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Case Report

Clinical Monitoring of Sympathetic and Parasympathetic Response with Neurotest during Neurofeedback Therapy in Panic Disorder: A Case Report

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Abstract

The purpose of this case report is to highlight the Neurotest as a useful and accessible questionnaire that may be integrated with different and well-established diagnostic and therapeutic tools. The Neurotest is a self-report questionnaire that investigates fluctuations in sympathic, parasympathetic (vagotonic) and GABAergic symptoms. It was administered for 15 weeks to a patient diagnosed with panic disorder. In the same period of time, 15 sessions of Neurofeedback training Alpha/Theta increase were performed with relevant clinical interviews aimed at mentalisation, self-monitoring and sharing of what observed in the progressive Neurotest assessments. Results show the normalization of the scores obtained with the psychometric scales (SCL-90-R, BDI, HAMD, HAMA) and the physiological Alpha and Theta EEG rhythms are restored together with the normotonia assessed by the Neurotest. Monitoring with Neurotest simplified the patient's compliance and sense of self-efficacy, the therapeutic alliance and targeting of treatments.

Keywords: *Neurotest; Sympathetic; Parasympathetic; Anxiety Disorders; Neurofeedback; Monitoring*

Abbreviations

DSM: Diagnostic and Statistical Manual of Mental Disorders; Ach: Acetylcholine; GABA: γ-Aminobutyric Acid; REM: Rapid Eye Movement; GAD: Generalized Anxiety Disorder; OCD: Obsessive Compulsive Disorder; SAD: Social Anxiety Disorder; PTSD: Post Traumatic Stress Disorder; ICD: International Classification of Diseases; NSAID: Non-Steroidal Anti-Inflammatory Drugs; PFC: Prefrontal Cortex; EEG: Electroencephalogram; HAMD: Hamilton Psychiatric Scale for Depression; HAMA: Hamilton Anxiety Rating Scale; SCL-90-R: Symptom Checklist-90-R; BDI: Beck Depression Index

Introduction

Panic disorder: Diagnostic features and neuroendocrine correlates

In compliance with the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [1], panic disorder is characterized by recurrent unexpected panic attacks consisting of the sudden onset of intense fear or discomfort that reaches its peak within minutes, during which at least four of the following symptoms occur: palpitations, sweating, fine or big tremors, dyspnea or feeling of suffocation; sensation of

asphyxia, pain or tightness in the chest, nausea or other abdominal discomfort, dizziness, sense of instability, "light-head" or faint sensation, chills or hot flashes, paresthesias, depersonalization or derealization, fear of losing control, fear of dying.

Panic disorder is diagnosed if at least one of the events is followed by: persistent concern about the onset of other attacks and/or their consequences; significant maladaptive behavioural changes. These psychophysiological alterations must not be attributable to another organic medical condition, another mental disorder or to the effects of substances.

Current estimated prevalence, in the USA and Europe, is 2-3% in both adults and adolescents. The specific data updated to 2022 referring to the Italian population show a total prevalence (weighted percentages) of panic disorder of 1.6% (0.9% male population, 2.2% female population) [20]. These data reveal that female population is more affected than the male one with a ratio of about 2:1 [1,20].

In both adults and adolescents this disorder, if untreated, tends to become chronic and it is frequently comorbid with other anxiety disorders, depressive disorder and bipolar disorder. Most patients report the presence of distressing events in the months preceding the first panic episode, whether they are stressful events on a socio-relational level or linked to a condition of illness or organic discomfort.

Current models of neural circuits involved in panic disorder underline the role of the amygdala, its structures and the mutual interactions between the sympathetic and parasympathetic nervous systems; this model occurs in all anxiety disorders.

Sympathicotonia and parasympathicotonia (vagotonia)

Accurate monitoring of sympathicotonic and vagotonic symptoms is useful in the treatment of diseases involving alterations in normotonia.

The term sympathicotonia indicates a psycho-organic condition in which the sympathetic system prevails, which has a stimulating, excitatory function and promotes contraction; it is a "fight or flight" response and its activation results in the consequent clinical signs [2]. This phase is characterized by the narrowing of peripheral blood vessels which manifests itself in cold hands and feet, increase in blood pressure with a decrease in vessel content and poor appetite with reduced functionality of the digestive tract and metabolism [2].

As far as the central nervous system is concerned, sympathicotonic activation stimulates brain activity and influences emotional behaviour characterized by a state of attention and hyper-activation (stress) useful for the individual who has to face an emergency situation.

Vagotonia, on the other hand, indicates a condition in which the parasympathetic system prevails. It generally follows the sympathicotonic phase and it is characterized by psycho-organic manifestations opposite to those described above; in particular, it causes a peripheral blood vessels dilation (warm hands and feet), decreased blood pressure with a consequent increase in *vessel content*, increased appetite, gastrointestinal function, and metabolism.

Heart rate depends on vagal tone and the presence of humoral substances in the bloodstream; if the individual is subjected to stressful stimuli, then the sympathetic nervous system control takes over.

The neurotransmitter that regulates the activation of these mechanisms is Acetylcholine (Ach).

The GABAergic system

γ-aminobutyric acid (GABA) is involved in central cardiovascular control and affects heart rate and blood pressure; it also has a key role in the control of the autonomic nervous system, for example in mechanisms underlying reproduction, energy and fluid balance.

The GABAergic system controls various functions such as appetite, sleep, sexual desire, and mood [3] and also takes part in the modulation of the sympathetic and parasympathetic systems [4,5].

Emotional stress - such as anxiety disorder - determines clinically significant effects on cardiovascular function through the Autonomic Nervous System; the vascular and cardiac modifications typical of emotional stress are different according to the prevalence of the sympathetic or vagal system, respectively with an increase in blood pressure and heart rate due to a sympathicotonic effect or vagal inhibition of cardiac rhythm activation [2].

Besides having a modulating role on various functions such as hunger, sleep and sexual desire, the GABAergic system also seems to play a role in promoting the hypothalamic centre for food intake by acting in an oxygenic way [4].

Reduced levels of GABA can hinder numbness and cause delayed insomnia. Activation of GABA-A receptors is also known to promote sleep; GABA-B receptors have also been shown to enhance brain activation-mediated behaviours such as wakefulness and REM sleep [5]. The GABAergic system is also involved in hedonic processes: subcortical GABA signals stimulate the hedonistic sphere at nucleus accumbens level and amplify emotional reactions to pleasant stimuli [5].

It also controls several psychological functions and has a correlation with anxiety. Numerous statistic evidences [1] demonstrate a greater prevalence of anxiety disorders (with and without panic attacks) in the female population; women are also more predisposed to develop symptoms consistent with specific anxiety spectrum disorders [6]: generalized anxiety disorder (GAD), obsessive compulsive disorder (OCD), social anxiety disorder (SAD), post-traumatic stress disorder (PTSD), specific phobias, panic disorder, agoraphobia.

Case Profile

The patient was examined and followed up at the Psychology service of the Magenta Medical Center in Milan. During her first visit, the informed consent was delivered and explained, including the specific item dedicated to the use of the case report (in anonymous form) for scientific and research purposes. The methods, purposes, peculiarities and limits of the clinical tools proposed in the rehabilitation process were explained and shared, in order to obtain a solid therapeutic alliance and to promote an internal locus of control on the part of the patient. A micro-team was created with the general practitioner and a psychiatrist consultant.

Anamnesis

The patient is a 19 year old female, attending the last year of linguistic high school and is a professional acrobatic dancer, she accessed the clinic in February 2022 following a referral from the general practitioner to whom she had referred for panic attacks which suddenly arose in the second half of January 2022. The attacks occur almost daily both at home and at school and rarely on the street or in recreation places.

The patient initially implements avoidance strategies thus making several school absences and drastically reducing her sociality. Although panic attacks have occurred for a few weeks, the presence of anxiety with somatic symptoms has been evident for about 6 to 10 months.

During the first visit, the patient reports an experience of great psychological suffering which caused social isolation, from the beginning of the pandemic to the moment we met.

Psychodiagnostic evaluation is performed, revealing a diagnosis of Panic Disorder DSM-5 300.01; International Classification of Diseases (ICD) -10-CM (F41.0).

Psychological examination

In December 2021, pathology from Human Herpesvirus-4 (Epstein-Barr EBV strain) was found with clinical manifestation associated with acute infectious mononucleosis lasting 4 weeks.

At the end of January 2022 positive for SARS CoV-2 with acute clinical manifestation of Covid-19 disease lasting 9 weeks (of which 2 with acute symptoms; 1 paucisymptomatic; 6 asymptomatic with presence of brain fog).

In both cases, the treatment was symptomatic (paracetamol, non-steroidal anti-inflammatory - non-steroidal anti-inflammatory drugs (NSAID), supplementation with group B vitamins).

Psychological examination results are shown in table 1.

Attitude towards the clinician	Collaborative but at times coerced
General Appearance	Adequate self-care and personal hygiene
Gestures	Hypomobile
Speech	Fluid only after stimulation
Consciousness	Oriented in the three domains (space, time, self)
Attention	Conative (concentration), not very spontaneous
Intellectual capacity	Normal
Perception	Not reported nor noticed misperceptions
Thought content	Ideation focused on the current clinical condition. Ideation at times not adhering to the plan of reality with contents of ruin and ruminative thoughts
Affectivity	Alternation of anxious manifestations with marked deflection of mood
Emotionality	Labile with sometimes theatrical manifestations
Illness consciousness	Good insight

Table 1*: The table describes the characteristics of the patient emerged from the psychological examination.*

Materials and Methods

The period of taking charge or care lasted about 15 weeks with weekly meetings of about 60 minutes each structured as follows: welcome and interview (20 minutes), compilation of the Neurotest and GABAergic Neurotest with discussion and observations (20 minutes), Neurofeedback training session (20 minutes). At the end of the treatment in the acute phase, monthly follow-up visits were agreed.

Neurotest

The Neurotest is a new paradigmatic tool in the monitoring of the biphasic trend of organic pathologies [2] since in every pathological condition it is possible to observe a sequence of fluctuations of sympathicotonic and vagotonic symptoms. The accentuation of parasympathicotonia or sympathicotonia provides important elements useful for monitoring the course of the disease and allows a more accurate approach to the therapeutic act.

Peci., *et al*. have developed the Neurotest, a self-report questionnaire useful for investigating the sympathetic-vagal symptomatology combined with the manifestation of the GABAergic system which correlates with specific observable clinical signs such as appetite, sleep, sexual desire (Table 2) [7].

These tools facilitate the monitoring of the sympathetic and parasympathetic systems, allowing a constant and meticulous verification of progress and/or variations in response to therapeutic acts, whether they are pharmacological, rehabilitative, or neuropsychological.

The use of the Neurotest in a clinical setting is particularly effective and immediate and can be totally self-administered after training and supervision of the patient in the first monitoring sessions. Each Neurotest variable listed is assigned a score between 1 and 3 in rela-

Neurotest				
Stimulus	Sympathetic	N°	Vagal	N°
Hunger	↓	3	↑	3
Eye	Dryness	2	Teary Eyes	1
Stomach	Meteorism	2	Stomach Acid	2
Cholecyst			Contraction	1
Intestine	↓	2	↑	2
Anal sphincter	Contraction	2	Relaxation	2
Nose itch	Present	2	Absent	
Hands	Cold	3	Hot	3
Sleepiness	<	2	>	2
Saliva	Dryness	1	Sialorrhea	2
Breathing	Relaxation	2	Contraction	1
Blood pressure	↑	2	↓	2
Heartbeat	↑	2	↓	2
Bladder sphincter	Contraction	2	Relaxation	2
Sexual organs	Premature	3	Frigidity	2
GABAergic NEUROTEST				
Stimulus	Normal	↓ GABA	↑ GABA	N°
Hunger	Normal	Absent	Present	2
Sleep	Normal	Absent	Present	3
Libido	Normal	Absent	Present	3

Table 2: *Correlation between sympathetic and parasympathetic stimulus [2].*

tion to the intensity of the symptoms (weak, medium, strong) perceived by the patient himself. The symptomatology investigated by the GABAergic Neurotest is instead measured in terms of the absence or presence of the clinical sign.

The research work of Peci., *et al*. made it possible to observe that all pathologies - be they psychological, organic or more often mixed - have two phases: the first is the sympathicotonic one in which the observable symptoms consist of: decreased appetite and intestinal peristalsis, gastric meteorism, dryness of eyes and fauces, contraction of the anal and bladder sphincter, reactivity of the nasal mucosa and of the sexual organs, decrease of drowsiness with increase of blood pressure and cardiac rhythm with generally cold peripheral limbs. The second phase, called vagotonic, is characterized by specular signs and symptoms, namely: increased appetite and intestinal peristalsis, gastric acidity, tearing and drooling, release of the anal and bladder sphincter, contraction of the gallbladder, non-responsiveness of the sexual organs, increased of drowsiness with decreased blood pressure and heart rate with generally warm peripheral limbs [2].

When the normal normotonic curve changes, the whole organism enters a state of neurovegetative alteration in which either the sympathetic or parasympathetic system dominates.

The curve phase, which follows a traumatic event or which the body considers as harmful, is visible in the upper part of the graph (Figure 1): the body is in a state of permanent stress, a state of alert which allows its activation with the purpose of solving the emergency. Vasoconstriction and elevated blood pressure typically occur in this stage.

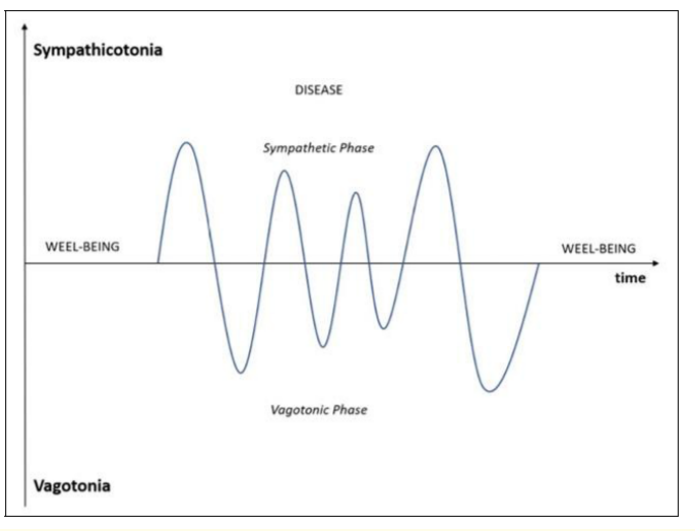

Figure 1: *From Peci., et al. 2020. The graph shows the alternation of the normotonic curve followed by the appearance of the sympathetic phase and subsequent parasympathetic phase during a pathological condition [2].*

The next stage is the resolution (or remedial process) stage. It is characterized by a vasodilation with a decrease in pressure with possible remedial symptoms such as fever, pain, inflammation, etc. It is the pathophysiological moment in which the body requires rest to facilitate the tissue healing processes of all organs and systems that had previously been subjected to high levels of prolonged stress.

The more intense the sympathicotonic phase, the more plausible it is to expect a subsequent equally intense vagotonic phase: to get out of the conflict, the body must react. Such reaction is visible in the graph as a peak of sympathicotonic activation, a phase called epileptoid crisis, that is an intense clinical manifestation of the patient's body reparative functions with a consequent and proportional vagotonic response which is normally followed by a restoration of normotonia [2,7,8].

In some cases, the patient's neurovegetative rhythm can persist in a condition of altered sympathicotonia or vagotonia not followed by an epileptoid crisis which can lead the body to a normotonic condition. In the first case the body experiences a condition of constant alert due to the maintenance of the sympathicotonic rhythm; in the second case there is instead a prolongation of the expression of the vagotonic phase following the epileptoid crisis with the typical associated symptoms. In both conditions the patient evolves into a chronic situation with different characteristics based on the persistence of the sympathicotonia/vagotonia.

The epileptoid crisis marks the transition towards a reparative phase (Figure 2), the clinician's task is therefore not to prevent but to consciously accompany and modulate the functional modifications that the body implements to restore normotonia.

Neurofeedback

Neurofeedback training is a clinical method able to effectively reduce anxiety symptoms [9,10]; it is also an innovative intervention technique based on neuromodulation and, by virtue of its non-invasiveness, it can also be used safely in addition to other pharmacological and non-pharmacological therapeutic approaches in patients starting from the childhood age.

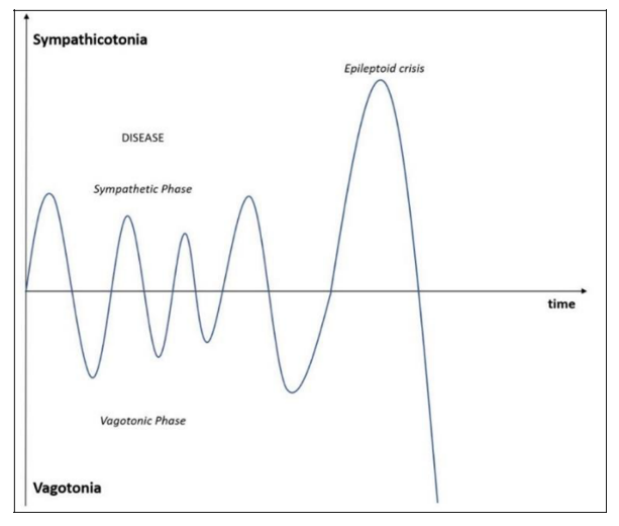

Figure 2: *From Peci., et al. 2020. The peak of the epileptoid crisis in sympathetic phase is followed by a peak in the vagotonic phase, so strong that the organism cannot react [2].*

Neurofeedback training protocols useful for the treatment of anxiety disorders are aimed at modifying the ability to regulate emotions, i.e. a behavioural response that can occur automatically or with the mediation of conscious strategies [11].

At a cortical level, emotional behaviour is regulated by a network of regions that includes the Prefrontal Cortex (PFC) and amygdala, which have both functional and structural mutual interconnections [12].

One of the possible ways to influence such an emotional regulation process is Neurofeedback training which uses the most recent biomedical real-time processing technologies (electroencephalogram (EEG) with interactive 2D/3D virtual reality interface) of biometric data to produce a dynamic scenario that can be used by the patient to effectively modulate their neural networks [13].

During a Neurofeedback training session, the patient learns to increase control over specific brain areas by receiving feedback (positive/negative/neutral reinforcement) corresponding to his own neural activity [13].

Patients are also encouraged by the clinician to develop meta-cognitive and meta-emotional strategies useful for improving results in the various suggested tasks. In the treatment of anxiety disorders, where emotion regulation appears to be dysfunctional, the PFC and amygdala may be specific targets of neurofeedback training.

Psychometric scales

The Hamilton psychiatric scale for depression (HAMD) [14]

Scale composed by 17 items that investigate the presence and intensity of somatic complaints, behavioural symptoms, cognitive symptoms, anxiety and mood. In answering the questions, the patient must refer to how she felt in the last week and has the possibility to choose between five alternative responses of increasing severity. Two independent interviewers are required for the administration of the interview and the calculation of the *interrater* reliability. The total score is given by the sum of the scores attributed by the interviewers themselves.

Hamilton anxiety rating scale (HAMA) [15]

Evaluation of clinical anxiety referred to a population of adults and adolescents. The scale is made up of 14 points, each of which is defined by a series of symptoms, measures of both psychological anxiety (mental agitation and psychological stress) and somatic anxiety (physical disorders related to anxiety). The score is obtained by evaluating the sum of the items. Each item is scored on a scale from 0 (not present) to 4 (severe).

The symptom checklist-90-R (SCL-90-R) [16]

It is a psychometric self-assessment tool. Designed to assess a broad range of psychological problems and symptoms of psychopathology. It is regulated for individuals aged 13 and over and consists of 90 items yielding nine scores along the primary symptom dimensions and three scores across global distress indices. The primary symptom dimensions that are assessed are: somatization, obsessive-compulsive disorder, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism, and a category of "additional elements" that help clinicians evaluate other aspects of the symptoms of the patients.

Beck depression index (BDI) [17-19]

The self-report questionnaire consists in 21 survey areas, which correspond respectively to the 21 items that make up the BDI. It investigates sadness, pessimism, sense of failure, dissatisfaction, sense of guilt, expectation of punishment, self-disappointment, self-blame, suicidal ideation, crying (weeping), irritability, indecision, doubt, social withdrawal, devaluation of one's body image, decline in work efficiency, sleep disturbance, fatigue, decreased appetite, weight loss, worries somatic, reduced libido.

Results

Neurotest in the clinical case

Methodological note: the Neurotest is a self-report tool whose scoring is set on discrete numerical values ranging from 1 to 3 for each symptom investigated in sympathicotonic or vagotonic manifestations. The evaluation of the expression of the GABAergic system evaluates the presence/absence of the associated clinical manifestations.

More precisely, the presence of a certain clinical sign (sympathetic or vagal) is associated with a specific number, that researchers [7] have established according to the "weight" of the symptom and its importance in the clinical setting. In 2020, Peci., *et al*. pointed at the need to review these scores in order to assign a more appropriate evaluation to the symptoms of the individual patient was subsequently explicated [2]. On several occasions the patient stated that she felt such a level of fluctuation in some symptoms that she asked to be able to use intermediate scores which, in her opinion, could better express her sensations.

Although not entirely methodologically correct, by exerting intermediate scores we decided to privilege compliance and the therapeutic alliance, also considering that a correct course of treatment would not have been invalidated by this choice, resulting from precise clinical reasoning.

The graph relating to the Neurotest (Figure 3) shows the oscillations of sympathicotonia and vagotonia during the different phases of the patient's therapeutic path. In particular, a peak of sympathicotonic symptoms is noted - in the presence of frequent panic attacks and severe anxiety - in the first period of taking charge; subsequently a prevalence of vagotonic symptoms accompanied by depressive experience and social withdrawal with extinction of panic attacks is observed. Finally, towards the conclusion of the therapeutic course, an approach of the curve to a clinical condition tending towards normotonia is observed.

The graph relating to the GABAergic component of the Neurotest (Figure 4) highlights the pathological oscillations of GABA levels measured through the presence/absence of associated symptoms. Low levels of this neurotransmitter are observed in conjunction with

Data	Simpaticotonia	Vagotonia
10/01/2022	29	-1
17/01/2022	30	-6
31/01/2022	14	-12
07/02/2022	2	-18
14/02/2022	0	-22
21/02/2022	14	-10
28/02/2022	4	-7
09/03/2022	10	-7
14/03/2022	4	-18
21/03/2022	19	-8
28/03/2022	18	-7
04/04/2022	17	-8
11/04/2022	17	-8
20/04/2022	15	-5
27/04/2022	12	-3

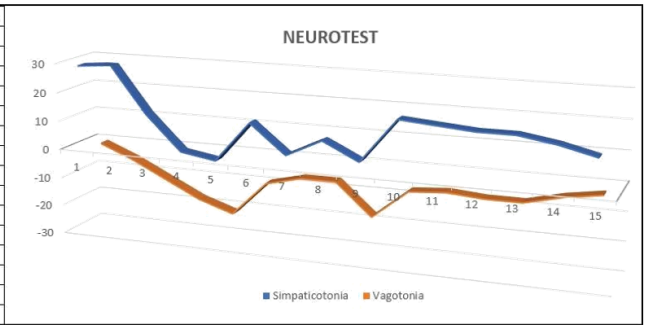

Figure 3: *The graph shows the alteration of the normotonic curve during the manifestation of the pathology in the case report.*

severe anxious symptoms with frequent panic attacks with successive and repeated oscillations up to a stable and normal condition at the end of the therapy.

Data	GABA
10/01/2022	-8
17/01/2022	-1
31/01/2022	5
07/02/2022	5
14/02/2022	-2
21/02/2022	5
28/02/2022	0
09/03/2022	3
14/03/2022	4
21/03/2022	3
28/03/2022	3
04/04/2022	4
11/04/2022	4
20/04/2022	3
27/04/2022	6

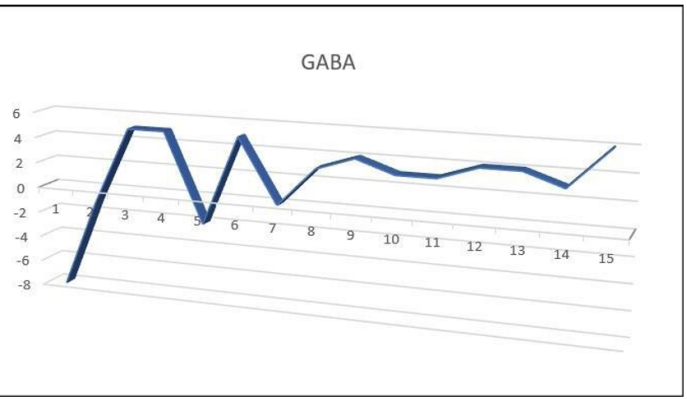

Figure 4: *The graph shows the alteration of the GABAergic curve during the pathological manifestation in the case report.*

Neurofeedback in the clinical case

The graphs relating to Neurofeedback training show an increase in minimum, maximum and average Alpha and Theta rhythms during the three phases of neuromodulation: Initial background (Figure 5), Training (Figure 6), Final background (Figure 7).

These cerebral rhythms are sub-threshold when associated with an anxious clinical condition while they tend to a progressive increase up to a normalization towards in end of the therapy.

Results of psychometric scales T0 and T1

The graphs relating to the psychometric scales performed at the time of taking charge (T0-Table 3) show evidence of clinically significant levels of anxiety and mood tone deflection; in particular, a strong presence of somatic symptoms is observed.

Date	Initial background		
	(C3-O1+C4-O2) : 6-13 Min	C3-O1+C4-O2) : 6-13 Max	C3-O1+C4-O2) : 6-13 Average
10/01/2022	1,837	11,896	6,867
17/01/2022	5,793	12,079	8,936
31/01/2022	4,437	12,887	8,662
07/02/2022	6,408	13,011	9,710
14/02/2022	7,259	12,994	10,127
21/02/2022	7,879	14,786	11,333
28/02/2022	8,998	14,906	11,952
09/03/2022	10,324	16,509	13,417
14/03/2022	9,101	18,119	13,610
21/02/2022	10,553	17,889	14,221
28/03/2022	11,099	20,905	16,002
04/04/2022	11,706	23,332	17,519
11/04/2022	11,801	24,721	18,261
20/04/2022	11,002	25,223	18,113
27/04/2022	13,806	28,691	21,249

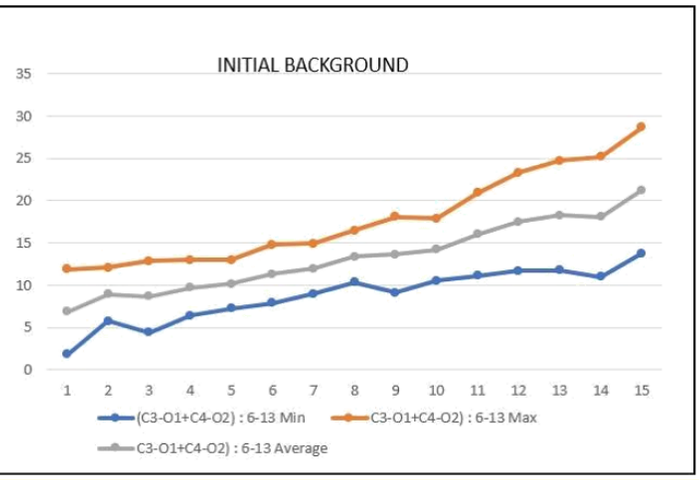

Figure 5: *The graph shows alpha Theta increase during the initial background - neurofeedback procedure in the case report.*

Date	Training		
	(C3-O1+C4-O2) 6-13 Min	(C3-O1+C4-O2) 6-13 Max	(C3-O1+C4-O2) 6-13 Average
10/01/2022	3,499	16,792	10,146
17/01/2022	3,507	15,787	9,647
31/01/2022	8,444	17,188	12,816
07/02/2022	9,098	21,116	15,107
14/02/2022	10,999	25,477	18,238
21/02/2022	10,764	27,664	19,214
28/02/2022	11,009	32,223	21,616
09/03/2022	12,661	39,818	26,240
14/03/2022	13,567	38,667	26,117
21/02/2022	13,568	39,009	26,289
28/03/2022	13,889	40,333	27,111
04/04/2022	14,002	41,113	27,558
11/04/2022	13,909	59,001	36,455
20/04/2022	14,545	59,98	37,263
27/04/2022	15,492	66,271	40,882

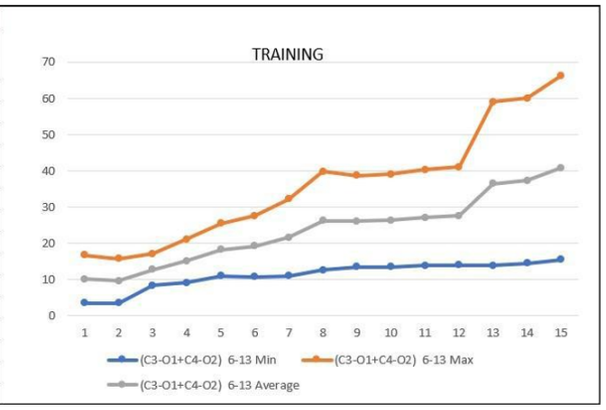

Figure 6: *The graph shows alpha theta increase during the training stage - neurofeedback procedure in the case report.*

Date	Final background		
	(C3-O1+C4-O2) 6-13 Min	(C3-O1+C4-O2) 6-13 Max	(C3-O1+C4-O2) 6-13 Average
10/01/2022	0,367	1,56	0,964
17/01/2022	2,875	1,789	2,332
31/01/2022	3,11	3,651	3,381
07/02/2022	3,764	8,021	5,893
14/02/2022	4,008	9,324	6,666
21/02/2022	4,221	12,415	8,318
28/02/2022	5,776	13,813	9,795
09/03/2022	5,634	14,511	10,073
14/03/2022	7,613	17,654	12,634
21/02/2022	8,623	18,067	13,345
28/03/2022	9,011	25,314	17,163
04/04/2022	10,222	29,883	20,053
11/04/2022	11,005	31,008	21,007
20/04/2022	11,096	31,165	21,131
27/04/2022	11,801	33,837	22,819

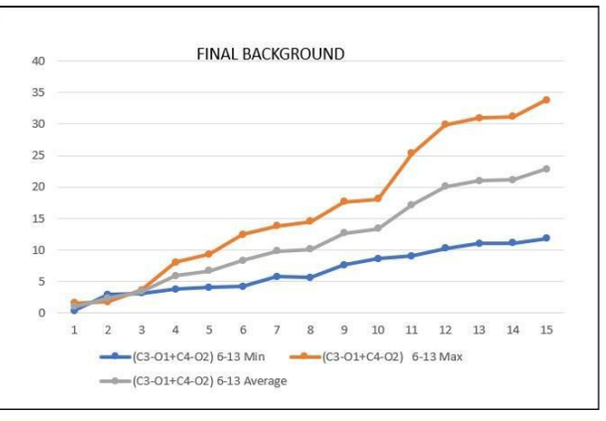

Figure 7: *The graph shows alpha Theta Increase during the Final background – Neurofeedback procedure in the case report.*

Global assessment-T0		
Test	**Score**	**Cut-off**
SCL-90-R	Global Symptom Index 1,622*	≥1
Subscale	SOM 1,917**	≥ 1
	OC 2,300***	
	INT 0,889	
	DEP 2,538***	
	ANX 1,700**	
	HOS 1,833*	
	PHOB 1,857*	
	PAR 0,667	
	PSY 0,800	
	SLEEP 0,000	
Depression		
Test	**Score**	**Cut-off**
BDI	18**	≥ 14
HAMD	14**	≥ 8
Anxiety		
Test	**Score**	**Cut-off**
HAMA	18**	≥ 10

Table 3: *Psychological assessment case report - T0 showing evidence of clinical depression and anxiety.*

The evaluation performed at the end of the clinical path (T1-Table 4) shows an extinction of anxiety and a reduction of depressive symptoms in the absence of somatization.

Global assessment – T1		
Test	**Score**	**Cut-off**
SCL-90	Global Symptom Index 0,722	≥ 1
Subscale	SOM 0,833	≥ 1
	OC 1,100*	
	INT 0,556	
	DEP 1,231*	
	ANX 0,500	
	HOS 0,833	
	PHOB 0,857	
	PAR 0,167	
	PSY 0,300	
	SLEEP 0,000	
	Depression	
Test	**Score**	**Cut-off**
BDI	13	≥ 14
HAMD	8	≥ 8
	Anxiety	
Test	**Score**	**Cut-off**
HAMA	7	≥ 10

Table 4: *Psychological assessment case report - T1 showing extinction of depressive and anxious symptoms.*

Discussion

From the performed Neurotest, an initial picture of marked sympathicotonic activation seems to emerge (in the first two weeks of evaluation the value of sympathicotonia was about 30; vagotonia -1 then -6) with reported and observed presence of panic attacks and somatic anxious symptoms.

From the third to the fifth week of therapy, parallel to the clinical interviews and neurofeedback training, a decrease in sympathicotonic symptoms (14; 2; 0) and an increase in vagotonia (-12; -18; -22) was observed.

The patient reported a decrease and then extinction of panic attacks with less intense anxious experiences. She also started completing the self-reports independently albeit a request for reassurance.

On the other hand, a deflection in mood, experienced as new and intolerable, emerged: as a team - sharing the therapeutic choice with the patient, it was opted to continue taking charge for another three weeks before evaluating changes; however, the patient was supported in openly manifesting any serious symptoms such as self-harming/anti-conservative ideas or experiences that were not compatible with carrying out normal daily activities.

Between the sixth and ninth week of clinical treatment and Neurotest monitoring, a rhythmic phase was recorded, characterized by rapid and marked oscillations between sympathicotonia (14; 4; 10; 4) and vagotonia (-10; -7; -7; - 18).

The patient verbalized intense but manageable mood lability, without recurrence of panic attacks, accompanied by an increased sense of self-efficacy, and better understanding with an adjustment of her psychophysiological states during exercises with interactive virtual reality scenarios.

In the following weeks, i.e. from the 10th to the 15th one, the values of sympathicotonia and vagotonia progressively consolidated towards a more stable pattern and closer to normotonic values. Specifically, the recorded sympathetic symptoms set between 12 and 19 (with slight fluctuations), while the vagotonic ones showed a similar trend, i.e., between -8 and -3. Symptom trends are showed in table 5.

Week of treatment	Sympathicotonic	Vagotonic
1 - 2	30	-1
		-6
3 - 5	14	-12
	2	-18
	0	-22
6 - 9	14	-10
	4	-7
	10	-7
	4	-18
10 - 15	12	-8
	19	-3

Table 5*: Symptom trends during the 15-treatment week.*

Clinical interviews and psychometric evaluations highlight an experience characterized by less labile emotionality, by a clinically significant reduction of anxious and depressive symptoms and by a better ability to self-regulate. The psychometric measurement turns out

to be within normal values after 15 weeks of treatment: the SCL Global Symptom Index score went from a value of 1.622 at T0 to a value of 0.722 at T1; the BDI score was 18 at T0 and 13 at T1; the initial HAMD score was 14 to decrease to 8 at a second evaluation; finally, the score on the pre-treatment HAMA scale was 18 then decreased to 7 in the final assessment (Table 3 and 4).

Data relating to treatment sessions with clinical Neurofeedback allow to observe a progressive increase in Alpha and Theta rhythms over the course of the fifteen weeks.

With regards to the Neurofeedback sessions, we highlight an initial phase relating to the first two sessions in which the rhythms being treated were markedly below the threshold.

Subsequently, between the third and fifth session, the patient began to interact with the operators and with the setting in a less dysfunctional way and the extinction of the panic attacks in daily life was an important facilitation for carrying out the sessions which progressively become rewarding to the patient as she observed the reinforcing feedback.

Although in the same weeks there was a clinically significant depressive experience, the clinical setting was perceived as a relief.

The central sessions in the treatment path, i.e. from the sixth to the ninth, were characterized by a moderate rhythmic fluctuation of the Alpha and Theta values with a certain emotional lability well tolerated by the patient. The final weeks of the clinical course, characterized by better emotional stability and restoration of psychophysiological parameters close to normotonia, were accompanied by EEG neural correlates which highlighted Alpha and Theta rhythms in the normative range without pathological oscillations.

Conclusion

Anxiety disorders are characterized by a dysfunctional activation that leads to a sympathicotonic psycho-organic alteration. An incorrect interpretation of physiological signals may lead the patient to develop cognitive and behavioral symptoms (such as fear, anguish, avoidance behaviours) significantly altering the quality of life.

The clinical pathway aimed at the reduction of acute symptoms in a patient diagnosed with panic disorder - DSM-5 diagnostic code 300.01; ICD-10-CM (F41.0) - showed evidence of efficacy measured with all clinical tools used (Neurotest, Neurofeedback, psychometric scales).

The Neurotest is a self-report evaluation tool of sympathetic-parasympathetic responses, monitored through a numerical scale; it is also useful for evaluating the effects of the therapies administered to the patient. In this clinical case, the Neurotest facilitated the understanding and sharing of the symptoms experienced by the patient, supporting and guiding the therapeutic choices of the clinical team, and allowing the patient to develop a better insight and reinforce compliance.

The preliminary Self Report evaluation of Neurotest indicated a sympathicotonia value of 29 (with a maximum value of 30 in correspondence with the epileptoid crisis) which decreased to 12 at the end of the treatment; the vagotonia value at T0 was -1 (with a peak of -22 in the reparative phase immediately following the epileptoid crisis) which settled at -3 at T1. The initial GABAergic Self Report Neurotest evaluation was -8 then passed to a value of 6 at the end of treatment.

Neuromodulation through treatment with clinical Neurofeedback produced the results of which the values at T0 and T1 are reported in relation to the section dedicated to Training (Figure 6):

- Alpha Theta Minimum T0 3.499; Alpha Theta Minimum T1 15,492
- Alpha Theta Max T0 16.792; Alpha Theta Max T1 66,271
- Alpha Theta Average T0 10.146; Alpha Theta Average T1 40.882.

The psychometric measurement turns out to be within normal values after 15 weeks of treatment (Table N.). The SCL Global Symptom Index score went from a value of 1.622 at T0 to a value of 0.722 at T1; the BDI score was 18 at T0 and 13 at T1; the initial HAMD score was 14 to decrease to 8 at a second evaluation; finally, the score on the pre-treatment HAMA scale was 18 then decreased to 7 in the final assessment.

In addition to the strictly evidence-based measurements, it is necessary to explain the clinical reasoning underlying the therapeutic choices. Panic Disorder is characterized by excessive attention paid to the internal world both in an organic and psychological sense; before therapy, our patient turned every proprioceptive and cognitive resource to an almost obsessive listening with the aim of anticipating the onset of a panic attack without relating the occurrence of this event to the context, thus depriving it of meaning. The panic attack, psycho-physiological culmination of sympathicotonic activation, becomes a "means of discharge" which allows a subsequent (momentary and partial) repair to then resume the same cycle with increasing rhythmicity: the patient had reached up to 5 panic attacks on the same day.

In this sense, the Neurotest has made it possible to establish a different way of relating the symptoms experienced and the outside world through sharing with the clinician, the clinical interview and mentalisation. The actual therapeutic act was therefore achieved through this mediation function which placed the patient at the centre of the treatments as an active part, worthy of listening to by the clinician, seen as a whole and not hidden in mere numerical values.

In view of this case study, a widespread integration of the Neurotest in clinical practice seems desirable as a tool to facilitate both the therapeutic alliance and the constant monitoring of the effects of the care.

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Volume 15 Issue 4 April 2023