

## Electrodermal Hyporeactivity as a Marker for Vulnerability to Suicide in Depression

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### Abstract

**Background:** Electrodermal orienting hyporeactivity has been found to be related to violent suicide attempts and death by suicide in depressed patients in several studies suggesting that hyporeactivity is a marker for vulnerability to suicide. Since suicide is rare from the perspective of individual clinics the number of suicides in studies use to be typically is low. To compensate for that, aggregate data from more than one study can be used.

**Aim of the Study:** The aims of the present study were to investigate the possible relationship between electrodermal hyporeactivity and death by suicide and to examine prerequisites for possible clinical application in suicide risk assessments.

**Methods:** Depressed patients (n = 136) from three independent clinics were investigated by habituation experiments on electrodermal orienting reactivity. The study design was blind to rule out the risk of confounding by indication which may appear when the test results are open to the clinical staff. Patients were investigated by a test of the habituation of electrodermal orienting responses to repeated identical neutral tone stimuli. Clinical diagnoses and ratings of depression were assessed.

**Results:** All ten suicide victims were electrodermally hyporeactive. The relationship between electrodermal hyporeactivity and suicide was highly statistically significant (p = 0.00058) and the risk of suicide was 25 times higher among hyporeactive than reactive depressed patients.

**Conclusions:** A strong statistically significant relationship between the objective data on electrodermal hyporeactivity and death by suicide was confirmed and, further, confident prerequisites were clinically significant for the application of a test of electrodermal reactivity as an objective support in suicide risk assessments in depressed patients.

**Keywords:** Electrodermal Hyporeactivity; Suicide Risk Assessment; Death by Suicide; Depression; Marker of Suicide; Confounding by Inclusion

### Abbreviations

EDOR: Electrodermal Orienting Reactivity; WHO: World Health Organization; PPV: Positive Predictive Value; NPV: Negative Predictive Value

### Introduction

Death by suicide is a serious medical threat to society. Close to 800 000 people committed suicide every year in the world during the year 2016 according to WHO [1]. One way to combat the tragically high suicide rate is to find a method that in the clinical daily work can

be used to detect patients at risk of suicide, in order to direct effective preventive measures to the patients who really need them. However, despite many great efforts during decades, it seems that research has not made enough progress in this respect. Three recent reviews on diagnostic methods for suicide risk detection agree that there is a serious lack of valid tools for suicide risk detection [2-4]. In one of them [2] it was concluded that in a time span of 40 years there is no evidence that more recent studies have greater statistical strength than older studies in discriminating high risk from low risk patients.

In contrast, progress has been achieved regarding an objective psychophysiological method that has repeatedly been suggested to be used as an additive objective support in clinical suicide risk assessments. The method is a habituation test of the electrodermal orienting reactivity (EDOR) to repeated neutral tone stimuli. One such a test was developed in the early 1980s by Thorell [5,6], on strictly scientific empiric and theoretical bases, and it is in use in ongoing clinical and experimental research.

The first report of low electrodermal reactivity in psychiatric patients with severe suicidal behavior (violent methods or death by suicide) was published in 1986 by Edman and co-workers [7]. The reactivity was measured in a standard test of the habituation of EDOR to repeated neutral tone stimuli. The year after, in 1987, results were published by Thorell [8] from a parallel and independent study on exclusively depressed patients. The depressed patients who made one or more suicide attempts in their life before the test occasion, habituated statistically significantly much more rapidly than those who had never made an attempt, according to available individual oral and written reports [8]. The results were further illustrated and described in a later publication [9]. The test was strictly founded on the distinguished scientist Sokolov's theory [10,11] on general and specific orienting reactions and their habituation.

In 1991, another, partly parallel and independent, study by Keller and co-workers [12] used yet another EDOR test in depressed patients. All suicide attempters who used a violent suicidal method habituated very rapidly (hyporeactive).

However, the focus of two of these reports were focused in EDOR in suicide attempts. But the aggregate information available regarding the objective information on death by suicide in relation to the also objective measure of electrodermal hyporeactivity in these blind studies has not been published before.

### Aim of the Study

The aims of the present study were (a) to investigate the possible relationship between electrodermal hyporeactivity and death by suicide for further theoretical insight and (b) to investigate prerequisites for possible clinical practical application in suicide risk assessment.

### Methods and Materials

The 35 subjects in the study by Edman and his group [7] were inpatients with varying psychiatric diagnoses at a psychiatric ward at the Karolinska Hospital in Stockholm, Sweden, intended for suicide attempters and patients with severe suicidal ideation. As part of the total patient group were 23 patients with a diagnosis of depression in the ages 21 to 67 years, 13 (57%) women and 10 (43%) men. These depressed patients were picked out to be included in the present analyses. Fourteen patients were hyporeactive and 9 reactive.

In the study by Thorell [8], 59 depressed, 37 in- and 22 outpatients, 25 hyporeactive and 24 reactive, were recruited from those who were to be treated with, or already received, anti-depressive therapy, in the psychiatric department of the University Hospital in Linköping, Sweden. There were 32 women (54%) and 27 men (46%) in ages from 18 to 69 years. The subject groups have been described in detail elsewhere [4,5]. Comparisons between 20 medicated and 20 unmedicated patients regarding antidepressants, matched for age, and comparisons between 21 drug-free patients and 10 patients medicated exclusively with antidepressants yielded no statistically significant difference in electrodermal reactivity.

The study by Keller and co-workers [12] included originally 72 patients at the Weissenau Depression Ward in Ravensburg, the University of Ulm, Germany. They were classified into (a) one group with attempted suicide in their most recent history, (b) a second group with severe suicidal thoughts and (3) a third group of patients without suicidal thoughts or attempts. However, since there was a shortage of patients for a complete match to the suicide attempters, the total number of patients was reduced by the Keller's group to 18 in each group, the total being 54 individually matched by age and gender. There were 28 hyporeactive and 26 reactive patients in this study. There is no information on the distributions of age and gender in that material.

All three studies were approved by local ethical research committees, respectively. In the individual studies, patients with alcohol abuse were excluded. Data is lacking regarding the individual time between test and suicide, but in two studies [7,8] the follow-up time was one year, and in the third study [12] the follow-up time could be extended to five years in some cases.

In the present study of only depressed patients, the case - control groups were the hyporeactive (case) and reactive (control) groups according to the test results, respectively. The outcome was suicide or survival.

The gender and age distributions of the total patient group is not available since information is lacking in the original report [12]. However, all studies agreed on the lack of age and gender differences in electrodermal reactivity. Further, there were no significant differences between medicated and non-medicated patients in any of the studies. The criteria for depression were similar in the studies. Almost all patients had a diagnose comparable to major depressive uni- or bipolar disorder or dysthymia.

The three studies have a common and unique feature in the field of electrodermal reactivity and suicide, that they are pioneer studies and, because of that, the only ones with a complete blind case-control design. It means, the clinical staff and the patients did not know the test result and were not aware of a possible relationship to suicide. Thus, the test results were not used when assessing the individual risk of suicide or planning possible suicide preventive measures. Such a design minimizes confounding by indication [13]. That type of confounding implies in the present research field that knowledge of the patients test result will influence the outcome in suicide or survival by directed suicide prevention to the assumed high-risk group.

The psychophysiological tests of electrodermal reactivity were performed, subsequent to a diagnosis of depression and informed consent, as early as possible in the hospitalization period. The test was administered by trained clinical staff with great experience of psychiatric work. Skin conductance and other psychophysiological signals were recorded continually during the test according to proposals for standardization [14]. The tests were similar in that after three or five minutes of silence a number of identical audio stimuli were presented in varying intervals. The stimuli were sinus tones in the frequency 1 kHz, 85 or 90 dB over general hearing threshold, with a 1s duration, given in 15 to 80 s intervals [9]. Habituation of the electrodermal response - the measure of electrodermal reactivity - was defined as the order number of the first of three consecutive stimuli that did not evoked a response.

The patients were informed differently in the studies, but in a standardized way within the studies. A common information given to the patients was that a sound will be heard now and then during the test and that no particular achievement was being required.

### Statistical methods

Odds ratios with associated confidence intervals and hypothesis tests are used for investigating differences in risk of suicide among reactive and hyporeactive patients.

Odds is the probability of an event to occur divided by the probability of the event not to occur. Let  $A$  denote an event of interest, and  $\Pr(A)$  denote the probability of  $A$  to occur. The odds of  $A$  is then defined as

$$O(A) = \frac{\Pr(A)}{1 - \Pr(A)}$$

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For comparing the odds of suicide among reactive and hyporeactive patients the odds ratio *OR* is calculated:

$$OR = \frac{O(A)}{O(B)} = \frac{\frac{\Pr(A)}{1 - \Pr(A)}}{\frac{\Pr(B)}{1 - \Pr(B)}}$$

The groups of hyporeactive/reactive patients and the events of suicide or survival founds a contingency table according to:

	Suicide	No suicide	Total
Hyporeactive	a	b	a + b
Reactive	c	d	c + d
Total	a + c	b + d	a + b + c + d

The odds ratio is then calculated by

$$OR = \frac{\frac{a/(a + b)}{b/(a + b)}}{\frac{c/(c + d)}{d/(c + d)}} = \frac{a/b}{c/d} = \frac{a \cdot d}{b \cdot c}$$

In the event of the value 0 in a cell, 0.5 is added to all cells in the table according to the Haldane-Anscombe correction [15].

### Results

The total number of patients with a diagnosis of depression was 136. Four patients committed suicide in the study by Edman and co-workers, two in that by Thorell and five in the study by Keller and group. One of the five patients who committed suicide in Keller's study was electrodermally reactive and had years of tranquillizer abuse and a subsequent withdrawal which may have influenced the EDA to be reactive. It is, in fact, known that drug withdrawal causes rebound effects that produces electrodermal over-reactivity without habituation [16,17]. Thus, the authors excluded that patient from computations as in the present analyses.

The distribution of patients in a 2 x 2 table of test result and outcome is shown in table 1.

Hyporeactive patients were overrepresented (100%) among the suicide victims. The statistical significance of the relationship between electrodermal reactivity and outcome was  $p = 0.00058$  (Fisher's exact test) (Table 1).

The odds ratio was 25.38 (95% CI = 1.35 - 410.07;  $p = 0.030$ ) which is 25.38 times higher risk of suicide among hyporeactive, relative to reactive depressed patients.

All suicide victims were hyporeactive (Table 1). Thus, the sensitivity of hyporeactivity to suicide was 100%. The specificity was 45%, *i.e.* almost half of the surviving patients were hyporeactive, and the Positive Predictive Value (PPV) 15%, *i.e.* a large majority among the hyporeactive patients survived. The Negative Predictive Value (NPV) was 100%, which means that none of the electrodermally reactive patients died by suicide.

	Frequencies			Fisher's exact p	OR	CI <sub>95</sub>	OR p
<b>Edman., et al. 1986</b>				0.13	8.14	0.39 - 172.07	0.18
<b>Test result/Outcome</b>	<b>Suicide</b>	<b>Survival</b>	<b>Totals</b>				
Hyporeactive	4	10	14				
Reactive	0	9	9				
Totals	4	19	23				
<b>Thorell 1987</b>				0.18	7.34	0.34 - 159.93	0.21
<b>Test result/Outcome</b>	<b>Suicide</b>	<b>Survival</b>	<b>Totals</b>				
Hyporeactive	2	23	25				
Reactive	0	34	34				
Totals	2	57	59				
<b>Keller., et al. 1991</b>				0.12	9.73	0.50 - 190.32	0.13
<b>Test result/Outcome</b>	<b>Suicide</b>	<b>Survival</b>	<b>Totals</b>				
Hyporeactive	4	24	28				
Reactive	0	26	26				
Totals	4	50	54				
<b>All three studies</b>				0.00058	25.38	1.46 - 442.56	0.027
<b>Test result/Outcome</b>	<b>Suicide</b>	<b>Survival</b>	<b>Totals</b>				
Hyporeactive	10	57	67				
Reactive	0	69	69				
Totals	10	126	136				

**Table 1:** The distribution of patients (frequencies) according to test result and outcome at the end of follow-up in three independent blind pioneer studies.

**Discussion**

The aims of the present report from three blind studies [7,8,12] were to use the aggregate objective information from three blind studies (a) in investigating a possible relationship between electrodermal reactivity and suicide/survival for further theoretical insight and (b) in investigating prerequisites for possible clinically practical application in suicide risk assessment.

The present study is the first ever that uses the two objectively assessed variables electrodermal hyporeactivity/reactivity and suicide/survival in a blind design.

**Significance of relationship**

The results pointed out a strong and statistically significant relationship,  $p = 0.00058$ , between electrodermal reactivity and suicide/survival. The direction of the relationship between the measure of electrodermal reactivity and the outcome into suicide or survival was that all suicide victims were electrodermally hyporeactive and no reactive patient committed suicide. The statistical strength of the relationship offers an important basis for the interpretation that hyporeactivity can be a marker for vulnerability to suicide in depression, and that reactivity signifies low risk of suicide, absence of vulnerability to suicide and maybe even a protector against suicide. Hyporeactivity is frequently found in schizophrenic patients and among psychopaths, however, up to now there is no published study that suggest such a relationship in any of these two groups.

The results from the data of the present study, are further supported by results from a study that showed that electrodermal hyporeactivity persists after two years in remission [18], and from a larger study that electrodermal hyporeactivity persists several years in later depressed episodes [19]. These results support the hypothesis that electrodermal hyporeactivity is a marker for vulnerability to suicide.

### Understanding the depressive suicide

The findings of statistically strong relationship between electrodermal hyporeactivity and suicide in the present report are valuable for further understanding the depressive suicide and for the clinical work in assessing risk of suicide. The currently emerging theory by Thorell on electrodermal hyporeactivity and death by suicide converge on the loss of the vital specific orienting responses described by Sokolov and co-workers [11]. The orienting reaction indicates an initiation of central processing of a stimulus [20]. Thus, it is the earliest step in processing events. The orienting reactions are information processing with emotional components [21]. The specific information processing is the successive building of a neuronal model of the neutral event from information via relevant sensory input. Each repeated stimulus elicits additional information processing until the memory model matches the input, which is the point when habituation occurs. The loss of specific orienting responses is the loss of the necessary learning and loss of optimal memory models of the everyday life. Further, the loss of specific electrodermal orienting responses implies the loss of normal emotional ties to the everyday life. Neutral events are thought to be of a wide range of types, for example, emotional signals in meetings with family members and friends, eating daily food, daily tasks etc.

There is another important dimension of the loss of specific orienting reactions. Hyporeactivity has been found to coincide with loss of fear of imminent pain [22]. Consequently, the presence of hyporeactivity implies that two important barriers against suicide are loosed: The loss of the biological ability to react cognitively and emotionally with normal curiosity and information processing of events in the everyday life, and, the loss of fear of imminent pain. Thus, the hyporeactive depressed person seems to be a victim of vital dysfunctions.

The formulation of a loss of interest in living and loss of fear of imminent pain reminds on parts of the interpersonal theory on suicide by Joiner [23]. Further, the research on hyporeactivity and suicide offers a neuropsychological explanation model of corresponding parts of that theory. The interpersonal theory of suicide posits that suicidal desire emerges when individuals experience intractable feelings of perceived burdensomeness and thwarted belongingness followed by near lethal or lethal suicidal behaviour in the presence of suicidal desire and capability for suicide [23]. However, the mechanism underlying electrodermal hyporeactivity indicates rather a loss of interest in living than a desire for death.

### Clinical application

The high odds ratio, being about 25 in the present study, offers clear and direct information to clinicians about which treatment approach, preventive or not, has the best odds of benefiting the patient [24]. In addition, the odds ratio concept enables the mediating of understandable information to the patient and relatives on the odds of suicide and survival [24] if not treated and protected properly.

The information on odds ratio is positive to use in the communication when informing about the severe need of individual suicide preventive measures.

The low specificity is an obvious consequence of the fact that the majority of hyporeactive patients did not commit suicide, for various reasons: there may be strong reasons for living, application of suicide preventive measures on clinically perceived risk of suicide, suicide attempts not leading to death, or lack of method and/or occasion to carry through a suicidal act. An immense amount of non-clinical events (*e.g.* a meeting with a significant person) and physical conditions (*e.g.* a fence) can prevent the performance of the suicidal act also in patients suffering from vulnerability to suicide. Obviously, specificity is not a valid estimator of the accuracy of a diagnostic test when influenced by so many and crucial external factors. But, as demonstrated in this report, the risk of suicide is still 25 times lower among the reactive patients.

The very high NPV agrees with the idea of general suicide rates of about 1 to 5 percent in hospitalized depressed patients. Of course, some up to now unidentified factor or factors must be in effect in keeping the rate at these levels which implies that almost all patients in low-risk groups are protected from suicide. However, the results from the present study, and the nature of the hyporeactive risk group, open for a more interesting and constructive explanation. It is suggested here, that being electrodermally reactive, i.e. owning healthy specific orienting reactivity, may be such a protecting barrier. That is, it is proposed that the usually observed high NPV in trials of diagnostic methods for risk of suicide can be an effect of orienting reactivity protecting from suicide.

### Limitations

It is important that conclusions must be limited to patients with a diagnosis of depression. Data is lacking for the application in other diagnoses.

The number of suicides was small in the present three studies, which limits the generalization of the results, but the relationship between hyporeactivity and suicide was statistically strongly significant. In addition, the consistent results over the three studies have particular significance since they are computed on data from three independent clinics and laboratories.

However, the three studies have given similar results in other important variables too. In all three studies it was observed that there was no statistically significant relationship between electrodermal reactivity and age, gender, depth of depression, symptoms of depression or treatment by anti-depressive medication. This observation points to some homogeneity of the different materials in the studies and strengthen the generalizability.

Another favourable fact for clinical implementing is that the distribution of the electrodermal reactivity score that underlies the dichotomization into hyporeactives and reactives is strongly bimodal in all studies which makes the classification of patients easy and reliable. The bimodality was specifically pointed out in the work by Keller and co-worker [12] and it is observable when analysing graphs by Thorell [8,9]. It is an ideal situation when constructing diagnostic tests.

A question can arise which particular conditions can bring about such a strong relationship with a sensitivity of 100% between hyporeactivity and suicide. It is important to point out that these two variables, in contrast to most other diagnostic instruments for suicide risk, are objectively measurable behaviours with assumed common function: the electrodermally hyporeactive and future suicide victims, ignore neutral events in a laboratory context as they ignore the perceived neutral everyday events. Ignoring neutral events is not necessarily an example of impaired perception of an event, but more probably a lack of the ability to put significance to it and to learn it.

The results are very clear, but the material is small, which may affect their generalizability. However, there are other published findings that support the conclusion of hyporeactivity as a marker for vulnerability to suicide. The study by Thorell [8] showed that low electrodermal reactivity was strongly related to suicide attempts anytime in life before the test, i.e. decades, of suicide attempts indicating a long-term vulnerability to suicide. Further, another study by Thorell [17] found that low electrodermal reactivity remained in remission after two years. Later research [18] has offered strong support to the hypothesis that electrodermal hyporeactivity remains in later depressive episodes after several years. These observations support that the electrodermal hyporeactivity is a marker of vulnerability to suicide in depressed patients and that clinical application may contribute to a substantial reduction of depressed suicides by persons coming in contact with the health care. The blind studies of objective measures may lead to the break the chain of non-successful trials of diagnostic test for the risk of suicide.

However, it is very important to keep in mind that the relationship between hyporeactivity and suicide cannot predict exact who will commit suicide. Prediction implies predestination that for suicide obviously does not exist since it can be prevented and even triggered. What could be done for a patient who is predicted to commit suicide, whatever action is taken?



### Conclusions

The results of the present study, based on three independent blind studies, were the observation of a strong and highly statistically significant relationship between the objective data on electrodermal hyporeactivity and death by suicide, and, that there are confident prerequisites for clinically practical application as an objective additional source of information in clinical suicide risk assessment in depressed patients. Most often in studies of presumed diagnostic tests of risk of suicide, the design is open, naturalistic, which means that the test result can be, and most often are, used as a support in the clinical judgement of risk and in planning the type of care and possible suicide preventive measures, conditions that lead to results which are confounded by indication [13]. The important ground for the findings in the present study is that they are based in a blind design that is not affected by confounding by indication.

It has been demonstrated here support for the hypothesis that electrodermal hyporeactivity is a marker of vulnerability to suicide, and that electrodermal reactivity may protect from suicide. On the ground that the risk of suicide is 25 times higher in the hyporeactive group relative to the reactive, it is suggested that a test of electrodermal reactivity can be used as an additive objective source of information in clinical suicide risk assessments with the goal to offer the right treatment to the right patients for survival.

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