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Neurobiological and Psychological Correlates of Suicidal Attempts and Thoughts of Death in Patients with Major Depression

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Depression · Suicide · Thoughts of death · Neurobiology · Psychophysiology · Fenfluramine

Abstract
Suicide is a major problem for psychiatry. Depression is the most common mental disorder related to suicidal behavior. The present study aimed at investigating the relationship between the symptomatology related to death, dying, and suicide and neurobiological factors in depressed patients. Fifty patients aged 21–60 years suffering from major depression were investigated. Schedules for Clinical Assessment in Neuropsychiatry version 2.0 and the International Personality Disorder Examination were used to assist the clinical diagnosis. The psychometric assessment included the Hamilton Depression Rating Scale, the Hamilton Anxiety Scale, the 1965 and 1971 Newcastle Depression Diagnostic Scales, the Diagnostic Melancholia Scale, the General Assessment of Functioning Scale, and the Personality Deviance Scale. Psychophysiological methods included electrooculogram, flash electroretinogram under photopic and scotopic conditions, and pattern-reversal visual evoked potentials. Biological markers included the 1-mg dexamethasone suppression test, the 30-mg dexfenfluramine challenge test, and brain ^{99m}Tc-HMPAO SPECT. Statistical analysis included one-, two-, and three-way Manova and Mancova and the Scheffé test as post hoc test. Patients without thoughts of death had higher self-confidence levels and less overdependency on others and intropunitiveness. The suicidal patients had a significantly prolonged pattern-reversal visual evoked potential latency in comparison with the other patients. The findings of this were related to the status of the patient at the time of the interview but not to his/her history. They also provide neurobiological data to support the need for a combined presence of self-directed aggression and a higher arousal level or disinhibition of self-directed aggressive thoughts in order for a patient to become suicidal. Further study is needed to test whether psychophysiological methods, which are noninvasive and easy to perform, are of value in the therapeutic planning and monitoring of responses.

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Introduction

Suicide is a major problem for psychiatry. Thoughts of death and suicidal ideation are what preexist and may lead to the manifestation of suicidal behavior. Although it is believed that patients who complete a suicidal act may differ from those who attempted and failed, in practice common features are so many that it is impossible to succeed in a reliable distinction. The old distinction between 'true' and 'superficial' attempts is considered to be unreliable and even dangerous, because it may lead to the underestimation of the danger the patient faces.

According to Stengel [1], the suicide rate varies from 10 to 20 per 100,000 people. However, Nasr [2] stressed the unsatisfactory way of recording attempts and assumed that the true rates are double or triple of those reported. Even according to official numbers, suicide was the 9th leading cause of death in the USA.

The suicidal rate in Greece is reported to be low (<5 per 100,000), but recording is even more problematic, and data are far from reliable due to cultural and religious matters. The use of firearms is not usual, because in Greece it is illegal to possess a gun. Men generally choose more violent ways (hanging, falling), while women choose poisoning [3, 4]. Internationally, the most common way of committing suicide is by taking large quantities of medication (50%) [5, 6], and in Greece this is reported to be even more common (80%) [7, 8].

Depression is the most common nosological entity related to the manifestation of suicidal behavior [9, 10], although proportions vary from 25 to 60%. It is reported that 15% of the patients with affective disorders will attempt suicide [11].

Thoughts of death and suicidal ideation are common symptoms in depressed patients, both before and after a suicidal attempt. However, this symptomatology is not concrete; many patients may fear that they will die, but do not wish to die, while others seem determined to kill themselves. It is not clear whether these states constitute consecutive phases or represent distinct symptoms and reflect a qualitatively different underlying psychopathology.

The aim of the present study was to investigate whether specific biological markers [dexamethasone suppression test DST), dexfenfluramine test], psychophysiological methods (pattern-reversal visual evoked potentials; PR-VEPs), and imaging methods, all with proven value in depression research, relate to death, dying, and suicide. A second approach was to investigate the role of self-directed aggression and suicidal tendency. The protocol permitted to approach the issue from different angles concerning the present clinical picture and the past history of the patient.

Patients and Methods

Fifty patients (15 males and 35 females) aged 21–60 (mean ± SD 41.0 ± 11.4) years, suffering from major depression according to DSM-IV [12], took part in the study. All provided written informed consent. Fourteen of them fulfilled the criteria for atypical features, 16 for melancholic features, and 32 for somatic syndrome (according to ICD-10). Also, 9 patients did not fulfill criteria for any specific syndrome.

All were inpatients or outpatients of the 3rd Department of Psychiatry, Aristotle University of Thessaloniki, University Hospital AHEPA, Thessaloniki, Greece. All were free from any medication for at least 2 weeks prior to the first assessment and diagnosis. In no case medication was interrupted in order to include the patient in the study. In addition, all were physically healthy with normal clinical and laboratory findings, including electroencephalogram and thyroid function, and without pathological findings on ophthalmological examination. There was a great effort to exclude all patients who due to special characteristics might contribute to the production of confounding results (e.g., obesity, puerperium, etc.). Also, a particular effort was made to exclude patients with alcohol or nicotine abuse.

No patient fulfilled criteria for catatonic or psychotic features or for seasonal affective disorder. Also, no patient fulfilled criteria for another DSM-IV axis I disorder, except for generalized anxiety disorder and panic disorder, and no one had a past history of manic or hypomanic episodes. Axis II disorders were also registered.

All patients had a history of no more than five distinct episodes, including the present one (mean 1.16 ± 1.53). All patients were right-handed, and the right eye was the dominant one.

It should be noted that all suicidal attempts were not 'violent' and were performed by swallowing of pills, drugs, or poison. The patients had a rather impulsive character, and no notes were prepared before attempting.

Clinical Diagnosis

The Schedules for Clinical Assessment in Neuropsychiatry version 2.0 [13] and the International Personality Disorders Examination (IPDE) [14, 15] were used to assist the clinical diagnosis which was reached by consensus of two examiners, according to DSM-IV criteria.

Laboratory Testing

This included blood and biochemical parameters, testing for pregnancy, T_3, T_4, thyroid-stimulating hormone, vitamin B_{12} and folic acid, and electroencephalogram.

Psychometric Assessment

This included the Hamilton Depression Rating Scale (HDRS) [16, 17], the Hamilton Anxiety Scale (HAS) [18], the 1965 and 1971 Newcastle Depression Diagnostic Scales (1965-NDDS and 1971-NDDS, respectively) [19], the Diagnostic Melancholia Scale (DMS) [19], the General Assessment of Functioning Scale (GAF) [12], and the Personality Deviance Scale (PDS) [20]. The PDS consists of the following subscales:

Extrapunitive Scale (ES). This consists of (1) HT (Hostile Thoughts) and (2) DO (Denigratory Attitudes Toward Other People). The ES and subscales are scored in such a way that high scores denote lack of the characteristic.

Intropunitive Scale (IS). The IS consists of (1) LSC (Lack of Self-Confidence) and DEP (Overdependency on Others). The IS and subscales are scored in such a way that high scores denote the presence of the characteristic.

Dominance Scale (DS). This consists of (1) MIN (Domineering Social Attitude) and (2) HA (Uninhibited Hostile Acts). The MIN is scored in such a way that high scores denote the presence of the characteristic, while HA has opposite properties.

Z-values were used for ES, IS, and DS and raw scores for the rest.

On the basis of clinical and psychometric data, the patients were divided into three groups. The first group included those without death thoughts (no thoughts of death at all or wondering whether life has no meaning), the second group included those with no specific thoughts about death (afraid that they will die or wish to die), and, finally, the third group included truly suicidal patients (thinking or planning suicide). If we attributed a score equal to 0 for the members of the first group, one equal to 1 for the members of the second group, and one equal to 2 for the members of the third group, then we take a new categorical variable which was named 'death thoughts rating' and is somewhat different from the rating of the HDRS item No. 3.

Data Concerning Personal and Family History and Stressful Life Events

The family history method [21–23] was used for this purpose. The questionnaire of Holmes [see 24] was used to search for stressful life events during the last 6 months before the onset of the symptomatology. The patients were carefully questioned concerning the presence of at least one first-degree predecessor with any type of dementia.

Psychophysiological Methods

Electro-Oculogram (EOG). This is a method for the study of the electrical and metabolic activity of the outer layers of the retina. During the adaptation of the retina to dark, the amplitude of the EOG gradually decreases, reaching a nadir (dark trough). During the adaptation to light (ganzfeld, 1,200 lx), the amplitude of the EOG gradually increases, reaching a zenith (light peak). The systematic development of the method of the EOG was made mainly by Arden et al. [25] and Arden and Kelsey [26], and the conditions for EOG recording have been coded by the International Society for Clinical Electrophysiology of Vision [27], and this was kept in the current study. However, some deviations from these conditions were inevitable. These included the use of three instead of four electrodes, the recording every 2 min for 12 min instead of every minute for a 15-min period, and not dilatated pupils. A video camera was used to verify that the patients were following the instructions and moved their eyes to catch the alternating lights.

The EOG was recorded from two electrodes attached to the outer canthus (Lc and Rc) and a third to the mideye (Mr). The movement of the eyes produces a change of potentials which is recorded by the electrodes. After the recording of several movements of the eyes, the averaging of potentials gives the mean potential for the given conditions (interaction of time with lighting conditions). The procedure includes recordings of eye movents every 2 min, for 12 min in the dark and subsequently 12 min under light conditions.

There is no difference of the recorded EOG curves between the two eyes when both are healthy [28]. The most widely used index for the interpretation of the EOG is the Arden ratio:

$$\text{Arden ratio} = \frac{\text{light} - \text{peak}}{\text{dark} - \text{trough}} \times 100 \quad (1)$$

The normal values of this index lie between 162 and 228, but values under 180 should be considered borderline.

Flash Electroretinogram (ERG). This is a method for the recording of retinal potentials following the fall of light stimuli. The ERG can be recorded after flash (f-ERG) or pattern-reversal (PR-ERG) stimulation. In the current study, binocular f-ERG was used. The ERG recordings have been coded by the International Society for Clinical Electrophysiology of Vision, and this was kept in the current study. However, some deviations from these conditions were inevitable. These included the use of skin electrodes and lack of maximum dilatation of the pupil. The f-ERG curve includes mainly the waves a and b. Wave a is photochemical in origin and is produced in the photoreceptors as their response to a light stimulus [29]. Wave b is produced by the bioelectrical activity of the neurons of the inner granule layer and the bipolar cells. It is neuronal in origin.

In the current study, f-ERGs were recorded under photopic conditions from two electrodes attached below the eyes (Lr and Rr) and a reference electrode attached at the mideye (Mr) from both eyes simultaneously (binocular).

Pattern-Reversal Visual Evoked Potentials. These were used for the assessment of the functioning of the visual cortex and indirectly to assess the general speed of neurotransmission in the CNS. The recording was made from each eye separately from sites Oz, O1, and O2 with the Fz as reference in order to better isolate the occipital cortex recordings as recommended by Chiappa [30], and P100 wave amplitude and latency were measured, since it is the sole waveform stable enough and having a low variability to be used in clinical trials and research [30]. Flash VEPs (f-VEPs), both under photopic and scotopic conditions, were recorded as well, in order to secure that the vision of the subjects was normal. This kind of VEPs requires only qualitative (presence of the curve and within a reasonable time range) but not quantitative analysis of amplitude and latency, because of a large variability in the normal population. The recording of f-VEPs was made from both eyes simultaneously under scotopic and photopic conditions from sites Oz, O1, and O2 with the Fz as reference, and P100 wave amplitude and latency were estimated. Flash VEP data are not reported in the current paper, because they are unsuitable for research purposes.

In the current study, the distance of the subject's head from the monitor was 150 cm. The size of the rectangles was 2.2 cm, and the frequency of the stimuli was 1 Hz. The contrast was 95%, and the luminance of the white rectangles was 250 cd/m^2. Every rectangle covered 60′ of the visual arc, and the whole checkerboard covered 25° of the visual arc. The time of analysis was 200 ms, the gain of amplifiers was 1,000 μV/cm, the time constant was 0.1 s, and the upper frequency response was 500 Hz (–3 dB). The movement of the checkerboard was from left to right.

Specific Issues. All recordings were conducted around midday (12.00–16.00 h), and there was no difference in the time of the day or the season of the year the groups were studied. The electrodes used in the current study were made of Ag-AgCl (Burden Neurological Institute, Bristol, UK). The impedance was below 5 kΩ at 40 Hz. All patients came from northern Greece (latitude 40–40.1° North).

Biological Markers

Dexamethasone Suppression Test. The DST mainly reflects the hypothalamic-pituitary-adrenal axis and the norepinephrine activity [31–37]. The 1-mg DST protocol demands the oral administration of 1 mg dexamethasone at 23.00 h of the 1st day and determination of the cortisol serum levels simultaneously and on the next day at 16.00 and 23.00 h. The cortisol levels (μg/dl) were measured using the luminance immunoassay (intra-assay reliability 4.9%; interassay variability 7.5%). The nonsuppression cutoff level was 5 μg/dl.

Dexfenfluramine Challenge Test. This is supposed to reflect the central serotonin activity [38–47]. The protocol of the 30-mg *d*-fenfluramine challenge test dictates an overnight fasting and the oral administration of 30 mg of the substance. The measurement of prolactin (and maybe of cortisol; not done in the current study) plasma levels was made in samples taken 15 min before the *d*-fenfluramine administration, at the time of administration, and 60, 120, 180, 240, and 300 min thereafter. The samples were taken through a heparinized intravenous catheter. The prolactin and cortisol responses are reported to be lower in depressed patients as compared with controls. In the current study, only prolactin was measured. The assay was the same as that used for the cortisol level determinations.

Brain Single-Photon Emission Computed Tomography (SPECT). This method [48] requires intravenous injection of 15 mCi (555 MBq) of the radioligand ^{99m}Tc-hexamethylpropyleneamine oxime (Ceretec®; Amersham, Little Chalfont, UK) to the patient. The procedure takes place in a quiet room, with the eyes open. The patient stays for about 15 min before the injection. Tomographic imaging takes place 10–30 min after the injection. A gamma camera (ADAC Laboratories, Milpitas, Calif., USA) was used. One hundred and twenty slices are taken, each corresponding to 20 s. The reconstruction of the images is made on a vertical axis with the use of a Butterworth filter (with a frequency of 0.50 Hz and a coefficient for correction of radiation attenuation of 0.12 cm^{-1}). The images are then related to three axes: a vertical, a horizontal, and a coronary. For quantified analysis, the region of interest is 4 × 4 pixels, corresponding to a brain tissue volume of 1.15 cm^3. The regional cerebral blood flow was determined in proportion to the cerebellar blood flow. The regions of interest included the cerebellum, the thalamus, the caudate nucleus, the globus pallidus, and the frontal, parietal, temporal (lateral and medium), and occipital lobes of both hemispheres. Brain stem blood flow and ratio right-to-left hemisphere were also calculated. All brain SPECT examinations took place between 10.00 and 14.00 h.

Statistics

The following grouping methods were used: (1) two groups defined by the presence or not of a recent suicide attempt;. (2) two groups defined by the presence or not of a suicide attempt ever in the past, and (3) three groups defined by the 'death thoughts rating' variable (A = no thoughts of death, B = nonspecific thoughts of death, C = suicidal ideation).

These patient groups were compared concerning: (1) clinical and demographic variables with one-way Manova; (2) DST and dexfenfluramine challenge test with one-way Mancova with age as covariate; (3) brain SPECT results with two-way Ancova with age as covariate; (4) EOG results with one-way Mancova with age as covariate; (5) ERG results with two-way Mancova with age as covariate, and (6) PR-VEPs results with three-way Mancova with age as covariate. Since 18 analyses were performed, the use of the Bonferroni correction defined the appropriate significance level at $p < 0.0027$ (0.05 divided by 18). The Scheffé test was used for post hoc comparisons. For these comparisons the $p < 0.05$ level was used to define significance.

Results

The Two Groups Defined by the Presence or Not of a Recent Suicide Attempt

Five patients (10%) from the total sample had recently attempted suicide. There was no difference in any of the variables between those who had and those who had not attempted suicide recently.

The Two Groups Defined by the Presence or Not of a Suicide Attempt Ever in the Past

Thirteen patients (26%) had attempted suicide at least once in the past. There was no difference in any of the variables between those who had and those who had not attempted suicide in the past.

The Three Groups Defined by the 'Death Thoughts Rating' Variables

Thoughts of death (criterion No. 9 according to DSM-IV) were present in 24 patients (48%). More specifically, 11 patients had no thoughts of death, 6 were wondering whether life has no meaning, and 9 were afraid that they will die (total so far 26 not fulfilling criterion No. 9); 14 were wishing to die, 7 were thinking of suicide, and 3 were planning their death (14 + 7 + 3 = 24 fulfilling criterion No. 9).

All patients with a recent attempt had also a positive previous history of a recent attempt. Four of them had thoughts of death at the time of the interview at the level of suicidal ideation, and all were women. Of the patients with a positive history of a suicide attempt, 8 had thoughts of death, and 5 had not. Six patients had suicidal ideation at the time of the interview.

The scoring of the variable 'death thoughts rating' produced 17 cases of '0' (group A: the 11 patients with no thoughts of death and the 6 who were wondering whether life has no meaning), 23 cases with '1' (group B: those 9 who were afraid that they will die and those 14 who were wishing to die), and 10 cases with '2' (group C: those 7 who were thinking of suicide and the 3 who were planning their death).

As all patients with a recent attempt had a positive history, they all received a score of 2. Of those with positive history, 1 received a score equal to 0, 6 one equal to 1, and 6 one equal to 2. 4 out of 17 patients with a score of 0, 4

Table 1. One-way Manova results concerning the comparison of clinical and demographic variables in the three clinical groups (mean ± SD)

Post hoc Scheffé test	No thoughts of death (A)	Nonspecific thoughts of death (B)	Suicidal ideation (C)	p		
				A vs. B	A vs. C	B vs. C
Age	41.88 ± 10.24	42.70 ± 10.50	37.00 ± 15.02	NS	NS	NS
Age of onset	34.41 ± 11.85	32.09 ± 11.42	27.00 ± 10.31	NS	NS	NS
Numberof episodes	1.29 ± 1.57	1.17 ± 1.72	0.90 ± 0.99	NS	NS	NS
Number of DSM criteria	5.76 ± 0.83	6.70 ± 1.26	7.40 ± 1.26	NS	*0.026*	NS
Number of atypical features	1.35 ± 0.61	1.26 ± 1.10	0.40 ± 0.70	NS	NS	NS
Number of melancholic features	1.94 ± 1.52	2.17 ± 1.40	3.40 ± 1.78	NS	NS	NS
Number of ICD criteria	6.12 ± 1.05	7.17 ± 1.11	8.20 ± 1.55	NS	NS	NS
Number of somatic syndrome criteria	3.94 ± 1.75	4.22 ± 1.81	5.90 ± 1.91	NS	NS	NS
GAF	58.82 ± 15.26	51.17 ± 11.01	41.00 ± 14.10	NS	NS	NS
NDDS-1965	3.68 ± 2.66	4.93 ± 2.07	5.90 ± 2.46	NS	NS	NS
NDDS-1971	−1.35 ± 17.67	−6.57 ± 17.41	−16.85 ± 22.37	NS	NS	NS
Endogenous axis of DMS	3.88 ± 3.00	4.22 ± 2.94	6.70 ± 3.06	NS	NS	NS
Reactive axis of DMS	6.65 ± 1.62	5.39 ± 2.43	5.10 ± 2.56	NS	NS	NS
Number of personality disorders (PD)	0.41 ± 0.62	0.26 ± 0.45	0.20 ± 0.42	NS	NS	NS
Number of PD criteria	3.47 ± 4.20	1.96 ± 3.34	1.80 ± 3.79	NS	NS	NS
Number of Life Events	2.88 ± 2.12	2.74 ± 1.84	0.80 ± 1.14	NS	NS	NS
HDRS-17	23.71 ± 3.69	24.13 ± 4.88	31.80 ± 5.43	NS	*0.009*	*0.012*
HDRS-21	26.00 ± 3.95	25.70 ± 5.70	34.00 ± 6.43	NS	*0.035*	*0.017*
HDRS depressed index	7.94 ± 2.36	10.65 ± 1.80	13.10 ± 2.47	*0.001*	*<0.001*	*0.011*
HDRS anxiety index	5.88 ± 2.45	5.35 ± 2.12	6.30 ± 3.02	NS	NS	NS
HDRS sleep index	3.47 ± 1.33	3.26 ± 2.14	4.50 ± 2.27	NS	NS	NS
HDRS nonspecific index	7.06 ± 1.95	5.35 ± 2.46	8.90 ± 2.69	NS	NS	*0.035*
HAS	34.29 ± 8.54	28.65 ± 11.91	31.90 ± 11.45	NS	NS	NS
HAS somatic subscale	18.24 ± 6.12	13.61 ± 7.77	14.10 ± 7.71	NS	NS	NS
HAS psychic subscale	13.12 ± 3.46	11.87 ± 4.78	14.50 ± 4.88	NS	NS	NS
PDS HT	18.31 ± 3.94	18.43 ± 3.01	18.50 ± 3.16	NS	NS	NS
PDS DO	13.88 ± 3.12	12.19 ± 3.61	11.38 ± 2.62	NS	NS	NS
PDS ES	0.91 ± 0.88	0.53 ± 0.92	0.35 ± 0.75	NS	NS	NS
PDS LSC	10.88 ± 1.75	15.19 ± 4.47	14.13 ± 5.11	*0.007*	NS	NS
PDS DEP	13.38 ± 2.78	16.76 ± 3.02	16.75 ± 3.88	*0.008*	NS	NS
PDS IS	−0.99 ± 0.95	0.66 ± 1.34	0.31 ± 1.72	*0.002*	NS	NS
PDS MIN	17.63 ± 4.35	14.90 ± 3.39	17.63 ± 2.92	NS	NS	NS
PDS HA	16.56 ± 3.61	19.24 ± 4.12	18.13 ± 2.80	NS	NS	NS
PDS DS	0.96 ± 1.23	0.98 ± 1.37	1.40 ± 0.78	NS	NS	NS

Wilks' lambda: 0.000832; Rao's R: 11.57437; d.f.: 64, 22; $p < 0.0001$.

out of 23 patients with a score of 1, and none of those with a score of 2 were men. The comparison of the three groups defined by the 'death thoughts rating' variable revealed the results shown in tables 1–6.

Concerning the clinicodemographic variables, it is interesting that the groups did not differ in terms of anxiety, and any difference in the clinical picture of depression reflects the differentiation of suicidal patients at interview (group C) from the other two groups. What is more interesting is that the PDS results suggest that group A is the one that differs from the other two which both were characterized by a low self-confidence, overdependeny on others, and intropunitiveness (table 1).

There was no difference between the three groups concerning the DST, dexfenfluramine (table 2), SPECT (table 3), EOG (table 4), and ERG (table 5) results. It should be mentioned and stressed that repetition of the analysis, including or excluding patients with significant weight

Table 2. One-way Mancova (with age as covariate) results concerning the comparison of DST and dexfenfluramine challenge test results in the three clinical groups (mean ± SD)

	No thoughts of death (A)	Nonspecific thoughts of death (B)	Suicidal ideation (C)
DST			
DST cortisol on day 1 at 23.00 h	5.58 ± 7.57	4.30 ± 2.89	4.54 ± 2.71
DST cortisol on day 2 at 16.00 h	3.47 ± 5.94	2.28 ± 3.25	2.86 ± 2.81
DST cortisol on day 2 at 23.00 h	3.61 ± 3.89	2.91 ± 3.76	2.28 ± 2.32
D-Fenfluramine challenge test			
Prolactin at –15 min	481.93 ± 191.21	698.08 ± 421.79	871.62 ± 504.89
Prolactin at 0 min	473.91 ± 231.55	687.76 ± 413.60	847.18 ± 456.13
Prolactin at 60 min	414.18 ± 187.93	607.66 ± 402.81	779.00 ± 419.34
Prolactin at 120 min	374.76 ± 169.90	623.90 ± 468.81	834.00 ± 459.31
Prolactin at 180 min	384.26 ± 200.32	652.33 ± 472.63	960.62 ± 609.22
Prolactin at 240 min	479.24 ± 224.84	799.39 ± 469.07	1,000.56 ± 577.16
Prolactin at 300 min	470.53 ± 198.28	717.78 ± 504.16	1,000.80 ± 568.02
Maximum prolactin change	40.48 ± 209.32	137.59 ± 232.94	210.14 ± 316.28

There are no significant differences between the groups, although the prolactin levels seem to increase from group A to group C.

Wilks' lambda: 0.585; Rao's R: 0.977207; d.f.: 22, 70; p = 0.5023.

Table 3. Two-way Ancova (with age as covariate) results concerning the comparison of SPECT results (z-values) in the three clinical groups (mean ± SD)

	No thoughts of death (A)	Nonspecific thoughts of death (B)	Suicidal ideation (C)
Brain stem	0.38 ± 0.78	0.57 ± 0.86	0.30 ± 1.06
Right frontal lobe	0.59 ± 1.40	0.08 ± 1.28	–0.60 ± 1.56
Left frontal lobe	–0.61 ± 2.29	–0.48 ± 1.65	–0.87 ± 1.66
Right parietal lobe	–2.18 ± 2.32	–1.06 ± 1.82	–1.57 ± 1.62
Left parietal lobe	–3.20 ± 2.52	–1.77 ± 2.10	–2.00 ± 2.07
Right lateral temporal lobe	–1.12 ± 1.61	–1.23 ± 1.27	–1.67 ± 1.82
Right medial temporal lobe	–1.04 ± 1.89	–1.36 ± 1.68	–1.67 ± 1.92
Left lateral temporal lobe	–2.20 ± 2.05	–1.58 ± 1.69	–1.63 ± 1.66
Left medial temporal lobe	–1.82 ± 2.32	–1.07 ± 1.50	–1.37 ± 1.70
Right occipital lobe	–0.18 ± 1.28	0.61 ± 1.17	0.20 ± 0.98
Left occipital lobe	–1.00 ± 0.59	–0.60 ± 0.83	–0.84 ± 0.48
Right thalamus	–0.45 ± 0.82	–0.16 ± 0.66	–0.23 ± 0.69
Left thalamus	–1.07 ± 1.17	–0.50 ± 0.81	–0.88 ± 0.67
Right caudate nucleus	–1.31 ± 1.51	–0.96 ± 1.13	–1.28 ± 1.10
Left caudate nucleus	–0.93 ± 1.59	–0.52 ± 1.51	–0.30 ± 0.70
Right globus pallidus	–0.68 ± 0.85	–0.38 ± 0.70	–0.47 ± 1.33
Left globus pallidus	–1.42 ± 1.24	–0.79 ± 0.75	–0.92 ± 0.32

There are no significant differences between the groups.

	d.f. effect	MS effect	d.f. error	MS error	F	p
1	2	1.474	46	0.726	2.031	0.143
2	16	1.457	752	0.129	11.325	<0.001
1, 2	32	0.150	752	0.129	1.167	0.243

1 = Death thoughts rating; 2 = brain region.

Table 4. One-way Mancova (with age as covariate) results concerning the comparison of EOG results in the three clinical groups (mean ± SD)

	No thoughts of death (A)	Nonspecific thoughts of death (B)	Suicidal ideation (C)
Left dark trough	161.65 ± 37.96	179.26 ± 69.52	205.60 ± 36.04
Left light peak	433.18 ± 89.51	446.43 ± 152.49	512.90 ± 109.85
Right dark trough	151.53 ± 64.69	174.26 ± 49.71	188.20 ± 42.16
Right light peak	359.82 ± 69.93	421.52 ± 116.54	430.80 ± 109.06
Left Arden ratio	277.22 ± 66.67	253.75 ± 34.52	250.31 ± 43.09
Right Arden ratio	258.35 ± 64.11	249.69 ± 53.94	228.88 ± 27.72

There are no significant differences between the groups.
Wilks' lambda: 0.667; Rao's R: 1.530; d.f.: 12, 82; p = 0.1299.

Table 5. Two-way Mancova (with age as covariate) results concerning the comparison of ERG results in the three clinical groups (mean ± SD)

	No thoughts of death (A)	Nonspecific thoughts of death (B)	Suicidal ideation (C)
Left-eye a-wave latency	0.51 ± 0.68	0.63 ± 1.13	0.20 ± 0.58
Left-eye b-wave latency	0.26 ± 0.78	0.54 ± 1.07	0.87 ± 1.03
Right-eye a-wave latency	−0.01 ± 0.64	0.36 ± 1.31	−0.09 ± 0.22
Right-eye b-wave latency	0.24 ± 0.85	0.50 ± 1.02	0.96 ± 0.98

There are no significant differences between the groups.

	Wilks' lambda	Rao's R	d.f. 1	d.f. 2	p
1	0.845	1.841	4	84	0.128
2	0.802	5.298	2	43	0.008
1, 2	0.960	0.438	4	86	0.780

1 = Death thoughts rating; 2 = eye.

loss or psychomotor retardation, did not change the above results, so these variables should not be considered as confounding variables for the current study.

On the contrary, there was a significant difference concerning the P100 latency of the PR-VEPs (table 6), suggesting again that groups A and B do not differ from each other; however, they both differ from group C. Suicidal patients manifested significantly prolonged PR-VEP latencies in comparison to the rest of the patients.

Discussion

The current study showed that 10% of the depressed patients from the study sample had recently attempted suicide and that 26% had attempted suicide at least once in the past. Also, 48% were experiencing some kind of thoughts of death at the time of the interview. None of the nonclinical variables assessed showed strength in the recognition of these patients. There was no difference in any of the variables between those who had and those who had not attempted suicide recently.

The three groups defined as (A) patients without thoughts of death at the time of the interview (34% of the

Table 6. Three-way Mancova (with age as covariate) results concerning the comparison of PR-VEPs results in the three clinical groups (mean ± SD)

	No thoughts of death (A)	Nonspecific thoughts of death (B)	Suicidal ideation (C)	p		
				A vs. B	A vs. C	B vs. C
Left-eye Oz latency	100.26 ± 5.28	102.65 ± 4.52	107.04 ± 9.92	NS	*0.0122*	NS
Left-eye O1 latency	100.59 ± 6.15	102.39 ± 3.84	106.92 ± 9.02	NS	*0.0173*	NS
Left-eye O2 latency	100.43 ± 5.99	102.72 ± 5.27	106.92 ± 9.12	NS	*0.0231*	NS
Right-eye Oz latency	101.60 ± 7.14	101.84 ± 6.14	108.36 ± 11.85	NS	*0.0411*	*0.0376*
Right-eye O1 latency	101.51 ± 7.29	100.98 ± 6.99	108.82 ± 11.91	NS	*0.0362*	*0.0158*
Right-eye O2 latency	101.81 ± 6.97	102.10 ± 5.79	108.41 ± 11.76	NS	*0.0386*	*0.0374*

There is a main effect of the clinical groups.

	d.f. effect	MS effect	d.f. error	MS error	F	p
1	2	1,444.325	46	171.280	8.433	*0.0008*
2	2	8.924	94	15.028	0.594	0.5543
3	1	5.981	47	8.103	0.738	0.3947
1, 2	4	18.002	94	15.028	1.198	0.3170
1, 3	2	2.719	47	8.103	0.336	0.7167
2, 3	2	1.949	94	6.607	0.295	0.7452
1, 2, 3	4	8.532	94	6.607	1.291	0.2790

1 = Death thoughts rating; 2 = recording site (Oz, O1, or O2); 3 = eye.

total sample), (B) patients with nonspecific thoughts of death (constituted 46% of the total sample), and (C) suicidal patients (20% of the total sample) did not differ in terms of anxiety, and the differences found concerning the depressive symptoms were the expected ones. An interesting finding was that patients with nonspecific thoughts of death as well as the suicidal ones were characterized by low self-confidence, overdependency on others, and high intropunitiveness. Concerning the laboratory and biological investigations, there were no differences between the three groups concerning DST, dexfenfluramine, SPECT, EOG, and ERG results. The only significant finding was the prolongation of P100 PR-VEP latency in the suicidal group in comparison to the two others.

The international literature suggests that the level of emotional arousal is of prime importance for the expression of aggression. It seems that the serotonin activity cannot be linked with aggression, when an adequate level of emotional alertness is not present [49]. The review of the results of the current study suggests that depressed patients without thoughts of death had a low level of self-directed aggression (as shown by their PDS scores) and a normal P100 latency. Patients with no specific thoughts of death had a high level of self-directed aggression and a normal P100 latency. Finally, suicidal patients, besides a high level of self-directed aggression, had also prolonged P100 latencies. Thus, it could be proposed that in our case, the P100 latency of the PR-VEPs could reflect either an increased level of arousal or a disinhibition problem.

The literature suggests that patients who attempted suicide may suffer from a decreased serotonin activity, at least in the brain stem. The problem may lie in the imbalance between the inhibition of behavior mediated through serotonin and the level of arousal mediated by catecholamines and particularly by acetylcholine [50, 51]. So, the patient may express aggression towards the environment or towards himself on the basis of a lower threshold. According to Depue and Spoont [50], the inhibition of behavior is mediated by serotonin and its release by norepinephrine and dopamine. A series of studies made clear that the above concerns only impulsive physical aggression and not physical aggression in general [52–55]. According to the results of the current study, these suggestions are expanded to include suicidal ideation and non-

violent suicide attempts. Coccaro and Kavoussi [56] reported that even the past history of serious impulsive aggressive behavior is related to serotonin disorders.

In a previous paper by our group (which was conducted on the same sample of patients) [57], the comparison of patients with 'fast' and 'delayed' PR-VEPs showed that the characterizing variables were stressful life events and melancholic symptomatology, respectively. These findings were in accord with the suggestions of Buchsbaum [58] and Buchsbaum et al. [59] that humans can be divided into 'reducers' (analogous to melancholics) and 'augmenters' (analogous to atypicals) by means of their psychophysiological response to an increasing intensity of external stimuli. Gender seems to play an important role also [60]. 'Reducers' are considered to protect themselves from sensory overload, perhaps as a compensatory adjustment for hypersensitivity at lower levels. In the current study, the suicidal patients were 'reducers'. Also, the results of the current study are in accord with those of the work of Shagass [61] and Shagass and Roemer [62] in that electrophysiological measures of psychotic and neurotic depressed patients deviate in opposite directions.

In contrast to flash visual evoked potentials, PR-VEPs are the most reliable and stable potentials, and it is generally accepted that they reflect the activity of the occipital cortex and in no case that of deeper structures [63]. However, the exact localization and the generating events are still unknown. The occipital pole seems to play a major role in the generation of affects by attributing an early meaning to the stimuli.

There are no data concerning the PR-VEPs in major depression, apart from the findings of our previous study [57]. The recording of event-related potentials under cognitive tasks that involve predominantly left- or right-hemisphere processing showed increased P300 latencies for the tasks involving the right hemisphere in melancholic and 'undifferentiated' patients, irrespective of the site of recording [64]. The advantage of pattern-reversal stimuli is that in contrast to event-related potentials, they do not demand high cooperation from the side of the subject.

Our knowledge on the biochemical basis of brain phenomena is limited; however, one can formulate a hypothesis to explain the results of the current study. A reduced serotonin activity (which is generally accepted to be a core biochemical disturbance in depression) could lead to an increase of the PR-VEP latency, but also it could lead to an increased appetite, except if the frontal lobe dopamine activity is also reduced. This is in accord with results of reports relating a low dopamine activity to the severity of depression [65]. Other reports also related specific symptoms (anhedonia) to low activities of both 5-HT_{1A} and dopamine receptors [66]. This model could well serve to explain the findings of the present study concerning the increased PR-VEP latencies in suicidal patients.

Concluding Remarks

The findings of the current study were related to the status of the patient at the time of the interview but not to his/her history. They also provide neurobiological data to support the need for a combined presence of self-directed aggression and higher arousal level or disinhibition of self-directed aggressive thoughts in order for a patient to become suicidal. What remains to be clarified is whether all these constitute state markers or whether there are also trait markers among them. This needs further study; however, the authors' impression is that the three clinical groups largely correspond to a chronological model of suicidality in depression, and in this frame all results reflect state markers. Even so, the current study provides some insight concerning the mechanism of suicidal development and at the same time suggests that the assessment of self-directed aggression could be an early sign that should alert the clinician. The presence of slow PR-VEPs could also serve as an alarming sign; however, there are no sufficient data, currently, to support this assumption. This may have not only theoretical implications; further study is needed to test whether psychophysiological methods, which are noninvasive and easy to perform (PR-VEPs), are of value in the therapeutic planning and monitoring of responses.

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