Skin Conductance Levels May Reflect Emotional Blunting in Behavioral Variant Frontotemporal Dementia

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Emotional blunting is a core diagnostic feature of behavioral variant frontotemporal dementia (bvFTD). The authors evaluated skin conductance as a measure of emotional blunting among 10 patients with bvFTD compared with 10 with Alzheimer's disease and 14 healthy control subjects. Despite responses to an auditory startle stimulus, skin conductance levels (SCLs) were lower in the patients with bvFTD compared with the other groups. The low SCLs significantly correlated with ratings of emotional blunting. The authors conclude that low SCLs in bvFTD indicate a low resting sympathetic state and low emotional arousal. The measurement of SCLs may be a useful noninvasive diagnostic test for bvFTD.

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Behavioral variant frontotemporal dementia (bvFTD) is a common neurodegenerative dementia among those 65 years of age or younger.[1] The diagnosis depends on the presence of behavioral disinhibition, apathy/inertia, loss of sympathy/empathy, perseverative/compulsive behaviors, hyperorality, and a dysexecutive neuropsychological profile.[1] Perhaps most characteristic of patients with bvFTD is their degree of emotional blunting.[2] These patients have impairments in self-referential emotions such as embarrassment,[3] in the recognition of emotions from faces,[4] and in both cognitive and emotional aspects of empathy.[5]

In bvFTD, emotional blunting may be related to low emotional arousal as expressed in a low resting state of the autonomic nervous system. The neuropathology of bvFTD affects the prefrontal, anterior cingulate, insular, and amygdalar regions involved in maintaining emotions through the autonomic nervous system.[3] Studies have investigated the autonomic nervous system origin of emotional blunting in bvFTD but have focused on the phasic or physiological reactivity aspects rather than the

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tonic or resting aspects.[2,6] These studies often use an aversive stimulus such as an auditory startle to investigate autonomic nervous system reactivity.[7] Normally, after a defensive motor startle and a short latency, there is an autonomic nervous system orienting response that lasts approximately 3–10 seconds, with changes in heart rate, blood pressure, respiration, and skin conductance.[8,9] Prior research has observed acoustic startle responses among patients with frontotemporal lobar degeneration but has not focused on resting state measures.[3,10,11] However, the neuropathology of bvFTD suggests that tonic levels of autonomic nervous system may be primarily reduced.

This study assesses differences in skin conductance among patients with bvFTD compared with patients with Alzheimer's disease and healthy control subjects. Of the major autonomic nervous system measures, skin conductance level (SCL) is the one that depends entirely on sympathetic tone. We use a paradigm that includes the introduction of an unwarned auditory startle stimulus to compare tonic SCLs with phasic skin conductance responses (SCRs) to aversive stimuli. On the basis of their clinical emotional blunting, we hypothesize that patients with bvFTD show low tonic SCLs despite the presence of SCRs. The results are discussed in terms of the implications for SCLs as a noninvasive measure for the differential diagnosis of bvFTD.

METHODS

Participants

This study was approved by the Institutional Review Boards of the University of California, Los Angeles, and Veterans Administration Healthcare Center, Greater Los Angeles. Participants were recruited from the University of California, Los Angeles, Neurobehavior Clinic. This study population was comprised of community-based, moderately impaired dementia patients who underwent a comprehensive neurobehavioral evaluation. The study excluded patients on beta-blocker medications and those with other severe medical, neurologic, or psychiatric disorders.

The patients with bvFTD (N=10) included in this study presented with progressive behavioral changes consistent with a decline in social interpersonal conduct, impairment in regulation of personal conduct, emotional blunting, and loss of insight into their disease. The clinical diagnosis of FTD was based on International Consensus Criteria for bvFTD.[1] The clinical diagnosis of FTD was further confirmed by the presence of frontal-anterior temporal predominant changes on fluorodeoxyglucose positron emission tomography neuroimaging. This study was limited to patients with bvFTD who had mild-to-moderate behavioral disturbances and did not require psychoactive medications for behavioral disturbances.

There were two comparison groups. The first consisted of 10 patients with Alzheimer's disease. These patients met the National Institute on Aging and the Alzheimer's Association criteria for clinically probable Alzheimer's disease after completing a diagnostic evaluation.[12] To match patients with FTD patients, patients with Alzheimer's disease were selected who had an early age of onset and who were only mildly impaired, i.e., comparable Mini Mental State Examination (MMSE) scores.[13] The second comparison group consisted of 14 healthy control subjects. They were selected from research volunteers according to age, sex, and education. None of the patients with Alzheimer's disease or healthy control subjects had an anxiety disorder or other history of psychiatric or neurological disease or were using medications that could interfere with the psychophysiological testing, with the possible exception of acetylcholinesterase inhibitors.

As part of the initial assessment, patients and controls were administered the Scale for Emotional Blunting,[2,14] which is a measure of three dimensions: absence of pleasure seeking behavior, affective blunting, and cognitive blunting. The patients underwent a dedicated interview designed to elicit emotional responses on the 16 items of the Scale for Emotional Blunting. The scale, which takes 15–30 minutes to complete, assessed the three dimensions on a three-point scale, where 0 is "condition absent," 1 is "slightly present or doubtful," and 2 is "clearly present." To complete the Scale for Emotional Blunting, the examiner asked questions regarding personal revelations, concern for one's condition, and feelings about relatives and others. In addition to an interrater reliability of 0.83, reliability coefficients reported from neuropsychiatric patients include a Kendall's coefficient of concordance of 0.77 ($p<0.01$).[14]

Procedures

While seated in a chair, the participants were attached to the recording device and headphones. The participants were instructed to relax, and baseline data were recorded for 5 minutes. The participants were subjected to an unwarned and unanticipated 115-dB acoustic burst of white noise for 100 msec. Skin conductance (SC) was recorded for 5 minutes before and 1 minute after the

TABLE 1. Participant Characteristics

	bvFTD (N=10)	Alzheimer's disease (N=10)	Healthy control subjects (N=14)	Significance
Age, years	62.60 (9.60)	55.8 (3.90)	55.80 (9.19)	Not significant
Sex, men/women	5/5	5/5	5/9	Not significant
Ethnicity, white	10	9	13	Not significant
Education, years	15.30 (2.75)	15.3 (2.26)	16.07 (2.09)	Not significant
Mini-Mental State Examination	23.66 (3.35)[a]	21.8 (3.90)[b]	29.28 (1.05)[a,b]	$p<0.001$
Scale for Emotional Blunting	12.0 (11.0)[a,c]	1.6 (0.74)[c]	0.00 (0.0)[a]	$p<0.01$

Standard deviations are shown in parentheses.
[a]bvFTD versus HC, $p<0.001$.
[b]AD versus HC, $p<0.001$.
[c]bvFTD versus AD, $p\leq0.001$.

startle stimulus. The procedure was done at approximately the same time of day (10:30 a.m.) for all participants. SC was continuously recorded using the Biopac base module (150MP system) and the skin conductance module (GSR 100C) (Biopac, Goleta, CA) and BiopacAcqKnowledge 4.1 software. Acquisition parameters were set at 5 μS/V, a low-pass 1-Hz filter, and no high-pass filter. Sampling rate was 31.25 Hz. The startle stimulus was administered using Superlab Pro 4.0 (Cedrus Corporation, San Pedro, CA).

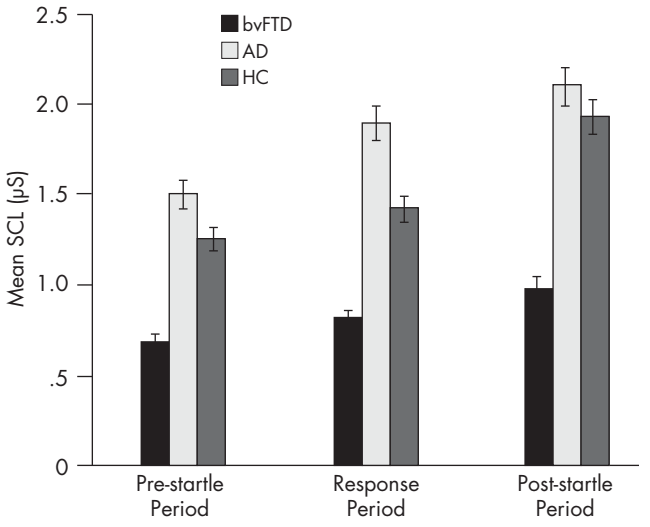
Physiological Measures The SC was measured by placing disposable electrodes pregelled with isotonic jelly (EL 507; Biopac Inc, Goleta, CA) on the palmar surface of the distal phalanges of the index and middle fingers of the right hand of the participant. The SC was processed using MATLAB 2006a to obtain values for each second. The prestartle period consisted of resting SCLs measured during the 20 seconds prior to the startle probe. During the subsequent response period, SCRs to the startle probe consisted of peak response amplitudes of 0.05 μS or more.[8,15] The amplitude of SCRs was determined by subtracting SC at the startle probe (0 seconds) from the highest SC in the response period. For all participants, SCRs were completed within 9 seconds; hence, we analyzed the duration of the response period as 9 seconds of data after the startle probe. The time of the peak SC response from the startle probe (0 seconds) was used as a separate variable. Peak response time represented the onset latency between stimulus and SCR onset plus the rise time between SCR onset and peak amplitude. The poststartle period was defined as the 20 seconds after the response period, i.e., the time from the ninth second to the 29th second after the startle probe.

Data Analysis Data analysis was conducted using SPSS version 20 (IBM, New York). Separate one-way analyses of variance (ANOVAs) were computed to assess group differences on the MMSE and Scale for Emotional Blunting. Each ANOVA was followed up by post hoc pairwise comparison analysis using Fisher's least significant difference corrections. An average SC for each time period was computed. Group differences in SC during the prestartle period (from 20 seconds before startle to 0 seconds), the response period (0–9 seconds), and the poststartle period (9–29 seconds) were assessed using a separate one-way ANOVA for each period. A repeated-measures ANOVA was used to examine differences in group responses in the three time periods. Greenhouse–Geisser corrections were applied for sphericity assumptions, and a follow-up contrast analysis was conducted to examine pairwise differences.

RESULTS

There were no significant differences on demographic variables between the patients with bvFTD, patients with Alzheimer's disease, and health control subjects. Although there were more women in the healthy control subject group than in the bvFTD or Alzheimer's disease groups, the differences were not statistically significant. As expected, the patients with bvFTD and AD had significantly more cognitive impairment (MMSE) compared with the healthy control subjects, but there were no significant differences between patients with Alzheimer's disease and bvFTD (overall $F=22.14$; $p<0.001$). Also as expected, the patients with bvFTD had significantly more emotional blunting (Scale for Emotional Blunting) than the patients with Alzheimer's disease and the healthy control subjects, but there were no significant differences between patients with Alzheimer's disease and healthy control subjects (overall $F=12.07$; $p<0.001$; Table 1).

FIGURE 1. Group Differences Before and After Startle Response



Bars represent 5% standard deviation.

Skin Conductance Levels

There were significant differences in overall SCLs for the groups, with lower levels observed in the bvFTD group compared with the other two groups ($F=3.61$, $p<0.05$). These findings were particularly significant for the resting prestartle period ($F=4.29$, $p=0.02$) and the response period ($F=4.22$, $p=0.02$), but did not persist into the poststartle period ($F=2.9$, $p=0.12$). When post hoc analyses were conducted, the resting prestartle differences were due to lower SCLs among the patients with bvFTD compared with the patients with Alzheimer's disease ($p<0.01$) and healthy control subjects ($p<0.05$), whereas the patients with Alzheimer's disease and healthy control subjects did not differ in resting prestartle SCLs. During the response period, patients with bvFTD continued to have significantly lower SCLs, particularly compared with the patients with Alzheimer's disease ($p<0.01$; Figure 1). Statistical control for whether the patients with bvFTD or AD were on acetylcholinesterase inhibitors did not have any effect on the SCL or SCR results.

Skin Conductance Responses

No significant group differences were observed in peak response time and amplitude of response during the response period (Table 2). There were seven patients with bvFTD who responded to the stimulus with at least a 0.05-μS change in SCLs compared with 9 patients with Alzheimer's disease and 13 healthy control subjects (nonsignificant group differences).

Correlations

The SC results did not significantly correlate with either sex or with the MMSE results. The Scale for Emotional Blunting correlated negatively with overall SCLs ($r=-0.40$, $p<0.05$). When the periods were examined, the Scale for Emotional Blunting was especially negatively correlated with the prestartle period ($r=-0.48$; $p<0.01$). The correlations for the response period were $r=-0.35$ and $p=0.05$ and for the poststartle period were $r=-0.35$ and $p=0.06$.

Repeated-Measures ANOVA

There was a main effect of period ($F=2.8$, $p<0.001$), and post hoc analysis revealed that the poststartle period had significantly higher SCLs compared with the response and prestartle periods ($p<0.001$). All groups showed higher SCLs during the response period compared with the prestartle period ($p<0.001$), indicating a response to the auditory startle.

DISCUSSION

This study evaluates emotional blunting in bvFTD by examining their SC levels and responses. It confirms the

TABLE 2. Skin Conductance Measures

	bvFTD (N=10)	Alzheimer's disease (N=10)	Healthy control subjects (N=14)	Significance
Prestartle period SCL, μS	0.69 (0.43) [a,b]	1.5 (0.88)[a]	1.26 (0.55)[b]	p=0.02
Response period SCL, μS	0.82 (0.73)[a]	1.9 (1.21)[a]	1.42 (0.63)	p=0.02
Peak response time, sec	4.70 (1.56)	5.33 (1.32)	5.21 (1.05)	Not significant
Amplitude, μS	0.25 (0.31)	0.31(0.23)	0.27 (0.32)	Not significant
Responders, >0.5 μS	7/10; 70%	9/10; 90%	13/17; 93%	Not significant
Poststartle period SCL, μS	0.99 (0.92)	2.10 (1.10)	1.93 (1.28)	Not significant

Standard deviations are shown in parentheses.
[a]bvFTD versus AD, $p<0.01$.
[b]bvFTD versus HC, $p<0.05$.

presence of an orienting response to startle measured by SCRs in patients with bvFTD, similar to responses in patients with Alzheimer's disease and in healthy control subjects. More significantly, this study documents lower SCLs throughout the prestartle and response periods among the patients with bvFTD compared with other groups. This indicates a low baseline sympathetic tone in bvFTD. In addition, scores on the Scale for Emotional Blunting negatively correlate with SCLs, particularly resting prestartle SCL. The implications of these findings are that patients with bvFTD have a low resting state of emotional arousal. Low SCLs may reflect some of the emotional blunting observed among patients with this disorder.

This is one of the few psychophysiological studies to compare patients with bvFTD with other patients with dementia such as Alzheimer's disease.[3,11] The low SCLs among the patients with bvFTD clearly distinguish them from patients with the far more common Alzheimer's disease. Distinguishing bvFTD from Alzheimer's disease can be difficult, particularly if the Alzheimer's disease is of early onset and accompanied by neuropsychiatric symptoms.[16] On pathology, approximately one in five patients diagnosed with bvFTD during life turn out to have the neuropathology of Alzheimer's disease.[16] Consequently, a simple, low-technology, and relatively available noninvasive test, such as SC, can be helpful in distinguishing patients with bvFTD. Parenthetically, in the present study, the patients with Alzheimer's disease show slightly higher SC measures than healthy control subjects, and, although not statistically significant, higher SC values could suggest decreased sensorimotor gating from entorhinal pathology in Alzheimer's disease.[17]

Previous research has shown no differences in physiological reactivity and general somatic activity to an unwarned acoustic startle stimulus among patients with bvFTD compared with healthy controls.[3,10,11,18,19] These studies, which often included bvFTD as part of a larger frontotemporal lobar degeneration group,[3,11,18,19] reported decreases in embarrassability in frontotemporal lobar degeneration based on facial expression coding,[3] in recognition of sadness and fear in film clips,[11] and in emotional regulation.[18,19] These studies measured emotional regulation, not with simple SCLs, but with physiological composite scores.[3,10,11] The use of physiological composite scores may have conflated the initial defensive motor response to an aversive startle stimulus with the subsequent autonomic or orienting response.

Rather than composite scores, SC may be the best autonomic nervous system measure for resting sympathetic state and emotional arousal. Unlike heart rate or blood pressure measures, it is a pure cholinergic, sympathetic measure without confounding parasympathetic influences from emotional situations. SCL reflects the baseline state of the sympathetic autonomic nervous system and also reflects the degree of relaxation and emotional arousal.[20] In contrast, SCR is a transient change in SCL caused by a significant or novel stimulus and can markedly increase with anxiety, stressors, and emotional influences on the orienting reaction.[21,22] Some studies suggest that the higher the resting SCL, the greater the SCR amplitude and the lower the stimulus strength needed for an SCR.[8,23] However, SCL and SCR are dissociable and may reflect different brain mechanisms.[24] As seen in this study, event-related SCR occurred in bvFTD, whereas SCLs remained low.

Areas affected by bvFTD, including the prefrontal regions, insulae, and amygdalae, influence SC and emotional arousal.[15] Increased ventromedial prefrontal activity can decrease SC,[25] whereas increased orbitofrontal activity can either increase or decrease SCLs.[24] The insular cortex, particularly on the right, and the adjacent anterior cingulate cortex are also involved in regulating SC: both tonic SCLs and phasic SCRs.[26–28] The amygdalae further modulate SCRs, especially from fear and other emotional activity.[29] From these studies, it is probable that the structures most implicated in the low SCLs found in bvFTD in the present study are the anterior insular and the adjacent anterior cingulate cortices of the brain.[3,6] In sum, the underlying mechanism for low SCLs in bvFTD and increased emotional blunting may be attenuation of the resting sympathetic state and consequently low emotional arousal from disease in these areas of the brain.

To our knowledge, this is the first study to focus on SCLs in patients with bvFTD compared with patients with Alzheimer's disease and healthy control subjects. Although bvFTD patients have a startle response, they have low SCLs compared with other groups. The findings indicate a low baseline sympathetic tone and suggest that a high threshold for reactivity contributes to the characteristic emotional blunting among patients with bvFTD. Furthermore, the measurement of SCLs could be useful as a simple, noninvasive test for bvFTD. Future research, using varying emotionally evocative stimuli, promises to clarify the value of this psychophysiological measure in the assessment of bvFTD.

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