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Psychiatric and cognitive function in patients with serotonin producing neuroendocrine tumors

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Cognitive and psychiatric problems are common in cancer patients, but literature on patients with neuroendocrine tumors (NET) is scarce. In a subset of these patients, the tumor produces serotonin, causing physical symptoms known as carcinoid syndrome. This peripheral overproduction of serotonin may cause central depletion of its precursor tryptophan, potentially resulting in cognitive and psychiatric problems. Therefore, we investigated cognitive and psychiatric function in patients with a serotonin overproduction and the association with this serotonin overproduction. Eighty-one patients with a serotonin-producing metastatic ileal NET underwent standardized neuropsychological and psychiatric assessment. Blood and urine samples were collected to determine concentrations of serotonin, its precursor tryptophan, and metabolite (5-HIAA). Multivariate normative comparison was applied to determine the prevalence of cognitive impairment. Separate linear regressions of serotonin, tryptophan, and 5-HIAA concentrations on cognitive function, depressive symptoms, and anxiety symptoms were performed, corrected for age, sex, education, and/or duration of illness. We found an 11% prevalence of cognitive impairment and a 20% prevalence of psychiatric disorders. Cognitive function was not related to measures of peripheral serotonin production. Unexpectedly, depressive symptoms were significantly associated with lower serum serotonin concentrations and elevated serum tryptophan concentrations. Cognitive symptoms of anxiety were also associated with elevated tryptophan concentrations. Concluding, cognitive or psychiatric problems occur in a minority of patients with NET and cannot be explained by tryptophan depletion following tumor-related serotonin production.

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INTRODUCTION

Cognitive and psychiatric problems frequently occur in patients with cancer, during or following their treatment, and can severely impair daily functioning and quality of life. About 30% of patients with a non-central nervous system cancer show cognitive impairments on neuropsychological tests, predominantly after systemic therapy, with memory, attention, and executive function most affected [1, 2]. Similarly, approximately 30–40% of patients experience clinically significant psychological distress, with an estimated point prevalence of depression between 6.5 and 14.3% [3, 4]. Factors consistently associated with depression in cancer are a previous episode of depression, lack of social support, and the cancer symptom burden including pain, inflammation, endocrine changes, and fatigue [5, 6].

Most research into cognitive and psychiatric function has focused on patients with breast cancer or other more common cancer types. Knowledge about cognitive and psychiatric function in patients with neuroendocrine tumors (NET) is limited. NET is a relatively rare cancer that develops from hormone secretive tissues [7]. Between 19 and 35% of patients with a NET present with excessive production of serotonin by tumor cells [8, 9], which can cause carcinoid syndrome, characterized by cutaneous flushing, diarrhoea, abdominal pain, and bronchospasms. Carcinoid syndrome has also been associated with neuropsychological and psychiatric symptoms, mainly based on case reports, but few empirical studies have been conducted [10].

Because NET is relatively rare, only small studies in patients with NET exist. Three studies investigated cognitive function in patients with carcinoid syndrome [11–13] using self-reported questionnaires and standardized neuropsychological tests. All three studies found cognitive problems across a wide range of cognitive functions. Patients themselves also reported complaints about their cognitive functioning.

Similarly, literature on psychiatric functioning in patients with NET is limited, with small sample sizes or the use of screening instruments instead of diagnostic interviews to assess prevalence of psychiatric problems. In studies using the Hospital Anxiety and Depression Scale (HADS) or derivatives to assess severity of

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depression and anxiety, the prevalence of moderate to severe depression or anxiety was 9–20% and 14–30%, respectively [14–16]. In contrast, when using psychiatric interviews in 20 carcinoid patients, 75% had an impulse control disorder and 15% had chronic but mild depressive symptoms [17].

Cognitive and psychiatric symptoms in patients with NET have been hypothesized to arise from tumor related serotonin [10], being a key neurotransmitter primarily important for the regulation of behaviour, mood, appetite, and sleep [18]. Serotonin dysfunction is implied in depression and anxiety disorders, largely based on the effectiveness of the medication that increases the availability of serotonin in the brain, although empirical evidence is mixed [19]. Serotonin cannot pass the blood-brain barrier, but the precursor tryptophan can enter the brain where it is synthesized to serotonin [20]. Therefore, cerebral serotonin synthesis depends on the systemic availability of tryptophan. In patients with a serotonin producing NET, approximately 60% of tryptophan intake is estimated to be used for peripheral serotonin production by tumor cells [21]. Consequently, this may deplete the central nervous system of tryptophan and hamper central serotonin production. In healthy controls, tryptophan depletion led to impaired verbal memory consolidation but did not affect other cognitive domains or mood [19, 22]. However, acute tryptophan depletion resulted in depressive symptoms in people with a positive personal or familial history of depression [19]. The central depletion of tryptophan and the resulting central serotonin deficit has been hypothesized to underlie the psychiatric symptoms and cognitive impairments observed in serotonin producing NET-patients [10]. Direct evidence from NET-patients supporting this theory is lacking.

Therefore, the aims of this study were 1) to systematically assess cognitive and psychiatric function with formal neuropsychological testing and psychiatric interviews in a large sample of patients with serotonin producing NET; and 2) to investigate the potential role of tumor-related serotonin production and tryptophan depletion as an underlying biological factor for cognitive and psychiatric symptoms in these patients.

MATERIALS & METHODS

Patients

Patients were diagnosed with a serotonin producing metastatic NET of the small intestine (SINET) and treated between 2010 and 2021 in the Netherlands Cancer Institute (NKI). To sample a variety of concentrations of serotonin, no cut-off was used for the serotonin concentration at time of study, as long as an elevated serotonin concentration was documented previously. Exclusion criteria were insufficient understanding of the Dutch language, a previous cerebrovascular accident, severe cognitive problems such as a diagnosis of dementia, or a delirium in the past three months. Patients using serotonin modulating medication, such as selective serotonin or serotonin and noradrenalin reuptake inhibitors (SSRI and SNRI) were excluded, since these medications are known to influence serum serotonin levels [23]. Patients with current chemotherapy or chemotherapy in the past 5 years were excluded from participation, as well as patients with a second malignancy in the past 5 years (except for adequately treated basal cell carcinoma of the skin), a life expectancy shorter than three months, or a severe psychiatric or neurological disorder that could interfere with neuropsychological testing, such as epilepsy, schizophrenia or autism (diagnosed before NET-diagnosis).

Procedures

Eligible patients were recruited through their NET physician or nurse practitioner. After informed consent, most patients had a hospital visit. For a few patients this was not possible, which was resolved by a house visit. One week before the visit, we sent questionnaires to be filled out beforehand. From four days until the day of the visit, patients followed a diet low in serotonin. During the visit, patients underwent neuropsychological assessment and psychiatric examination. Blood samples were collected to determine serotonin (5-HT), tryptophan (TRP) and 5-Hydroxyindoleacetic acid (5-HIAA). A 24-h urine sample was collected for determining urinary 5-HIAA excretion.

Demographic and illness related measures

The patients' medical records provided medical variables, including year of NET diagnosis and tumor burden as measured by chromogranin A levels. We additionally obtained demographic (age, gender, educational level) and illness related measures (current medication, previous use of psychoactive medication, previous psychiatric history, psychiatric family history, estimated delay time in diagnosis (i.e., time difference between first doctors visit and confirmed NET diagnosis)) before the start of the assessment.

Neuropsychological assessment

Based on previous findings on cognitive problems in NET patients and the availability of high-quality Dutch normative data for these tests, our neuropsychological test battery consisted of 7 neuropsychological tests: the Rey Auditory Verbal Learning (15WT) (Dutch version of the Rey Auditory Verbal Learning Test; [24]), Rivermead Behavioral Memory Test – Story recall (RBMT) [25], Trail Making Test A and B (TMT) [26], Stroop Color-Word Test [27], Lexical Fluency (LF) [28], Semantic Fluency (SF) [29], and Boston Naming Test (BNT) [30], covering the domains of memory, attention, executive function, and language. In addition, the Dutch version of the National Adult Reading Test (NART) [31] was included to assess premorbid intelligence and the Mini-Mental State Examination (MMSE) [32] as dementia screener. For a detailed overview of the tests' corresponding cognitive domains and outcome measures, see Supplementary Table 2. All tests were conducted in Dutch. Finally, the computerized Facial Expression Recognition Task (FERT) (P1vital®; www.p1vital.com) was administered to assess emotional processing, of which results will be reported elsewhere.

Psychiatric examination

Current and past psychiatric disorders were assessed with the Structured Clinical Interview for Diagnostic Statistical Manual-5 Disorders, Clinician Version (SCID-5-CV) [33], which has excellent reliability and clinical validity [34]. Prevalence of current disorders was assessed for the past month and lifetime, for mood disorders, anxiety disorders, stress related disorders, substance abuse disorders, and psychotic disorders. Additionally, we administered the Beck Anxiety Inventory (BAI) [35] and Inventory of Depressive Symptoms Self Report (IDS-SR) [36] to measure severity of anxious and depressive symptoms, respectively; the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-C30 (QLQ-C30) [37] and NET-specific EORTC QLQ-GINET-21 [38] to measure quality of life; and the Irritability Questionnaire (IRQ) [39] and State-Trait Anger Expression Inventory (STAXI-2) [40] to measure irritability and anger, respectively. We here report on findings from the SCID, BAI, and IDS only.

Biochemical measurement

Venous blood samples were collected in vacutainer tubes: RST for 5-HT, SST for TRP and 5-HIAA, and EDTA for thrombocyte count (all Becton Dickinson). Serum was obtained after centrifugation at 2500 g for 10 min for RST tubes and 1700 g for 10 min. Serum samples were stored at −20 °C until analyses. 5-HT concentration was expressed per circulating platelets and therefore platelet count was performed from EDTA anti-coagulated tube on Xn2000 analyser (Sysmex) within an hour after blood collection. The 24-h urine samples were collected using 3 L brown polypropylene bottles containing 250 mg each of $Na_2S_2O_5$ and EDTA as stabilizers. Urine samples were acidified to pH 4.0 with acetic acid and stored at −20 °C. 5-HT in serum as analysed by the method used in routine clinical practice at the Netherlands Cancer

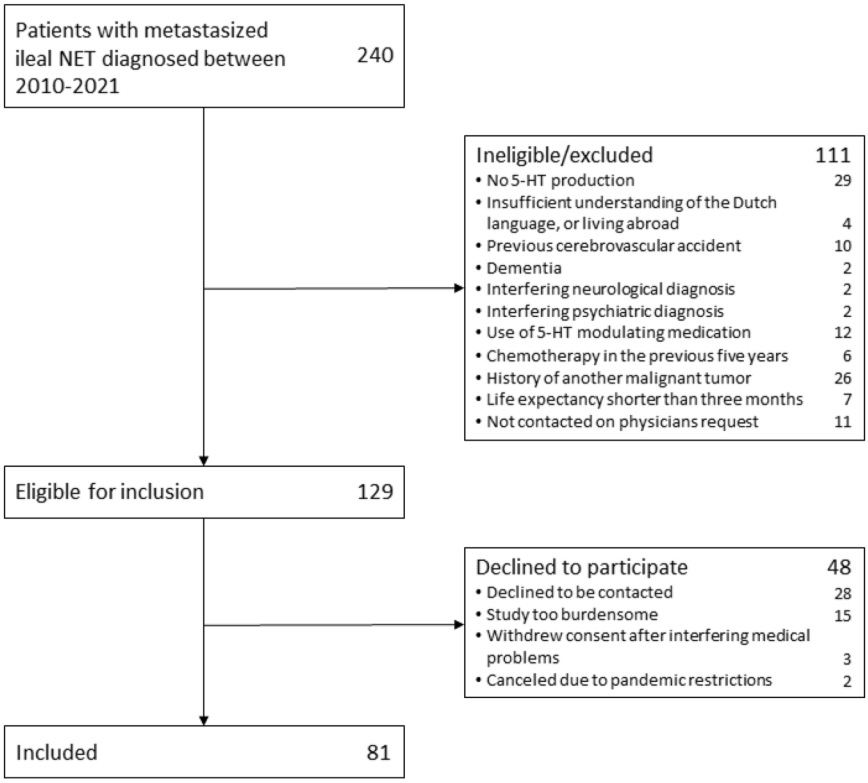

Fig. 1 Flowchart of inclusion and exclusion.

Institute [41]. Serum TRP and 5-HIAA together with the analysis of the urine samples was performed at the University Medical Centre Groningen [42].

Statistical analyses

To detect a medium effect size in a linear regression analysis with four predictors, a power of 0.80 and an alpha set to 0.05, the calculated sample size was 85 patients. Neuropsychological test scores were analysed using Advanced Neuropsychological Diagnostics Infrastructure (ANDI). ANDI is an online tool for conducting normative comparisons with a database containing normative data of over 26.000 healthy controls [43]. Normative comparisons are corrected for age, sex, and educational level.

For descriptive purposes, neuropsychological test scores were converted to standardized z-scores based on univariate comparisons. To assess the prevalence of cognitive impairment, expressed as the percentage of patients classified as cognitively impaired, Multivariate Normative Comparison (MNC) was applied. MNC compares an individual's entire profile of test scores to that of the normative sample in a single comparison, thereby controlling the false positive rate. The cut-off for classification as cognitively impaired was based on the fifth percentile corresponding to a one-sided alpha of 0.05 [44, 45]. A binomial test was used to compare the observed prevalence to the expected false-positive rate of 5%. Additionally, MNC was performed separately for the domains of memory, attention, and executive function.

Apart from this dichotomous outcome, MNC also provides a continuous measure: the Hotelling's T^2 statistic. This measure reflects the degree of cognitive deviation of each patient compared to the normative sample. To investigate peripheral 5-HT production as a determinant for decreased cognitive performance, three separate linear regression analyses were performed on the Hotelling's T^2 statistic with either 5-HT, TRP, and 5-HIAA serum levels as predictor. Age, sex, and educational level were included as covariates. Because 5-HIAA values were skewed and not normally distributed, these were log-transformed before the regression analyses. The Hotelling's T^2 was also calculated separately for the domains of memory, attention, and executive function. Linear regression analyses were repeated per cognitive domain.

We calculated IDS total scores and mood, anxiety, and sleep subscale scores [46, 47] for severity of depressive symptoms. We calculated BAI total scores and cognitive and somatic subscale scores [48, 49] for symptoms of anxiety. The relations between peripheral 5-HT production and severity of depressive and anxious symptoms were investigated using linear regression analyses on the IDS and BAI total scores and subscales with 5-HT, TRP, or log-transformed 5-HIAA levels as predictor. Age, sex, and duration of illness were included as covariates.

All analyses were performed using SPSS 27 (IBM, Amonk, NY), p-values were considered significant at <0.05.

RESULTS

Patients & demographics

Of 240 patients with a metastasized SINET that were receiving care at the NKI between 2010 and 2021, 129 were eligible for inclusion. Of these, 81 agreed to participate (Fig. 1; Table 1. Medication use in Supplementary Table 1).

Cognitive function

Nine out of 81 (11.1%) patients were identified as cognitively impaired using MNC, which was significantly elevated compared to the norm group ($p = 0.02$). When applying MNC separately per cognitive domain, 7 (8.6%) showed impaired memory, 12 (14.8%) impaired attention, and 5 (6.2%) impaired executive function. The average degree of cognitive deviation in the NET sample compared to the normative sample as expressed by the Hotelling's T^2 statistic was 1.03 ($SD = 0.58$) (per cognitive domain, memory: $M = 1.10$, $SD = 0.87$; attention: $M = 1.29$, $SD = 1.23$; executive function: $M = 0.81$, $SD = 0.90$). Standardized z-scores based on univariate comparison with the norm-group are

Table 1. Demographic and clinical characteristics.

Characteristic	Total sample ($N = 81$)
Age, M (±SD) [range]	63 (±9) [45–86]
Sex, N (%)	
Female	40 (49)
Education[a], N (%)	
Low	1 (1)
Medium	43 (53)
High	37 (46)
Work status, N (%)	
Working	22 (27)
Unemployed	2 (3)
Sick leave/disability	19 (24)
Retired	36 (44)
Homemaker	2 (3)
Clinical characteristics	
Current NET treatment, N (%)	
No treatment	17 (21)
Lanreotide	22 (27)
Octreotide	26 (32)
PRRT[b]	3 (4)
Combined[c]	13 (16)
Previous treatment, N (%)	
No treatment/wait and see	7 (9)
Tumour resection	43 (53)
Tumour resection + liver embolization	8 (10)
Lanreotide	7 (9)
Octreotide	5 (6)
PRRT[b]	5 (6)
Combined[c]	6 (7)
Use of somatostatin, N (%)	
Yes	61 (75)
Tumour stage at diagnosis, N (%)	
I	42 (52)
II	37 (46)
III	1 (1)
Unknown	1 (1)
Diagnosis, M (SD)	
Delay (months)[d]	45 (107)
Illness duration (months)[e]	36 (28)
Chromogranin A (µg/L)	
Mdn [IQR]	104 [861]
Unreliable, N (%)[f]	15 (19)
Missing, N (%)[f]	3 (5)

[a]Education according to Verhage (1964). Low = Verhage 1 and 2; Medium = Verhage 3, 4, and 5; High = Verhage 6 and 7.
[b]PRRT = Peptide Receptor Radionuclide Therapy.
[c]Combined = Lanreotide/Octreotide + PRRT.
[d]Delay = Time between first symptoms and diagnosis (in months).
[e]Illness duration = time between diagnosis and test date in months.
[f]Due to use of proton-pump inhibitors.

presented for all neuropsychological test outcomes (Fig. 2). Patients performed significantly worse than the norm group on tests of information processing speed, lexical fluency, and immediate memory recall of semantically related information,

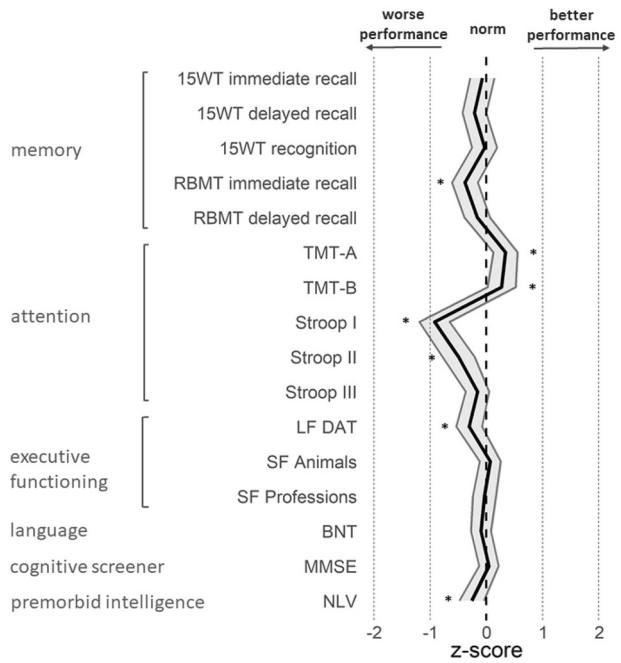

Fig. 2 Cognitive function. Average cognitive performance of the NET sample relative to the norm group (dotted line at 0). Visualized are standardized z-scores based on univariate comparison ±95% confidence interval (shaded area).* indicates significant deviation from the normative mean.

but significantly better on tests of focused and divided attention. Notably, estimated premorbid intelligence was also significantly lower than the norm group.

Psychiatric function

The SCID was missing for 1 patient. Sixteen of the 80 remaining patients (20%) received a diagnosis based on the SCID. Three (3.8%) were diagnosed with major depressive disorder. Adjustment disorder with depressed mood, anxious mood or a combination of depressed and anxious mood, was present in 10 (12.5%), alcohol abuse in 2 (2.5%), and agoraphobia in 1 (1.2%). NET patients reported an average IDS total score of 16.9 ($SD = 9.8$; Cronbach's $\alpha = 0.86$), with an average score of 5.2 ($SD = 4.8$; Cronbach's $\alpha = 0.82$) for the subscale mood, an average score of 6.2 ($SD = 4.2$; Cronbach's $\alpha = 0.73$) for the subscale anxiety, and an average score of 3.5 ($SD = 2.1$; Cronbach's $\alpha = 0.43$) for the subscale sleep. For symptoms of anxiety, NET patients reported an average total BAI score of 7.8 ($SD = 6.3$; Cronbach's $\alpha = 0.84$), consistent with mild anxiety symptoms [49], with an average score of 2.3 ($SD = 3.0$; Cronbach's $\alpha = 0.82$) for the cognitive subscale, and an average score of 5.4 ($SD = 4.4$; Cronbach's $\alpha = 0.80$) for the somatic subscale.

Biochemical analysis

Biochemical analysis revealed an average 5-HT serum level of 25.8 ^{9}Plt ($SD = 15.3$, range 4.1–67.4, Upper limit of normal (ULN) 5.8 nmol/10^{9}Plt), an average TRP serum level of 58.7 µmol/L ($SD = 11.9$, range 32.4–103.4, normal between 40–65 µmol/L), an average 5-HIAA serum level of 710.5 nmol/L ($SD = 1232.9$, range 26.7–8097.9), and a 24 h 5-HIAA urinary excretion of 217.9 mmol/L ($SD = 341.4$, range 10.8–1902.6).

Serotonin metabolism & cognitive function

To investigate the relation between 5-HT production and cognitive function, 5-HT serum levels, TRP serum levels, and 5-HIAA serum levels were regressed on the Hotelling's T in three separate linear regression analyses, correcting for age, sex, and educational level (Table 2; urinary 5-HIAA levels in Supplementary

Table 2. Serotonin metabolism & cognitive function.

Outcome	Predictors	Beta	SE beta	Standard beta	t-value	p-value	R^2	SD (residual)	F-value	p-value
5-HT serum levels										
Overall cognitive function	Constant	1.204	0.612		1.966	0.053	0.043	0.581	0.853	0.496
	5-HT	0.000	0.004	−0.011	−0.095	0.925				
	Age	0.005	0.007	0.074	0.658	0.513				
	Sex	0.101	0.130	0.088	0.782	0.437				
	Education	−0.094	0.064	−0.166	−1.461	0.148				
Memory function	Constant	0.267	0.932		0.286	0.776	0.021	0.884	0.406	0.803
	5-HT	−0.001	0.007	−0.010	−0.089	0.929				
	Age	0.013	0.011	0.140	1.227	0.224				
	Sex	0.067	0.197	0.039	0.342	0.734				
	Education	−0.005	0.098	−0.006	−0.048	0.962				
Attention	Constant	2.357	1.301		1.812	0.074	0.047	1.234	0.942	0.445
	5-HT	0.000	0.009	0.006	0.052	0.959				
	Age	−0.004	0.015	−0.027	−0.241	0.810				
	Sex	0.356	0.276	0.145	1.292	0.200				
	Education	−0.191	0.137	−0.158	−1.397	0.166				
Executive function	Constant	0.821	0.930		0.883	0.380	0.079	0.882	1.635	0.174
	5-HT	0.003	0.007	0.055	0.494	0.623				
	Age	0.010	0.011	0.105	0.944	0.348				
	Sex	−0.375	0.197	−0.211	−1.905	0.061				
	Education	−0.100	0.098	−0.114	−1.028	0.307				
TRP serum levels										
Overall cognitive function	Constant	1.231	0.748		1.647	0.104	0.045	0.587	0.862	0.491
	TRP	−0.001	0.006	−0.020	−0.173	0.863				
	Age	0.005	0.007	0.082	0.708	0.481				
	Sex	0.089	0.135	0.077	0.662	0.510				
	Education	−0.094	0.066	−0.165	−1.437	0.155				
Memory function	Constant	1.357	1.117		1.215	0.228	0.051	0.877	0.997	0.415
	TRP	−0.013	0.009	−0.183	−1.570	0.121				
	Age	0.011	0.011	0.114	0.998	0.321				
	Sex	−0.026	0.202	−0.015	−0.129	0.898				
	Education	−0.024	0.098	−0.028	−0.247	0.805				
Attention	Constant	2.061	1.592		1.295	0.199	0.047	1.250	0.919	0.457
	TRP	0.003	0.012	0.033	0.283	0.778				
	Age	−0.003	0.016	−0.019	−0.164	0.871				
	Sex	0.376	0.288	0.151	1.305	0.196				
	Education	−0.186	0.140	−0.152	−1.333	0.187				
Executive function	Constant	0.454	1.120		0.406	0.686	0.102	0.880	2.101	0.089
	TRP	0.008	0.009	0.104	0.917	0.362				
	Age	0.012	0.011	0.124	1.111	0.270				
	Sex	−0.391	0.202	−0.218	−1.932	0.057				
	Education	−0.121	0.098	−0.136	−1.228	0.223				
5-HIAA serum levels[a]										
Overall cognitive function	Constant	1.205	0.713		1.689	0.095	0.044	0.587	0.859	0.493
	5-HIAA	−0.007	0.053	−0.015	−0.130	0.897				
	Age	0.005	0.007	0.085	0.740	0.462				
	Sex	0.092	0.133	0.079	0.690	0.493				
	Education	−0.096	0.067	−0.167	−1.427	0.158				
Memory function	Constant	0.194	1.082		0.179	0.858	0.021	0.890	0.402	0.806
	5-HIAA	0.030	0.081	0.044	0.365	0.716				
	Age	0.012	0.011	0.131	1.123	0.265				

Table 2. continued

Outcome	Predictors	Beta	SE beta	Standard beta	t-value	p-value	R^2	SD (residual)	F-value	p-value
	Sex	0.048	0.202	0.027	0.235	0.815				
	Education	−0.011	0.102	−0.013	−0.109	0.913				
Attention	Constant	2.960	1.512		1.958	0.054	0.056	1.244	1.102	0.362
	5-HIAA	−0.100	0.113	−0.103	−0.882	0.381				
	Age	−0.002	0.016	−0.013	−0.118	0.906				
	Sex	0.328	0.283	0.132	1.158	0.251				
	Education	−0.214	0.142	−0.175	−1.505	0.137				
Executive function	Constant	0.278	1.060		0.262	0.794	0.117	0.872	2.441	0.054
	5-HIAA	0.114	0.079	0.163	1.442	0.154				
	Age	0.010	0.011	0.099	0.893	0.375				
	Sex	−0.393	0.198	−0.218	−1.980	0.051				
	Education	−0.093	0.100	−0.105	−0.936	0.352				

5-HT 5-hydroxytryptamine, *TRP* tryptophan, *5-HIAA* 5-hydroxyindoleacetic acid.
Significant p-values are highlighted in bold.
[a]Log transformed.

Table 3). Neither 5-HT levels, nor TRP or 5-HIAA levels significantly predicted cognitive function (all $p > 0.05$). The regression analyses were repeated per cognitive domain. Again, neither 5-HT, nor TRP or 5-HIAA levels significantly predicted memory function, attention, or executive function.

Serotonin metabolism & depressive symptoms

The relation between 5-HT production and depressive symptoms was investigated by regressing 5-HT serum levels, TRP serum levels, and 5-HIAA serum levels on the IDS scores, correcting for age, sex, and duration of illness (Table 3; urinary 5-HIAA levels in Supplementary Table 3). 5-HT level could not significantly predict severity of total depressive symptoms, or the mood subscale. For the IDS subscale anxiety, however, 5-HT level was a significant predictor for symptom severity, with lower 5-HT predicting higher symptoms. TRP levels could significantly predict the IDS total score, IDS mood subscale, and IDS anxiety subscale, but in contrast to our hypotheses, higher TRP levels were associated with more severe symptomatology. 5-HIAA serum levels did not predict IDS total score, the IDS mood subscale, and the IDS anxiety subscale. Age and sex were significant predictors in all models, with younger age associated with increased severity of symptoms and females reporting more severe symptoms than males. None of the regressions on the IDS subscale sleep were significant.

5-HT metabolism & symptoms of anxiety

Similar regression models were used with the severity of anxious symptoms (BAI) as outcome (Table 4; urinary 5-HIAA levels in Supplementary Table 3). All three regression models on the total BAI score were significant, but only age, sex, and/or duration of illness significantly predicted symptoms of anxiety, while 5-HT, TRP, or 5-HIAA levels did not. For the BAI cognitive subscale, the models including 5-HT or 5-HIAA levels were not significant. TRP levels, on the other hand, significantly predicted symptoms on the cognitive subscale, with the same direction as for the anxiety subscale of de IDS: higher TRP levels were associated with more anxious symptoms. For the BAI somatic subscale, all regression models were significant. However, the only significant predictors were age, sex, and duration of illness, but not 5-HT, TRP, or 5-HIAA levels. Again, younger age was associated with more severe symptoms of anxiety, and females reported more symptoms than males.

DISCUSSION

We aimed to evaluate cognitive and psychiatric functioning in patients with a serotonin overproducing NET and investigate the relation to peripheral serotonin concentrations. We hypothesized that peripheral serotonin overproduction would cause peripheral and central tryptophan depletion, resulting in serotonin deficiency in the brain and associated cognitive and psychiatric symptoms. Our findings show an 11% prevalence of cognitive impairment and a 20% prevalence of psychiatric disorders, but only a 3.8% prevalence of major depressive disorder. Cognitive function was not associated with any measure of peripheral serotonin overproduction. Opposed to our hypotheses, higher tryptophan concentrations were associated with severity of depressive symptoms and lower serotonin concentrations only with the anxiety subscale of depression. Higher tryptophan concentrations were also associated with the cognitive subscale of anxiety. These findings are in contrast with the hypothesis that increased peripheral serotonin and decreased tryptophan is associated with more severe symptoms of depression and anxiety. Therefore, tumor-related serotonin overproduction is unlikely to be the mechanism that causes psychiatric or cognitive symptoms in patients with a SINET.

Prevalence of cognitive dysfunction

Previous (small) studies in patients with a NET showed impaired sustained attention [13], visual perception and immediate and/or delayed verbal memory recall [11, 12], and phonetic fluency and processing speed [12]. In our study, information processing speed within the domain of attention appeared to be most affected. Unlike prior studies, delayed recall of verbal memory was not affected, however, we found impaired immediate recall on some tests. Furthermore, we found impaired lexical but not semantic fluency, corroborating Pasieka et al. [12]. Therefore, our study confirms the existence of subtle cognitive impairments in a large sample of patients with a serotonin producing NET.

Contrary to what has been suggested in previous literature, cognitive problems are not more prevalent among patients with serotonin producing NETs than with other cancers and cognitive impairment was only present in a minority of the patients. The use of more stringent criteria for classification of impairment may partly explain this discrepancy. MNC was applied for cognitive impairment detection, which takes into account the correlational structure between tests while comparing the whole profile of neuropsychological test scores to that of the norm group. By determining whether the profile as a whole is deviant, the risk of finding false positives is greatly reduced [44].

Table 3. Serotonin metabolism & depressive symptoms.

Outcome	Predictors	Beta	SE beta	Standard beta	t-value	p-value	R^2	SD (residual)	F-value	p-value
5-HT serum levels										
IDS total score	Constant	41.291	7.334		5.630	**<0.001**	0.179	9.123	4.134	**0.004**
	5-HT	−0.098	0.070	−0.153	−1.399	0.166				
	Age	−0.343	0.112	−0.322	−3.072	**0.003**				
	Sex	3.567	2.124	0.183	1.680	0.097				
	Duration	−0.059	0.040	−0.169	−1.487	0.141				
mood subscale	Constant	17.408	3.646		4.774	**<0.001**	0.134	4.536	2.934	**0.026**
	5-HT	−0.021	0.035	−0.067	−0.596	0.553				
	Age	−0.176	0.055	−0.341	−3.170	**0.002**				
	Sex	−0.004	1.056	0.000	−0.004	0.997				
	Duration	−0.017	0.020	−0.098	−0.841	0.403				
anxiety subscale	Constant	15.229	3.135		4.858	**<0.001**	0.188	3.893	4.355	**0.003**
	5-HT	−0.067	0.030	−0.243	−2.210	**0.030**				
	Age	−0.115	0.048	−0.252	−2.398	**0.019**				
	Sex	1.918	0.914	0.229	2.097	**0.039**				
	Duration	−0.028	0.017	−0.186	−1.625	0.108				
sleep subscale	Constant	4.738	1.683		2.815	0.006	0.091	2.093	1.891	0.121
	5-HT	−0.015	0.016	−0.106	−0.919	0.361				
	Age	−0.017	0.026	−0.074	−0.672	0.504				
	Sex	1.176	0.487	0.277	2.414	0.018				
	Duration	−0.011	0.009	−0.142	−1.188	0.239				
TRP serum levels										
IDS total score	Constant	24.939	9.302		2.681	**0.009**	0.240	8.868	5.829	**<0.001**
	TRP	0.229	0.087	0.275	2.640	**0.010**				
	Age	−0.351	0.110	−0.326	−3.185	**0.002**				
	Sex	4.649	2.134	0.236	2.179	**0.032**				
	Duration	−0.048	0.037	−0.138	−1.302	0.197				
mood subscale	Constant	9.488	4.565		2.079	**0.041**	0.218	4.351	5.172	**<0.001**
	TRP	0.117	0.043	0.291	2.754	**0.007**				
	Age	−0.171	0.054	−0.328	−3.160	**0.002**				
	Sex	0.486	1.047	0.051	0.464	0.644				
	Duration	−0.017	0.018	−0.098	−0.911	0.365				
anxiety subscale	Constant	7.365	4.003		1.840	0.070	0.236	3.812	5.627	**<0.001**
	TRP	0.106	0.037	0.298	2.843	**0.006**				
	Age	−0.127	0.048	−0.276	−2.673	**0.009**				
	Sex	2.430	0.924	0.288	2.631	**0.010**				
	Duration	−0.018	0.016	−0.121	−1.125	0.264				
sleep subscale	Constant	4.412	2.228		1.980	0.051	0.082	2.124	1.657	0.169
	TRP	0.004	0.021	0.020	0.175	0.862				
	Age	−0.023	0.026	−0.098	−0.872	0.386				
	Sex	1.187	0.511	0.276	2.323	0.023				
	Duration	−0.008	0.009	−0.108	−0.926	0.357				
5-HIAA serum levels[a]										
IDS total score	Constant	44.202	8.655		5.107	**<0.001**	0.174	9.241	3.905	**0.006**
	5-HIAA	−0.662	0.878	−0.086	−0.755	0.453				
	Age	−0.371	0.115	−0.344	−3.219	**0.002**				
	Sex	3.436	2.173	0.174	1.581	0.118				
	Duration	−0.052	0.041	−0.150	−1.275	0.206				
mood subscale	Constant	18.724	4.272		4.383	**<0.001**	0.141	4.561	3.045	**0.022**
	5-HIAA	−0.217	0.433	−0.059	−0.502	0.617				
	Age	−0.184	0.057	−0.352	−3.224	**0.002**				

Table 3. continued

Outcome	Predictors	Beta	SE beta	Standard beta	t-value	p-value	R^2	SD (residual)	F-value	p-value
	Sex	−0.132	1.072	−0.014	−0.123	0.903				
	Duration	−0.017	0.020	−0.099	−0.823	0.413				
anxiety subscale	Constant	17.643	3.702		4.766	**<0.001**	0.178	3.952	3.965	**0.006**
	5-HIAA	−0.594	0.380	−0.180	−1.561	0.123				
	Age	−0.129	0.050	−0.280	−2.601	**0.011**				
	Sex	1.906	0.937	0.226	2.033	**0.046**				
	Duration	−0.025	0.018	−0.169	−1.415	0.161				
sleep subscale	Constant	5.221	1.986		2.629	0.010	0.085	2.120	1.728	0.153
	5-HIAA	−0.109	0.201	−0.065	−0.541	0.590				
	Age	−0.022	0.026	−0.092	−0.813	0.419				
	Sex	1.165	0.499	0.271	2.337	0.022				
	Duration	−0.010	0.009	−0.130	−1.050	0.297				

5-HT 5-hydroxytryptamine, *TRP* tryptophan, *5-HIAA* 5-hydroxyindoleacetic acid, *IDS* inventory of depressive symptomatology.
Significant p-values are highlighted in bold.
[a]Log transformed.

Prevalence of psychiatric diagnosis and symptoms

The prevalence of a psychiatric diagnosis was slightly lower than in other studies in cancer patients with advanced disease [4, 50] or in more heterogeneous samples [3]. Adjustment disorder was the most prevalent diagnosis at 12.5%. The prevalence of depression was 3.8% and lower than previously reported in NET [14–16] or in patients with advanced cancer [3, 4]. Structured interviews such as the SCID generally result in a lower prevalence than classification based on cut-offs for clinically relevant symptoms [51]. Notably, when cut-off criteria were applied to the IDS [36], this indeed suggested a prevalence of 40.7% for mild depressive symptoms and 14.8% for moderate to severe depressive symptoms. A similar pattern was present in a population with patients with advanced cancer, in which a diagnosis of depression was 6% based on the SCID, but a prevalence of 36% was estimated when cut-off criteria were applied to a questionnaire [52]. This indicates that NET patients experience distress and clinically relevant depressive symptoms, but more often meet diagnostic criteria for an adjustment disorder than a depressive disorder.

Serotonin metabolism

As a central neurotransmitter within the brain, serotonin is known to regulate both mood and a broad spectrum of cognitive functions, including memory processes, attention, and executive functions [18]. Reduced serotonin neurotransmission has been associated with impaired cognitive functioning in several brain disorders, including Alzheimer's disease and schizophrenia [53]. Cognitive function, however, was not associated with peripheral measures of serotonin, its metabolite 5-HIAA or its precursor tryptophan. Therefore, we conclude that tryptophan depletion following tumor-related peripheral serotonin production does not seem to be a mechanism underlying cognitive problems in patients with a serotonin producing NET.

Similarly, disturbances in the serotonergic system are thought to underlie psychiatric problems such as depression and anxiety. However, no conclusive direct evidence exists that tryptophan depletion per se causes depressive symptoms [19]. In a large study with three cohorts of postmenopausal women, the association between serotonin concentrations and depression was only present in women using antidepressants but absent in women with depression who did not use antidepressants [54]. Previous observations show that the use of SSRIs lowers the measured levels of serum serotonin in SINET patients, so serum serotonin measurements in SSRI users may be unreliable [23]. However, the same study also found an inverse relation between tryptophan and severity of depression in women not using antidepressants [54], which is the opposite of the positive association between depression severity and tryptophan concentrations found in our study. Low tryptophan has been hypothesized as the missing link between somatic and psychiatric states, through a mechanism in which inflammation causes increased degradation of tryptophan and central depletion [21]. The Netherlands Study of Depression and Anxiety (NESDA) investigated this hypothesis but found similar tryptophan levels between depressed and non-depressed individuals and no association between depressive symptoms and tryptophan levels [55]. Tryptophan degradation, expressed as the ratio between the amino acid kynurenine and tryptophan (KYN/TRP) was slightly lower in the group with a current depression, suggesting decreased tryptophan degradation, but this difference disappeared after correction for antidepressant use [55]. Therefore, our finding that tryptophan is positively associated with the severity of depressive symptoms remains puzzling. Because the association was consistently found for multiple outcomes, including the total score on the IDS, both subscales of the IDS, and the cognitive subscale on the BAI, even after controlling for possible confounding factors, it likely reflects a genuine association and not merely a false positive or coincidental finding. More research is necessary before we are able to truly comprehend its meaning.

Strengths and limitations

Our study is the first to investigate cognitive and psychiatric function in tandem with changes in the serotonin system in a large sample of patients with a serotonin producing NET. Strengths of the study include the administration of an extensive, standardized neuropsychological test battery, the use of a multivariate method for normative comparison, and the assessment of psychiatric function with both self-reported psychiatric symptom questionnaires as well as a structured psychiatric interview.

An important limitation of this study is that all biochemical measures were peripheral, whereas central serotonin and tryptophan metabolism are more directly related to cognitive and psychiatric function. Speculatively, transportation of tryptophan over the blood-brain barrier could be hampered, for example through a shift in dietary amino acid intake or for another unknown reason. This would result in an increase in peripheral tryptophan accompanied with decreased cerebral

Table 4. Serotonin metabolism & symptoms of anxiety.

Outcome	Predictors	Beta	SE beta	Standard beta	t-value	p-value	R^2	SD (residual)	F-value	p-value
5-HT serum levels										
BAI total score	Constant	23.912	4.653		5.139	**<0.001**	0.196	5.788	4.630	**0.002**
	5-HT	−0.033	0.045	−0.080	−0.740	0.461				
	Age	−0.239	0.071	−0.351	−3.381	**0.001**				
	Sex	2.624	1.347	0.210	1.947	0.055				
	Duration	−0.042	0.025	−0.189	−1.681	0.097				
cognitive subscale	Constant	7.628	2.366		3.224	0.002	0.067	2.943	1.363	0.255
	5-HT	−0.018	0.023	−0.093	−0.802	0.425				
	Age	−0.072	0.036	−0.224	−2.008	0.048				
	Sex	−0.087	0.685	−0.015	−0.127	0.899				
	Duration	−0.008	0.013	−0.080	−0.665	0.508				
somatic subscale	Constant	15.897	3.140		5.064	**<0.001**	0.242	3.905	6.067	**<0.001**
	5-HT	−0.017	0.030	−0.061	−0.576	0.566				
	Age	−0.164	0.048	−0.346	−3.434	**<0.001**				
	Sex	2.730	0.909	0.314	3.003	**0.004**				
	Duration	−0.033	0.017	−0.214	−1.966	0.053				
TRP serum levels										
BAI total score	Constant	18.942	6.116		3.097	**0.003**	0.202	5.831	4.674	**0.002**
	TRP	0.065	0.057	0.122	1.140	0.258				
	Age	−0.238	0.073	−0.344	−3.283	**0.002**				
	Sex	2.898	1.403	0.229	2.065	**0.042**				
	Duration	−0.039	0.024	−0.174	−1.599	0.114				
cognitive subscale	Constant	1.837	2.988		0.615	0.541	0.146	2.849	3.166	**0.019**
	TRP	0.078	0.028	0.308	2.786	**0.007**				
	Age	−0.064	0.035	−0.194	−1.793	0.077				
	Sex	0.305	0.685	0.051	0.444	0.658				
	Duration	−0.008	0.012	−0.076	−0.671	0.504				
somatic subscale	Constant	16.178	4.154		3.895	**<0.001**	0.238	3.960	5.764	**<0.001**
	TRP	−0.006	0.039	−0.015	−0.148	0.882				
	Age	−0.171	0.049	−0.355	−3.472	**<0.001**				
	Sex	2.660	0.953	0.303	2.792	**0.007**				
	Duration	−0.030	0.017	−0.195	−1.830	0.071				
5-HIAA serum levels[a]										
BAI total score	Constant	26.889	5.455		4.929	**<0.001**	0.204	5.824	4.728	**0.002**
	5-HIAA	−0.672	0.553	−0.136	−1.215	0.228				
	Age	−0.235	0.073	−0.339	−3.230	**0.002**				
	Sex	2.539	1.369	0.201	1.854	0.068				
	Duration	−0.048	0.026	−0.215	−1.856	0.067				
cognitive subscale	Constant	9.866	2.741		3.599	<0.001	0.099	2.927	2.028	0.099
	5-HIAA	−0.517	0.278	−0.222	−1.861	0.067				
	Age	−0.065	0.037	−0.199	−1.777	0.080				
	Sex	−0.115	0.688	−0.019	−0.167	0.868				
	Duration	−0.014	0.013	−0.135	−1.093	0.278				
somatic subscale	Constant	16.568	3.705		4.471	**<0.001**	0.239	3.956	5.812	**<0.001**
	5-HIAA	−0.154	0.376	−0.045	−0.410	0.683				
	Age	−0.167	0.049	−0.348	−3.388	**0.001**				
	Sex	2.685	0.930	0.306	2.887	**0.005**				
	Duration	−0.033	0.018	−0.212	−1.873	0.065				

5-HT 5-hydroxytryptamine, *TRP* tryptophan, *5-HIAA* 5-hydroxyindoleacetic acid, *BAI* beck anxiety inventory.
Significant p-values are highlighted in bold.
[a]Log transformed.

tryptophan, which could potentially explain the association with increased depressive symptoms. Measures of serotonin, tryptophan, and 5-HIAA in cerebral spinal fluid could elucidate such questions but were considered too invasive for this study. Future studies should explore the kynurenine and serotonergic pathways in NET patients as well as the role of other hormonally active peptides secreted by the NET. Another limitation is that we focused solely on serotonin metabolism in relation to cognitive and psychiatric function. As described previously, neuroendocrine tumor cells produce not only serotonin but a variety of hormonally active peptides and neuroamines. Perhaps, these other peptides also play a role. Finally, we did not investigate the potential effects of the treatments that patients underwent, including somatostatin analogues (SSA). Evidence suggests that these may also affect cognitive and psychiatric function. For instance, somatostatin functions as a neurotransmitter and may be relevant for cognition [56] and mood [57]. Octreotide seemed to facilitate memory in memory-impaired and cognitively intact adults [58]. The individual effects of these treatments on cognitive and psychiatric function remain to be investigated in patients with a NET.

CONCLUSIONS

While the role of serotonin in psychiatric function remains incompletely understood, our results show that a minority of patients with serotonin overproducing neuro-endocrine tumors develop cognitive or psychiatric problems. Because we do not find associations between increased peripheral serotonin production with cognitive or psychiatric symptoms, the hypothesis that SINET cause long term 5-HT depletion resulting in cognitive and psychiatric illness is questionable. Future research should unravel the mechanisms underlying these problems.

DATA AVAILABILITY

Anonymized data are available upon reasonable request to the corresponding author.

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AUTHOR CONTRIBUTIONS

MJL: performed the data analysis and prepared the manuscript, METT: designed the study, helped with data collection, and helped write the manuscript. HHR: designed the study, helped with data collection and analysis and helped write the manuscript. MvF: helped with data analysis and interpretation and helped write the manuscript. CMK: designed the study, helped with data collection and reviewed the manuscript, WHMV: helped design the study, helped collect the data and reviewed the manuscript, JRS: collected the data and reviewed the manuscript, PCS: collected the data and reviewed the manuscript, EHH: collected the data and reviewed the manuscript, IPK: helped with data analysis and interpretation and reviewed the manuscript, HGR: designed the study, helped with data analysis and interpretation and helped write the manuscript, SBS: designed the study, supervised data collection, supervised data analysis and interpretation, helped write the manuscript, FEdV: designed the study, supervised data collection, supervised data analysis and interpretation, helped write the manuscript.

COMPETING INTERESTS

The authors declared no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This cross-sectional study was approved by the Medical Ethical Committee of the NKI (NL6123803117) and carried out in accordance with the principles of the Declaration of Helsinki and following institutional guidelines and regulations. All patients provided written informed consent.

ADDITIONAL INFORMATION

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