMSE, WMS, VLTR, RCFT, TMT, SCWT, LDST, DDT, FFT, FAS, GIT-synonyms	Patients with long-term cure of acromegaly show a higher prevalence of psychopathology and more maladaptive personality traits, but not more cognitive dysfunction compared to both matched controls and treated NFMA patients.

uk: unknown, RT: radiotherapy, SMS: somatostatin, H-W test: Hamburg-Wechsler test, D2-A test: d2-aufmerksamkeitstest, FPI: Freiburger personality inventory, STAI: State-trait-anxiety inventory, ROCFT: Rey-Osterrieth complex figure, COWAT: Controlled oral world association test, WMS: Wechsler memory scale, WRMT: Warrington recognition memory test, NART: National adult reading test, AVLT: Auditory verbal learning test, RMTF: Recognition memory test for faces, SNST: Stroop neuropsychological screening test, TMT: Trail making test, AMI: Autobiographical memory inventory, RMT: Recognition memory test, WAIS: Wechsler adult intelligence scale, NHP: Nottingham health profile, EPI: Eysenck personality inventory, PFT: Rosenzweig Picture frustration test, Bf-S: Befindlichkeitsskala, GBB: Giessener beschwerdebogen, RFC: Rey figure copy, SCOLP: Speed and capacity of language processing, EMQ: Everyday memory questionnaire, HADS: Hospital anxiety and depression questionnaire, GHQ: General health questionnaire, SF36: Short form health status questionnaire, GWBS: General well being schedule, SCI DSM-IV : Structural clinical interview for DSM-IV, DCPR: Diagnostic criteria for psychosomatic research, PSI: Psychosocial index, MOS: Medical outcomes study short form General health survey, EPQ-RK: Eysenck and cloninger personality questionnaire, TPQ: Tridimensional personality questionnaire, DIA-X/M-CIDI: Composite international diagnostic interview for DSM-IV, MASQ-30: Mood and anxiety symptoms questionnaire, DAPP: Dimensional assessment of personality pathology, MMSE: Mini mental state examination, VLTR: Verbal learning test of rey, RCFT: Rey complex figure test, SCWT: Stroop color word test, LDST: Letter-digit substitution test, DDT: Digit-deletion test, FFT: Figure fluency test, GIT: Groninger Intelligence test

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