OPEN

# Can We Clinically Recognize a Vascular Depression?

## *The Role of Personality in an Expanded Threshold Model*

*Bela R. Turk, Michael E. Gschwandtner, Michaela Mauerhofer, and Henriette Löffler-Stastka*

**Abstract:** The vascular depression (VD) hypothesis postulates that cerebrovascular disease may ''predispose, precipitate, or perpetuate'' a depressive syndrome in elderly patients. Clinical presentation of VD has been shown to differ to major depression in quantitative disability; however, as little research has been made toward qualitative phenomenological differences in the personality aspects of the symptom profile, clinical diagnosis remains a challenge.

We attempted to identify differences in clinical presentation between depression patients (n = 50) with (n = 25) and without (n = 25) vascular disease using questionnaires to assess depression, affect regulation, object relations, aggressiveness, alexithymia, personality functioning, personality traits, and counter transference.

We were able to show that patients with vascular dysfunction and depression exhibit significantly higher aggressive and auto-aggressive tendencies due to a lower tolerance threshold. These data indicate that VD is a separate clinical entity and secondly that the role of personality itself may be a component of the disease process. We propose an expanded threshold disease model incorporating personality functioning and mood changes. Such findings might also aid the development of a screening program, by serving as differential criteria, ameliorating the diagnostic procedure.

(*Medicine* 94(18):e743)

**Abbreviations**: AREQ = Affect Experience and Affect Regulation Q-sort, BDI = Beck Depression Inventory, CTQ = Countertransference Questionnaire, FAF = Freiburg Agression Questionnaire, IIP = Inventory of Interpersonal problems, SCORS = Social Cognition and Object Relations Scale, SWAP-200 = Shedler-Westen Assessment Procedure-200, TAS-20 = 20 Item Toronto-Alexithymia-Scale, VD = vascular depression.

## INTRODUCTION

The vascular depression (VD) hypothesis stated that cerebrovascular disease may ''predispose, precipitate or perpetuate'' a depressive syndrome in some elderly patients.[1,2]

Whilst this broad definition attempts to encompass both clinical and morphological substrate of an expression of late life depression, divergent diagnostic concepts, both in criteria and approach complicate the diagnostic and scientific investigation.[3]

Clinical presentation of VD has been shown to differ to major depression in quantitative disability; however, as little research has been made toward qualitative phenomenological differences in the personality aspects of the symptom profile; clinical diagnosis remains a challenge.[4] The need for investigations into psychological and interpersonal factors has been stressed.[5] Refinement of the VD hypothesis has led to varying emergent criteria. On the contrary, a functional and treatment outcome-based proposal to population definition; the depressed executive function (DED),[6] on the other hand, imaging hallmarks, which characterize vascular elicited deterioration in regional brain function, such as white matter lesions (WML) or subcortical ischemic lesions (SIL), characterized by white matter hyper-intensities and deep white matter hyper-intensities (WMH and DWMH), in MRI imaging are described.[7,8]

## METHOD

In this case-controlled study, we investigated the phenomenological differences in personality and interpersonal functioning between depressive patients, with, and without vascular dysfunction.

The symptom profile assessment was performed on 2 groups and focused on depression, affect regulation, object relations, aggressiveness, alexithymia, personality functioning, personality traits, and counter transference.

As a lack of consensus on criteria complicates the eligibility criteria of VD,[3] we attempted to bypass these manifold classifications by selecting the concurrent underlying pathology as our inclusion criteria: vascular dysfunction.

Subjects included in the VD group were patients pertaining both: a diagnosis of depression or depressive episode (ICD-10 F31.3, F31.4, F31.5, F32, F33) and a diagnosis of peripheral vascular disease (ICD-10 I73.9).

Patient recruitment was performed at 2 hotspots, consecutively including all in-patients who fulfilled the aforementioned criteria during a predefined matched-pairs enrollment period of 12 months. Matching concerned sex and age (±2 years).

Both groups were assessed using 4 self-assessment methods: The Beck Depression Inventory (BDI), the Freiburg Aggression Questionnaire (FAF), the Inventory of Interpersonal Problems (IIP), and the 20-Item Toronto-Alexithymia-Scale (TAS-20). Additionally 4 expert-rated scores were performed: The Shedler-Westen Assessment Procedure-200 (SWAP-200), the Affect Experience and Affect Regulation Q-sort (AREQ), the Social Cognition and Object Relations Scale (SCORS), and the Countertransference Questionnaire (CTQ).

Editor: Frank R. Heinzel.
Received: May 19, 2014; revised: March 3, 2015; accepted: March 16, 2015.
From the Department for Psychoanalysis and Psychotherapy (BRT, MM, HLS); Department for Angiology (MEG), Medical University Vienna, Austria.
Correspondence: Henriette Löffler-Stastka, Department for Psychoanalysis and Psychotherapy, Medical University Vienna, Währinger Gürtel 18-20, A-1090 Vienna, Austria (e-mail: henriette.loeffler-stastka@meduniwien.ac.at).
The authors have no funding and conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000000743

The study complied with the Helsinki Declaration and was approved by the ethics committee of the Medical University of Vienna.

## MEASUREMENTS

### Expert Ratings

#### SWAP-200

The SWAP-200 is a 200-item Q-sort test, an expert rating, which describe the patient's enduring patterns of personality functioning.[9] The procedure[10] provides an SWAP-200 diagnosis, a patient's T-score profile representing both dimensional and categorical diagnoses by correlating the patient's Q-sort profile with empirically derived prototypes, either representing the current Axis II categories (SWAP.T)[11] or empirically derived prototypes (SWAP.QT).[12] Validity and reliability of the instrument have been described in several studies by their authors. For our purpose, the SWAP items were translated into German with sufficient convergence shown in retranslation[13] Concerning inter-rater reliability across the institutions involved in the present study, the 2 independent raters obtained k-coefficients of median = 0.69 (range 0.28–0.84).

#### AREQ

The AREQ[14] is a 98-item observer-based Q-sort, which provides an assessment of affect regulation and experience. It is conducted similarly to the SWAP-200, using a different fixed distribution, without correlational analysis. It yields 3 factors of affect experience: socialized negative affect (eg, guilt), positive affect (eg, interest), and intense negative affect (eg, anger). The affect regulation dimension includes 3 factors: reality-focused response (eg, goal-directed coping), externalizing defenses (eg, projection), and avoidant defenses. Internal consistency of the factors in previous research is acceptable to high, as is external validity of the factor scores.[14] In our survey the inter-rater reliability showed sufficient consistency (median-K = 0.70, range 0.10–0.95). Further psychometric details for the German translation have been described previously[15]

#### SCORS

The SCORS[16] uses a 7-point scaling system, which consists of scoring criteria for the assessment of 4 dimensions in object relations/social cognition: complexity of representations of people, affect-tone of relationship paradigms, understanding of social causality, and capacity for emotional investment in relationships and morals standards. Using graduate student raters, Niec et al[16] obtained reliabilities (uncorrected) in the range of 0.72 to 0.94, for our study we found interrater-reliablity stable at k = 0.77 for 2 independent raters.

#### CTQ

The CTQ[17] is a 79-item clinician-report questionnaire designed to provide a normed, psychometrically valid instrument for assessing countertransference patterns in psychotherapy. Scree plot, percentage of variance accounted for, and parallel analysis were used to select the number of factors to rotate. To create factor-based scores for use in this and subsequent studies, items loading $\geq$0.50 for factors 1 and 2, $\geq$0.40 for factor 3, and $\geq$0.375 for factors 4 to 8 were included to maximize reliability (coefficient alpha). Inter-correlations among the 8 factors ranged from −0.16 to 0.58, with a median of 0.30. An 8-factor model was subsequently chosen, accounting for 69% of variance, the factors being as follows: overwhelmed/disorganized, helpless/inadequate, positive, special/overinvolved, sexualized, disengaged, parental/protective, and criticized/mistreated. To illustrate the close association of countertransference reactions to personality pathology, Bentan et al correlated the 8 factors of the CTQ with the 3 clusters of DSM-IV Axis II disorders (A odd/eccentric, B dramatic/erratic, and C anxious/fearful) in a sample of 181 patients.

Partial correlation showed: cluster A (odd/ eccentric) disorders to have a significant association with the criticized/mistreated factor (partial $r = 0.17$, $P < 0.05$); cluster B (dramatic/erratic) disorders to be associated with the overwhelmed/disorganized (partial $r = 0.43$, $P < 0.001$), helpless/inadequate (partial $r = 0.16$, $P < 0.05$), disengaged (partial $r = 0.24$, $P < 0.001$), and sexualized factors (partial $r = 0.24$, $P < 0.001$), as well as having a negative correlation with positive countertransference (partial $r = -0.22$, $P < 0.01$); cluster C(anxious) disorders to be associated with the parental/protective factor (partial $r = 0.24$, $P < 0.001$).

In a second analysis, borderline personality disorder displayed association with the special/overinvolved factor partial $r = 0.23$, df = 170, $P = 0.002$). Narcissistic personality disorder on the other hand, significantly correlates with the disengaged factor (partial $r = 0.30$, df = 170, $P < 0.001$), in contrast to other duster B disorders.[17]

For all Q-sort based expert ratings, the internal stability of both raters was assured by intrarater-reliability calculations ($\kappa \geq 0.7$ over a period of 1 year). For all expert measurements a precise description about conduction of the assessment procedures (duration, assessment with fixed distribution, calculation, theoretical background, training, etc.) is given in Schumacher (2005).[18]

### Patients' Self-Ratings

#### IIP

The IIP evaluates the patient's problems in relating to other people.[19] This self-report measurement refers to a final set of 8-item circumplex scales, which are arranged in a 2-dimensional semantic field with the dimensions ''affiliation'' (cold versus nurturant behavior) and ''dominance'' (competitive versus submissive behavior).

#### BDI

The BDI is a self-rating instrument, examining the severity of depression. The BDI consists of 21 questions, with 4 possible answers, as to how the person was feeling in the last 7 days before the examination. The cumulative value of the 21 questions of the test reflects the severity of depression. The standard cutoffs 0 to 9: indicates minimal depression, 10 to 18: indicates mild depression, 19 to 29: indicates moderate depression, and 30 to 63: indicates severe depression. The BDI has be shown to be reliable, valid, and sensitive as an indicator of depression severity.[20]

#### FAF

The Questionnaire for aggressivity, FAF educes information on the tendency toward aggressive behavior.[21] The inventory includes 77 items, which are also represented in the Freiburger Personality Inventory. The majority of the items are ego-statements, whereby possible answers are ''yes'' or ''no''. The first

**TABLE 1.** Recorded Vascular Risk Profile of the VD Group (n = 25) and Non-VD Group (12 of n = 25)

| Vascular Risk Profile | | | | | | |
|---|---|---|---|---|---|---|
| | Vascular Disease Group | | | Nonvascular Disease Group | | |
| | Min | Max | σ | Min | Max | σ |
| Rutherford Staging | 3 | 6 | 0.9 | 0 | 0 | 0 |
| | Interquartile range | | Median | Interquartile range | Median | |
| LDL in md/dL | 91 | | 81.2 | 42.5 | 54.4 | |
| Triglycerides in mg/dL | 99 | | 162 | 51 | 125.5 | |
| HbA1c | 2.15 | | 5.9 | 0.3 | 5.6 | |
| | Percent of group | | | Percent of group | | |
| Carotid stenosis or carotid stent present | 28% | | | 0% | | |
| Diagnosed coronary heart disease | 72% | | | 0% | | |
| Taking lipid lowering medication | 72% | | | Not recorded | | |
| Taking anti-hypertensive medication | 72% | | | Not recorded | | |
| Taking diabetes medication | 36% | | | Not recorded | | |
| History of smoking | 40% | | | Not recorded | | |
| Obesity (BMI 30+) | 40% | | | Not recorded | | |

item is a ''warming-up''-item. Ten statements are assigned to the openness scale, which is a control scale that allows open responses. The other items are distributed to 5 aggression scales: spontaneous aggression, reactive aggression, excitement, auto-aggression, and aggression inhibition. The first 3 scales are used for calculating the cumulative values (amount of aggression). Validity: there are significant differences between criminal offenders and control subjects. Some patient groups differ in the FAF. Men show higher values than women especially on the first 2 scales, and people of the lower classes had higher values than people of the middle class. Reliability: the internal consistency of aggressiveness scales ranges between 0.65 and 0.79. The total scale for aggressiveness has a value of 0.85. The openness scale has an alpha of 0.61. The scale is based on the standardization sample of the Freiburger Personality Inventory from 1970 (N = 630). Age and sex specific T, stanines, and percentage ranges are alleged. For comparing the mean values and standard deviations of the standardization sample, criminal offenders, psychotherapy patients, and psychosomatic patients have been calculated. The instrument can be used in scientific investigations for aggressive behavior and also in clinical fields, for example, in psychiatric and psychotherapeutic diagnostic procedures. The FAF finds use in clinical and forensic science.[21]

### TAS-20

The TAS-20 is a self-assessment questionnaire with 20 items measuring alexithymia by answering the items on a 5-points Likert scale.[22] Three subscales are covered by the 20 questions: the ability to describe emotions, to identify emotions and the tendency toward externalizing thinking. The sum of all items provides the entire alexithymia score. The cutoff value for alexithymia is 61. No alexithymia is below 51. The existence of alexithymia is likely between 52 and 60. The German version of the TAS-20 fulfills the quality criteria sufficiently. The internal consistency according to Cronbach α is 0.7. The test—retest reliability is 0.71.[23] Convergent validity is reasonable, as the 3 subscales match with the construct of alexithymia. The TAS-20 is applicable and traceable in patient and general populations. It is also applicable in different languages and in different cultures.[24]

### Statistics

Mann–Whitney U tests were performed using IBM SPSS Statistics 21, level of significance was determined $\alpha = 0.05$.

## RESULTS

### Description of the Sample

All subjects provided written, informed consent and were recruited from 2 hotspots, the University Clinic of Internal Medicine II at the Vienna General Hospital and the Department of Psychiatry at the Otto-Wagner Hospital in Vienna. 50 Total patients were recruited, with n = 25 in each group. Mean age = 61.8 years, minimum = 25 years, maximum = 78 years, and standard deviation = 11.8 years.

Vascular disease in the VD group (n = 25) was assessed according to Rutherford (minimum = 3, maximum = 6, and standard deviation = 0.93) and Fontaine (minimum = 2b maximum = 4) criteria. Additionally, carotid stenosis (above 70%) or postcarotid stent operation was present in 16% of patients in the VD group. The vascular risk profile is shown in Table 1. The matched non-VD group (n = 25) showed no diagnosis of vascular disease and some vascular risk factors were only obtainable for 12 of the non-VD group.

Group comparison of questionnaire results between patients with VD and patients with depression or depressive episode (non-VD) showed some significant differences. An overview is given in Table 2.

### Self-Assessment

The total mean BDI score of the VD group was significantly lower, indicating a difference in depression severity. The VD group showed significantly higher FAF-mean values for the subscales ''Auto-aggression,''''Excitability,'' and ''Aggression Inhibition.'' The VD groups IIP-mean subscale values in ''Dominating/Controlling,'' ''Cold/Distant,'' ''Accommodating,'' and ''Socially Inhibited'' were significantly lower. The mean total TAS-20 alexithymia score and each of the 3 subscale values ''Difficulty Describing Feelings,'' ''Difficulty

**TABLE 2.** Self-Assessment Instruments

| Questionnaire Batteries | Non-VD Group | | VD Group | | Significance | |
|---|---|---|---|---|---|---|
| | Mean | σ | Mean | σ | Z | *P* |
| BDI-Score | 23.33 | 8.81 | 13.78 | 5.59 | −2.256 | 0.024* |
| FAF | | | | | | |
| Spontaneous aggression | 1.77 | 0.19 | 1.86 | 0.07 | −0.940 | 0.340 |
| Reactive aggression | 1.48 | 0.35 | 1.70 | 0.23 | −1.440 | 0.150 |
| Excitement | 1.40 | 0.17 | 1.64 | 0.24 | −1.950 | 0.050* |
| Auto-aggression | 1.35 | 0.32 | 1.72 | 0.22 | −2.350 | 0.010** |
| Aggression inhibition | 1.25 | 0.32 | 1.50 | 0.20 | −1.748 | 0.080 |
| IIP | | | | | | |
| Too domineering/controlling | 1.27 | 0.76 | 0.51 | 0.35 | −2.265 | 0.024* |
| Too vindicative/self-centered | 1.81 | 0.71 | 0.75 | 0.55 | −2.925 | 0.003** |
| Too cold/distant | 2.08 | 0.83 | 1.09 | 0.69 | −2.573 | 0.010** |
| Too socially inhibited | 2.51 | 0.88 | 0.97 | 0.64 | −3.057 | 0.002** |
| Too nonassertive | 2.23 | 1.24 | 1.38 | 0.83 | −1.506 | 0.132 |
| Too self-sacrificing | 2.00 | 0.81 | 1.50 | 0.78 | −1.241 | 0.215 |
| Too overly accommodating | 2.22 | 0.68 | 1.05 | 0.75 | −2.752 | 0.006** |
| Too intrusive/needy | 1.45 | 0.78 | 1.82 | 0.81 | −0.895 | 0.371 |
| Total TAS20 score | 23.82 | 27.72 | 51.00 | 10.50 | −3.261 | 0.001*** |
| Difficulty identifying feelings | 6.82 | 8.10 | 13.55 | 4.30 | −2.920 | 0.003** |
| Difficulty describing feelings | 8.21 | 10.32 | 14.91 | 4.56 | −2.699 | 0.007** |
| Externally oriented thinking | 8.79 | 10.02 | 22.55 | 0.92 | −4.460 | 0.000*** |
| AREQ | | | | | | |
| Socialized negative affect | 4.64 | 1.39 | 3.83 | 1.59 | −1.320 | 0.184 |
| Positive affect | 2.74 | 0.92 | 2.68 | 1.08 | −0.223 | 0.823 |
| Intensive negative affect | 3.64 | 0.71 | 2.12 | 1.11 | −2.746 | 0.006** |
| Reality-focused response | 2.83 | 0.72 | 3.62 | 1.44 | −2.160 | 0.030* |
| Externalizing defenses | 2.51 | 0.94 | 2.19 | 1.21 | −0.440 | 0.650 |
| Avoidant defenses | 2.81 | 0.41 | 3.43 | 1.38 | −2.520 | 0.010** |
| Total CTQ score | 1.79 | 0.57 | 1.11 | 0.52 | −2.563 | 0.010** |
| Critisized/mistreated | 2.39 | 1.02 | 1.29 | 0.67 | −2.390 | 0.010** |
| Helpless/inadequate positive | 1.91 | 0.70 | 1.77 | 0.73 | −0.222 | 0.820 |
| Parental/protective | 1.64 | 0.66 | 1.11 | 0.54 | −1.503 | 0.130 |
| Overwhelmed/disorganised | 1.40 | 0.44 | 1.11 | 0.46 | −0.673 | 0.500 |
| Special/overinvolved | 1.20 | 0.42 | 0.91 | 0.34 | −1.090 | 0.950 |
| Sexualised | 1.08 | 0.38 | 0.95 | 0.38 | −0.610 | 0.950 |
| Disengaged | 1.94 | 0.49 | 1.55 | 0.89 | −1.370 | 0.160 |
| SCORS Complexity of representations of people | 3.22 | 0.97 | 3.78 | 1.71 | −1.320 | 0.180 |
| Affect-tone of relationship paradigms | 4.11 | 1.53 | 4.44 | 2.18 | −0.690 | 0.480 |
| Capacity for emotional investment in relationships | 2.89 | 1.69 | 4.00 | 1.93 | −1.430 | 0.150 |
| Capacity for emotional investment in moral standards | 3.89 | 1.16 | 4.11 | 1.69 | −0.830 | 0.400 |
| Understanding of social causality | 2.89 | 2.08 | 3.89 | 1.76 | −1.250 | 0.210 |
| Self-worth | 3.00 | 1.41 | 4.00 | 2.06 | −1.390 | 0.160 |
| Identity and Coherence of the self | 3.89 | 1.05 | 4.89 | 2.02 | −2.130 | 0.030* |
| SWAP | | | | | | |
| Dysphoric (depressive) | 49.18 | 3.65 | 4.94 | 17.56 | −0.440 | 0.960 |
| Schizoid | 52.56 | 5.34 | 43.78 | 16.96 | −1.542 | 0.122 |
| Anti-social | 48.83 | 7.80 | 39.97 | 16.63 | −0.839 | 0.402 |
| Obsessional | 50.13 | 3.57 | 49.28 | 18.83 | −0.750 | 0.450 |
| Paranoid | 48.58 | 7.60 | 37.83 | 15.17 | −2.252 | 0.024* |
| Histrionic | 47.71 | 6.25 | 38.98 | 15.70 | −1.634 | 0.102 |
| Narcisstic | 46.26 | 7.41 | 41.23 | 17.38 | −0.391 | 0.691 |
| Borderline | 47.17 | 5.84 | 33.25 | 13.17 | −2.870 | 0.004** |
| Schizotypal | 53.06 | 8.01 | 40.03 | 15.50 | −2.605 | 0.009** |

Levels of significance: $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. AREQ = Expert-rating instruments: Affect Experience and Affect Regulation Q-sort, BDI = Beck Depression Inventory, CTQ = Countertransference Questionnaire, FAF = Freiburg Aggression Questionnaire, IIP = Inventory of Interpersonal Problems, SCORS = Social Cognition and Object Relations Scale, SWAP-200 = Shedler-Westen Assessment Procedure, TAS-20 = Toronto Alexithymia Scale.

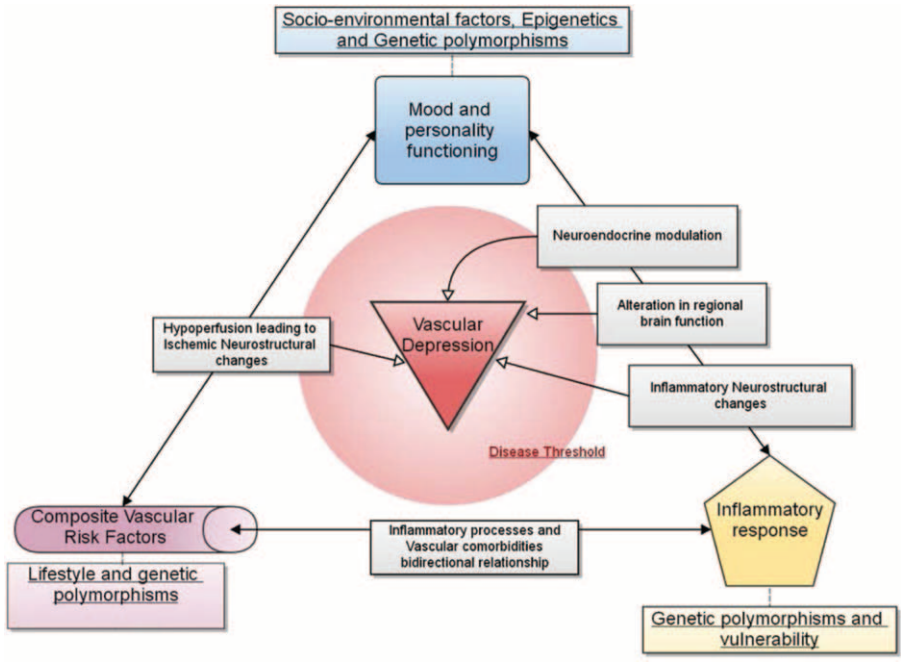


**FIGURE 1.** An expanded threshold model outlining relationships of influencing factors: inflammatory response, changes in mood, and vascular risk. Multiple pathologies (gray) are emergent of these interacting factors, which after multiple ''hits,'' break through the disease threshold and manifest in the symptoms of vascular depression.

Identifying Feeling,'' and ''Externally-Oriented Thinking'' were significantly higher in the VD group.

### Expert-Rating

Our AREQ-data show significantly lower mean subscale values in ''intense negative affect'' and significantly higher subscale values in ''reality-focused response'' and ''avoidant defense.'' The CTQ subscales in the VD group show significantly lower mean values for ''criticized/mistreated'' and ''helpless/inadequate.'' The VD group showed significantly higher SCORS-mean subscale values of ''Identity and coherence of self.'' The VD group showed significantly lower SWAP-200 mean subscale personality prototype values for ''paranoid,'' ''borderline,'' and ''schizotypal.''

## DISCUSSION

Our results show higher aggressive tendencies and increased alexithymia in VD patients. This evidence may support either a causative relationship between personality functioning and VD; these changes attributed to an alteration of regional brain function or contrariwise, certain interpersonal factors may predispose toward VD.

Our data may indicate that depression in the context of vascular dysfunction or VD is a separate entity to nonorganic depression, both quantitatively and qualitatively.

We postulate that the role of personality may be a component of the disease process. In order to illustrate changes in personality functioning in a biological context, we briefly outline current models.

Lesion generation has been attributed to endothelial damage giving rise to a pathological hemodynamic and cerebrovascular regulation which in turn is unable to maintain stable cerebral blood flow.[25–29]

This hypo-perfusion model has been shown to lead initially to an impaired protein synthesis, crucial in both cognitive and affective processing.[30,31] Further vascular dysfunction culminates in the ischemic injury of specific tissue, subcortical white matter being especially sensitive due to its limited supply by terminal arterioles with little to no collateral flow.[32]

Multiple neuro-pathological post-mortem studies show conflicting evidence between lesion location and quantity, imaging and clinical severity.[33–36] Xekardaki et al have suggested, that the neuroanatomical alteration for cognitive and affective dysregulation may be relevant in the presence of a ''second hit'' phenomenon, such as an episode of acute brain compromise as shown in poststroke depression, or as an accumulation of age-related neurodegenerative changes.

This ''Second Hit'' theory is consistent with the Threshold model conceptualized by Taylor et al, whereby manifold pathoetiological factors contribute progressively and inter-dynamically toward a threshold of VD vulnerability, culminating later in the manifestation of affective and cognitive symptoms, VD.[1,35] A recent systematic review and meta-analysis by Valkanova et al[37] presented strong evidence between key diseases (cardiovascular disease, diabetes, and stroke) and depression in addition to the composite vascular risk (composite measure of vascular risk factors).

Contributing or associated factors such as immune activation can be either a characteristic of depression or precipitate depressive symptoms.[26–28,38–40] Several central and peripheral pro-inflammatory mechanisms have been identified which are associated with changes in mood,[41] implicating Interleukin 1-beta, indoleamine 2,3-dioxygenase, and the Kynurenine pathway in modulating serotonin and tryptophan release as well as reducing neurotrophic support.[42–46]

This inflammatory process has been shown to lead to an increased synthesis of detrimental tryptophan catabolites that promote hippocampal damage and apoptosis,[45,47] structural

volume reductions which correlated in some neuro-pathological post-mortem series.[48]

Furthermore, a reduction in the gluco-corticoid receptor response is disrupted by the pro-mediators, attributing an alteration in neuroendocrine function to the same disease process.[49] Not only are these pro-inflammatory processes subject to genetic polymorphisms,[50,51] thereby accounting as vulnerability elements, but are affected by lifestyle and personality factors. The relationship between inflammation and vascular disease has been well documented in the pathology of atherosclerosis and vascular dysfunction.[52]

We propose that a separate factor of personality function (or interpersonality functioning) may be pivotal to the contribution of ''hits'' toward the disease manifestation threshold. Personality functioning or mood changes may not just be bi-directionally affected by both inflammatory response and composite vascular risk factors, but may also be influenced by socio-environmental, genetic polymorphisms (Ancelin), and epigenetic modulation of behavior modifying systems. One of these systems may be the hypothalamic-pituitary-adrenocortical axis (HPA), dysfunction thereof seen in late life depression and VD.[53] Additionally, genetic polymorphisms of HPA-axis related genes are associated with cardiovascular risk and inflammatory response.[54]

Epigenetic modulations of the cortisol receptor, a feedback inhibitor within the HPA system have been attributed to (adverse) life events[55] of even later generations of life events.[56] A persons unique biography may thereby sculpt the personality functioning factor, as measured by interpersonal functioning. Intertwined with neuro-inflammatory states and composite vascular risk, predisposed or altered personality functioning may contribute toward the disease threshold, or personality functioning may be altered as a result of vascular dysfunction. Our proposed threshold model, depicted in Figure 1 allows epigenetic, environmental, and interpersonal interactions to be taken into consideration.

## Future Diagnostics

Consistent with the VD hypothesis, a high prevalence of clinically significant depression symptoms in patients with stenosis of the carotid artery was reported on multiple occasions.[52,57] These vascular-associated depressive symptoms have been shown in almost all cases to be more resistant to pharmacologic treatment, and improvement was obtained by improvement of cerebral blood flow using placement of a carotid stent.[52] A revision of the definition of ''asymptomatic carotid stenosis patients'' has been suggested, calling for additional markers, as current treatment algorithms suggest referral for further carotid artery evaluation, delaying treatment as depression is not considered a symptom of carotid stenosis.

## Limitations

Our enrollment period of 12 months limited the sample size of subgroups of vascular disease, most importantly perhaps in differentiating between and expanding the population of carotid and distal vascular lesions. With regard to the small sample size, the association between VD and the questionnaire read-outs may also be coincidental.

Using larger subgroup populations, future studies should generate composite cardiovascular risk profiles[37] and compare these to both auto-aggression and alexithymia scores in order to eliminate the possibility of selection bias, as subsets of vascular disease show a stronger influence on depression.

## REFERENCES


1. Taylor WD, Aizenstein HJ, Alexopoulos GS. The vascular depression hypothesis: mechanisms linking vascular disease with depression. *Mol Psychiatry.* 2013;18:963–974.
2. Alexopoulos GS, Meyers BS, Young RC, Kakuma T, Silbersweig D, Charlson M. Clinically defined vascular depression. *Am J Psychiatry.* 1997;154:562–565.
3. Brunoni AR, Bensenor IM, Alves TC, et al. Therapeutic interventions for vascular depression: a systematic review. *Rev Bras Psiquiatr.* 2011;33:400–409.
4. Licht-Strunk E, Bremmer MA, van Marwijk HWJ, et al. Depression in older persons with versus without vascular disease in the open population: similar depressive symptom patterns, more disability. *J Affect Disord.* 2004;83:155–160.
5. Sneed JR, Culang-Reinlieb ME. The vascular depression hypothesis: an update. *Am J Geriatr Psychiatry.* 2011;19:99–103.
6. Alexopoulos GS. Clinical presentation of the ''depression-executive dysfunction syndrome'' of late life. *Am J Geriatr Psychiatry.* 2002;10:98–106.
7. Krishnan KR, Hays JC, Blazer DG. MRI-defined vascular depression. *Am J Psychiatry*. 1997;154:497–501.
8. Pimontel MA, Culang-Reinlieb ME, Morimoto SS, et al. Executive dysfunction and treatment response in late-life depression. *Int J Geriatr Psychiatry.* 2011;27:893–899.
9. Shedler J, Westen D. Refining the measurement of axis II: a Q-sort procedure for assessing personality pathology. *Assessment.* 1998;5:333–353.
10. Westen D, Muderrisoglu S. Assessing personality disorders using a systematic clinical interview: evaluation of an alternative to structured interviews. *J Pers Disord.* 2003;17:351–369.
11. Westen D, Shedler J. Revising and assessing axis II, Part II: toward an empirically based and clinically useful classification of personality disorders. *Am J Psychiatry.* 1999;156:273–285.
12. Westen D, Shedler J. Revising and assessing axis II, Part I: developing a clinically and empirically valid assessment method. *Am J Psychiatry.* 1999;156:258–272.
13. Loffler-Stastka H, Ponocny-Seliger E, Fischer-Kern M, et al. Validation of the SWAP-200 for diagnosing psychostructural organization in personality disorders. *Psychopathology.* 2007;40:35–46.
14. Westen D, Muderrisoglu S, Fowler C, et al. Affect regulation and affective experience: individual differences, group differences, and measurement using a Q-sort procedure. *J Consult Clin Psychol.* 1997;65:429–439.
15. Loffler-Stastka H, Ponocny-Seliger E, Fischer-Kern M, et al. Utilization of psychotherapy in patients with personality disorder: the impact of gender, character traits, affect regulation, and quality of object-relations. *Psychol Psychother.* 2005;78:531–548.
16. Niec LN, Russ SW. Children's internal representations, empathy, and fantasy play: a validity study of the SCORS-Q. *Psychol Assess.* 2002;14:331–338.
17. Betan E, Heim AK, Zittel Conklin C, et al. Countertransference phenomena and personality pathology in clinical practice: an empirical investigation. *Am J Psychiatry.* 2005;162:890–898.
18. Schumacher J, Leppert K, Gunzelrnann T, et al. Die Resilienzskala - Ein Fragebogen zur Erfassung der psychischen Widerstandsfähigkeit als Personmerkmal. [Resilience Scale (Wagnild GM, Young HM, 1993) - German version]. *Zeitschrift für Klinische Psychologie, Psychiatrie und Psychotherapie.* 2005;53:16–39.
19. Gude T, Moum T, Kaldestad E, et al. Inventory of interpersonal problems: a three-dimensional balanced and scalable 48-item version. *J Pers Assess.* 2000;74:296–310.

20. Wang Y-P, Gorenstein C. Psychometric properties of the Beck Depression Inventory-II: a comprehensive review. *Rev Bras Psiquiatr.* 2013;;35:416–431.
21. Ille R, Lahousen T, Rous F, et al. Personality profile and psychic deviations in offenders examined for psychiatric-forensic appraisal. *Nervenarzt.* 2005;76:52–60.
22. Parker JDA, Taylor GJ, Bagby RM. The 20-Item Toronto Alexithymia Scale. III. Reliability and factorial validity in a community population. *J Psychosom Res.* 2003;55:269–275.
23. Bach M, Bach D, de Zwaan M, et al. Validation of the German version of the 20-item Toronto Alexithymia Scale in normal persons and psychiatric patients. *Psychother Psychosom Med Psychol.* 1996;46:23–28.
24. Taylor GJ, Bagby RM, Parker JDA. The 20-Item Toronto Alexithymia Scale. IV. Reliability and factorial validity in different languages and cultures. *J Psychosom Res.* 2003;55:277–283.
25. Greenstein AS, Paranthaman R, Burns A, et al. Cerebrovascular damage in late-life depression is associated with structural and functional abnormalities of subcutaneous small arteries. *Hypertension.* 2010;56:734–740.
26. Broadley AJM. Arterial endothelial function is impaired in treated depression. *Heart.* 2002;88:521–523.
27. Paranthaman R, Greenstein A, Burns AS, et al. Relationship of endothelial function and atherosclerosis to treatment response in late-life depression. *Int J Geriatr Psychiatry.* 2012;27:967–973.
28. Tiemeier H. Cerebral haemodynamics and depression in the elderly. *J Neurol Neurosurg Psychiatry.* 2002;73:34–39.
29. de la Torre JC. Cerebral hemodynamics and vascular risk factors: setting the stage for Alzheimer's disease. *J Alzheimers Dis.* 2012;32:553–567.
30. Martin KC, Barad M, Kandel ER. Local protein synthesis and its role in synapse-specific plasticity. *Curr Opin Neurobiol.* 2000;10:587–592.
31. Kleim JA, Bruneau R, Calder K, et al. Functional organization of adult motor cortex is dependent upon continued protein synthesis. *Neuron.* 2003;40:167–176.
32. Moody DM, Bell MA, Challa VR. Features of the cerebral vascular pattern that predict vulnerability to perfusion or oxygenation deficiency: an anatomic study. *AJNR Am J Neuroradiol.* 1990;11:431–439.
33. Xekardaki A, Santos M, Hof P, et al. Neuropathological substrates and structural changes in late-life depression: the impact of vascular burden. *Acta Neuropathol.* 2012;124:453–464.
34. Chen C-S, Chen C-C, Kuo Y-T, et al. Carotid intima-media thickness in late-onset major depressive disorder. *Int J Geriatr Psychiatry.* 2005;21:36–42.
35. Thomas AJ. A neuropathological study of vascular factors in late-life depression. *J Neurol Neurosurg Psychiatry.* 2001;70:83–87.
36. Thomas AJ, Perry R, Kalaria RN, et al. Neuropathological evidence for ischemia in the white matter of the dorsolateral prefrontal cortex in late-life depression. *Int J Geriatr Psychiatry.* 2002;18:7–13.
37. Valkanova V, Ebmeier KP. Vascular risk factors and depression in later life: a systematic review and meta-analysis. *Biol Psychiatry.* 2013;73:406–413.
38. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol Psychiatry.* 2009;65:732–741.
39. Maes M. Depression is an inflammatory disease, but cell-mediated immune activation is the key component of depression. *Prog Neuropsychopharmacol Biol Psychiatry.* 2011;35:664–675.
40. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends Immunol.* 2006;27:24–31.
41. Alexopoulos GS, Morimoto SS. The inflammation hypothesis in geriatric depression. *Int J Geriatr Psychiatry.* 2011;26:1109–1118.
42. Tsao C-W, Lin Y-S, Chen C-C, et al. Cytokines and serotonin transporter in patients with major depression. *Prog Neuropsychopharmacol Biol Psychiatry.* 2006;30:899–905.
43. O'Connor JC, Andre C, Wang Y, et al. Interferon- and tumor necrosis factor-mediate the upregulation of indoleamine 2,3-dioxygenase and the induction of depressive-like behavior in mice in response to bacillus Calmette-Guerin. *J Neurosci.* 2009;29:4200–4209.
44. O'Connor JC, Lawson MA, Andre C, et al. Lipopolysaccharide-induced depressive-like behavior is mediated by indoleamine 2,3-dioxygenase activation in mice. *Mol Psychiatry.* 2008;14:511–522.
45. Maes M, Leonard BE, Myint AM, et al. The new ''5-HT'' hypothesis of depression: Cell-mediated immune activation induces indoleamine 2,3-dioxygenase, which leads to lower plasma tryptophan and an increased synthesis of detrimental tryptophan catabolites (TRYCATs), both of which contribute to the onset of depression. *Prog Neuropsychopharmacol Biol Psychiatry.* 2011;35:702–721.
46. Koo JW, Duman RS. IL-1 is an essential mediator of the antineurogenic and anhedonic effects of stress. *Proc Natl Acad Sci U S A.* 2008;105:751–756.
47. Stone TW, Behan WMH. Interleukin-1β but not tumor necrosis factor-α potentiates neuronal damage by quinolinic acid: Protection by an adenosine A2A receptor antagonist. *J Neurosci Res.* 2007;85:1077–1085.
48. McKinnon MC, Yucel K, Nazarov A, et al. A meta-analysis examining clinical predictors of hippocampal volume in patients with major depressive disorder. *J Psychiatry Neurosci.* 2009;34:41–54.
49. Pace TWW, Hu F, Miller AH. Cytokine-effects on glucocorticoid receptor function: relevance to glucocorticoid resistance and the pathophysiology and treatment of major depression. *Brain Behav Immun.* 2007;21:9–19.
50. Wong M-L, Dong C, Maestre-Mesa J, et al. Polymorphisms in inflammation-related genes are associated with susceptibility to major depression and antidepressant response. *Mol Psychiatry.* 2008;13:800–812.
51. Cerri AP, Arosio B, Viazzoli C, et al. The -308 (G/A) single nucleotide polymorphism in the TNF- αgene and the risk of major depression in the elderly. *Int J Geriat Psychiatry.* 2010;25:219–223.
52. Mlekusch W, Mlekusch I, Minar E, et al. Is there improvement of ''vascular depression'' after carotid artery stent placement? *Radiology.* 2006;240:508–514.
53. Ancelin M-L, Carrière I, Scali J, et al. Angiotensin-converting enzyme gene variants are associated with both cortisol secretion and late-life depression. *Transl Psychiatry.* 2013;3:e322.
54. Sayed-Tabatabaei FA, Oostra BA, Isaacs A, et al. ACE polymorphisms. *Circ Res.* 2006;98:1123–1133.
55. McGowan PO, Sasaki A, D'Alessio AC, et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat Neurosci.* 2009;12:342–348.
56. Yehuda R, Daskalakis NP, Lehrner A, et al. Influences of maternal and paternal PTSD on epigenetic regulation of the glucocorticoid receptor gene in Holocaust survivor offspring. *Am J Psychiatry.* 2014;171:872–880.
57. Steffens DC, Stechuchak KM, Oddone EZ. How asymptomatic is asymptomatic carotid stenosis? *Radiology.* 2007;244:317–318author reply 318-9.