

Transcranial direct current stimulation improves the QT variability index and autonomic cardiac control in healthy subjects older than 60 years

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Background: Noninvasive brain stimulation technique is an interesting tool to investigate the causal relation between cortical functioning and autonomic nervous system (ANS) responses.

Objective: The objective of this report is to evaluate whether anodal transcranial direct current stimulation (tDCS) over the temporal cortex influences short-period temporal ventricular repolarization dispersion and cardiovascular ANS control in elderly subjects.

Subjects and methods: In 50 healthy subjects (29 subjects younger than 60 years and 21 subjects older than 60 years) matched for gender, short-period RR and systolic blood pressure spectral variability, QT variability index (QTVI), and noninvasive hemodynamic data were obtained during anodal tDCS or sham stimulation.

Results: In the older group, the QTVI, low-frequency (LF) power expressed in normalized units, the ratio between LF and high-frequency (HF) power, and systemic peripheral resistances decreased, whereas HF power expressed in normalized units and α HF power increased during the active compared to the sham condition ($P < 0.05$).

Conclusion: In healthy subjects older than 60 years, tDCS elicits cardiovascular and autonomic changes. Particularly, it improves temporal ventricular repolarization dispersion, reduces sinus sympathetic activity and systemic peripheral resistance, and increases vagal sinus activity and baroreflex sensitivity.

Keywords: transcranial direct current stimulation, QT variability, heart rate variability, autonomic nervous system, aging

Introduction

Aging is an important risk factor for coronary disease, heart failure, and sudden cardiac death. According to the classic multifactorial theory proposed by Zipes and Wellens,¹ aging brings about a sudden increase in sympathetic activity along with diminished vagal nerve activity. Both changes act singly or in concert as transient events triggering malignant ventricular arrhythmias. For this reason, sudden and unexpected events with high emotional content, such as earthquakes, terrorist attacks, sexual activities, or anger, can lead to sudden cardiac death, especially in older subjects or patients with structural heart disease.²⁻⁴

In the last decade, many observations suggested that the insular cortex (IC) has a central role in favoring sudden cardiac death. The right insula is considered as the site where both sympathetic hyperactivity and left ventricular repolarization dispersion originate during acute stroke or transient ischemic attacks.⁵⁻⁸ Other studies indicated that the left IC intervenes in baroreflex and parasympathetic control.^{6,7,9,10}

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Recently, it has been suggested that transcranial direct current stimulation (tDCS) over the temporal cortex (TC) can reach subcortical areas, such as the IC located just below the TC.^{11,12} tDCS modulates spontaneous neuronal network activity through the application of weak electrical currents to different cortical areas. At the neuronal level, the primary mechanism of action is the induction of polarity-dependent changes in cortical excitability.¹³ Unfortunately, most of the existing studies have been designed with the aim to understand the safety of noninvasive brain stimulation using cardiovascular parameters and not to study the brain-heart relationship.

The TC and IC have been associated with autonomic nervous system (ANS) control and the awareness of emotional feelings from the body,¹¹ and it has been demonstrated that tDCS, applied over T3 targeting the left IC, increases the parasympathetic modulation in athletes at rest. Results have been replicated further showing that such effects remain during light and moderate exercise also, as indexed by the delayed vagal withdrawal.¹² The authors conclude that besides the direct effects of anodal tDCS on the TC, this stimulation might also have reached subcortical areas, such as the IC.

Despite these promising results, up to now no studies have investigated tDCS-induced changes in parasympathetic sinus and cardiac function, sympathetic cardiovascular activity, and temporal ventricular repolarization. To overcome this limitation, we tested whether tDCS could increase parasympathetic sinus and cardiac function, reduce sympathetic cardiovascular activity, and improve temporal ventricular repolarization dispersion in healthy older subjects who particularly have an ANS control characterized by low baroreflex sensitivity,^{14,15} decreased heart rate variability,¹⁵⁻²¹ and increased myocardial temporal dispersion.²² Power spectral analysis of short-period RR, systolic blood pressure (SBP), and QT interval variability was used to evaluate ANS activity and temporal repolarization dispersion.²²⁻²⁷

Subjects and methods

Participants

The final sample was composed of 29 participants younger than 60 years (17 women and 12 men; mean age = 35.97 [10.9]; range 23–57 years) and 21 participants aged 60 years or older (10 women and 11 men; mean age = 69.67 [6.25] years). Only one participant was non-Caucasian. Ten subjects had to be excluded from the analyses because of missing data or excessive artifacts. Patients were recruited from public advertisement and from staff and students of Policlinico Umberto I. Patients younger than 18 years, history of head

injury, major medical neurological or psychiatric disorder, cognitive impairment, history of substance or alcohol abuse or dependence, diagnosis of heart disease, obesity (body mass index >30 kg/m²), and pregnancy were excluded. Finally, sedentary subjects with low coronary risk factors were selected. All the participants were medication-free and provided written informed consent. Written informed consent was obtained for publication of the associated image. The bioethical committee of S Lucia Foundation, Rome, Italy, approved the study. Participants were compensated for their time.

Procedure

A randomized, sham-controlled, within-subjects design was used. Subjects were randomized in a counterbalanced order to receive both tDCS stimulation conditions. Data were assessed in 2 nonconsecutive days. All sessions occurred between 12 pm and 4 pm. Subjects were asked to avoid drinking coffee and smoking cigarettes 24 hours prior to the sessions. The experimental protocol was completed within a week.

tDCS

An anodal or a sham tDCS was applied in a counterbalanced random order over T3 (2 mA during 15 minutes) using the brain STIM device (E.M.S. srl, Bologna, Italy; Figure 1). A cathodal tDCS condition was not included because it is well proven that anodal tDCS increases cortical excitability, whereas the effects of cathodal tDCS are still a matter of debate.²⁸ The electric current was applied using a pair of sponges soaked in saline solution (140 mM of NaCl dissolved in Milli-Q water) involving both electrodes (35 cm²).²⁹ The electrodes (anodal and cathodal) were connected to a constant current stimulation device with three power batteries.



Figure 1 Photograph taken during T3 anodal transcranial direct current stimulation (tDCS) in a representative subject.

Note: Photograph by the author.

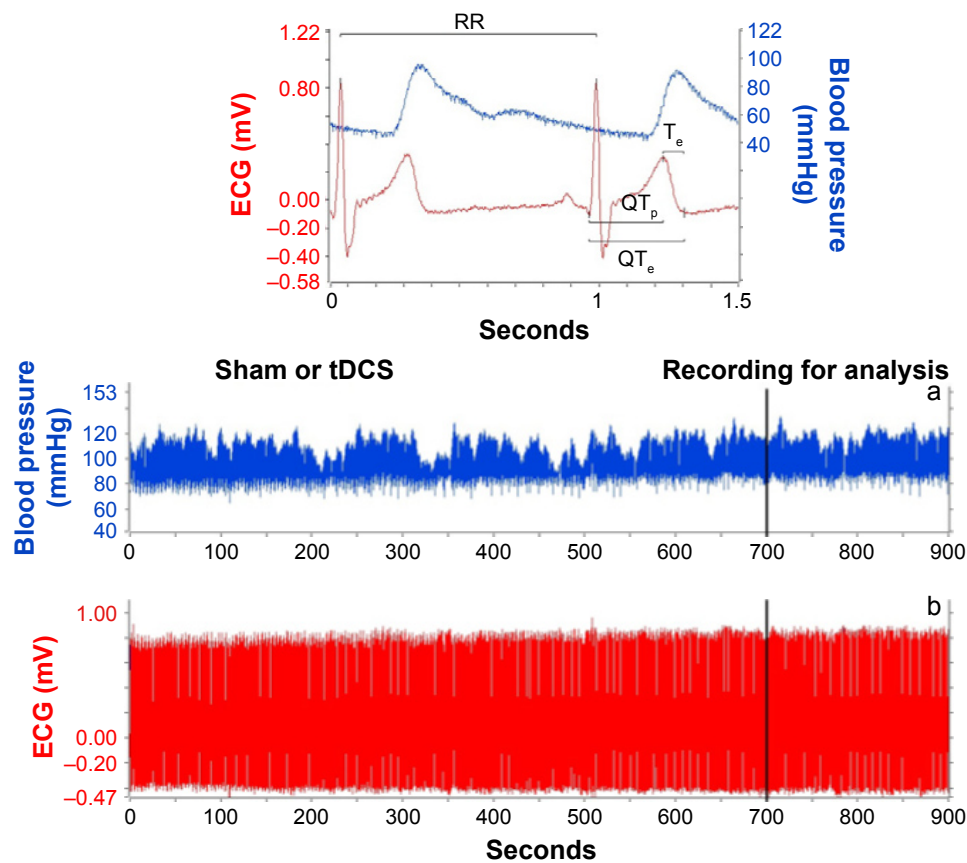


Figure 2 An example of a 15-minute recording during sham or real anodal transcranial direct current stimulation (tDCS).

Notes: (a) shows in detail the examined electrocardiogram (ECG) and blood pressure variables (b). The following intervals were measured: RR, QT_e (from the Q wave to the T wave end), QT_p (from the Q wave to the T wave peak), and T_e (difference between QT_e and QT_p).

The breathing cycle was controlled (15 breaths/min; 0.25 Hz) throughout the testing sessions.³⁰ The continuous electrocardiogram (ECG) and beat-to-beat blood pressure recordings were made along the experiment; however, only the last 5 minutes of each registration (anodal and sham) was used for the analyses (Figure 2).

For the anodic stimulation targeting left IC, the anode was placed over T3 area according to the international EEG 10–20 system. The cathode was placed over the supraorbital contralateral area (Fp2) and fixed by elastic bands. The electrodes were placed in the same position of the anodal stimulation to perform the sham condition. However, the stimulator was turned off after 30 seconds.³¹ When sham began participants felt a tingling or an itching sensation identical to the tDCS but received no further current. This procedure allowed participants to remain “blind” to the stimulation polarity received during the test and ensured a sham control effect.³²

Physiological data processing

ECG and beat-to-beat blood pressure (Finometer™; FMS, Arnhem, the Netherlands) signals were acquired

and digitalized with a custom-designed card (National Instruments USB-6008; National Instruments, Austin, TX, USA) at a sampling frequency of 500 Hz. Points used for the ECG segment analysis were detected automatically by a classic adaptive derivative/threshold algorithm. Software for data acquisition, storage, and analysis was designed and produced by our research group with the LabView program (National Instruments). After a linear interpolation, an expert cardiologist (GP) checked the different points and, when needed, manually corrected the mistakes with an interactive software.^{14–17,33} All ECG and blood pressure data were analyzed in a single-blind fashion. None of the evaluators knew whether participants received anodal or sham tDCS.

Heart rate, blood pressure, QT variability, and other hemodynamic variables (stroke volume, cardiac output, and peripheral resistances) were obtained from the last 5-minute segments in ECG and beat-to-beat blood pressure recordings. From the same 5-minute ECG segment (Figure 2), the corrected QT_e, QT_p, and T_e intervals were obtained according to the formulas proposed by Bazett (QT_e/RR^{0.5}; QT_p/RR^{0.5}; T_e/RR^{0.5}), Friedericia (QT_e/RR^{0.33}; QT_p/RR^{0.33}; T_e/RR^{0.33}), Lilly

($QT_e/RR^{0.4}$; $QT_p/RR^{0.4}$; $T_e/RR^{0.4}$), and Framingham ($QT_e + [0.154 \times \{1,000 - RR\}]$; $QT_p + [0.154 \times \{1,000 - RR\}]$; $T_e + [0.154 \times \{1,000 - RR\}]$).²⁶

The following intervals from the respective time series in ECG recordings were measured: RR, QT_e (from the Q wave to the T wave end), QT_p (from the Q wave to the T wave peak), and T_e (difference between QT_e and QT_p) (Figure 2).^{24,26,27} Therefore, the mean and variance values for each of these intervals were calculated and then the original formula proposed by Berger et al³⁴ was used to calculate three different QT variability indexes (QTVIs) (Figure 3).^{24,26,27}

$$QT_e VI = \log_{10} \left\{ \frac{[[QT_e \text{ variance}]/[QT_e \text{ mean}]^2]}{[[RR \text{ variance}]/[RR \text{ mean}]^2]} \right\}$$

$$QT_p VI = \log_{10} \left\{ \frac{[[QT_p \text{ variance}]/[QT_p \text{ mean}]^2]}{[[RR \text{ variance}]/[RR \text{ mean}]^2]} \right\}$$

$$T_e VI = \log_{10} \left\{ \frac{[[T_e \text{ variance}]/[T_e \text{ mean}]^2]}{[[RR \text{ variance}]/[RR \text{ mean}]^2]} \right\}$$

From the same 5-minute ECG and BP segments, the total power of RR intervals and SBP (TP_{RR} and TP_{SBP}) and their total spectral density were also determined.³⁵ For RR and SBP, the following spectral components were calculated: a high-frequency (HF_{RR} and HF_{SBP}) component (from 0.15

to 0.40 Hz), a low-frequency (LF_{RR} and LF_{SBP}) component (from 0.04 to 0.15 Hz Eq), and a very low-frequency (VLF_{RR} and VLF_{SBP}) component (<0.04 Hz Eq). LF and HF central frequencies (Figure 4) were also measured. The α index was calculated by dividing the square root of the spectral density for heart rate by the square root of the corresponding spectral density for SPB, as described by Robbe et al³⁶ and later by other investigators:^{14,33,37,38} $\alpha LF = \sqrt{LF_{RR}} / \sqrt{LF_{SBP}}$; $\alpha HF = \sqrt{HF_{RR}} / \sqrt{HF_{SBP}}$ (Figure 4).

The same ECG intervals, together with beat-to-beat SBP recordings, were also used to analyze power spectra with an autoregressive algorithm also for QT_e , QT_p , and T_e intervals. The same order of autoregressive model in sham or during tDCS in the same subject was used, normally the order used by the model was between 10 and 20 (sham or tDCS order: 16 ± 4). Cross-spectral analysis was then used to evaluate the reciprocal influence (coherence function) between RR, QT_e , QT_p , and T_e .^{22,32,39,40}

Coherence expresses the fraction of power at a given frequency in either time series and provides an index of a linear relationship between the input and output signals. The coherence function $\gamma[f]$ was then computed according to the following formula:^{22,32,39,40}

$$\gamma[f] = \frac{|P_{xy}[f]|^2}{P_{xx}[f]P_{yy}[f]}$$

where f is frequency, $P_{xx}[f]$ is the RR interval spectrum, $P_{yy}[f]$ is the QT interval spectrum, and $P_{xy}[f]$ is the cross spectrum. The coherence function measures the degree of linear interaction between RR and QT interval oscillations as a function of their frequency. The value of the coherence function ranges between 0 and 1. Mean coherences were measured by averaging $\gamma[f]$ over the frequency bands: from 0 to 0.50 Hz.

Statistical analysis

To better understand the influences of anodal tDCS on the autonomic functioning of elderly people, participants were grouped according to age: <60 and ≥ 60 years. Unless otherwise indicated, all data are expressed as mean \pm standard deviation. Data with skewed distribution are given as median and interquartile range (75th percentile to 25th percentile). Categorical variables were analyzed with the χ^2 test.

One-way analysis of variance was used to compare data for the normally distributed variables between the two groups with different age. On the contrary, Mann–Whitney test was used to compare non-normally distributed variables (as evaluated

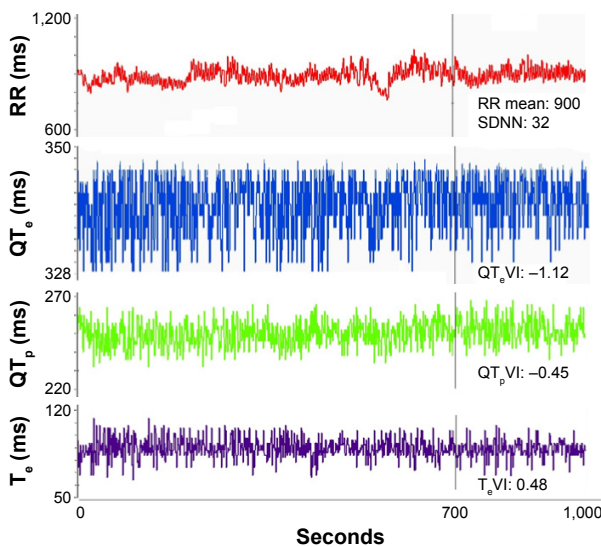


Figure 3 Example of a 5-minute ECG recording: RR, QT_e (from the Q wave to the T wave end), QT_p (from the Q wave to the T wave peak), and T_e (difference between QT_e and QT_p) intervals and relative variability indexes: SDNN, $QT_e VI$, $QT_p VI$, and $T_e VI$.
Abbreviations: ECG, electrocardiogram; SDNN, standard deviation of all R-R intervals.

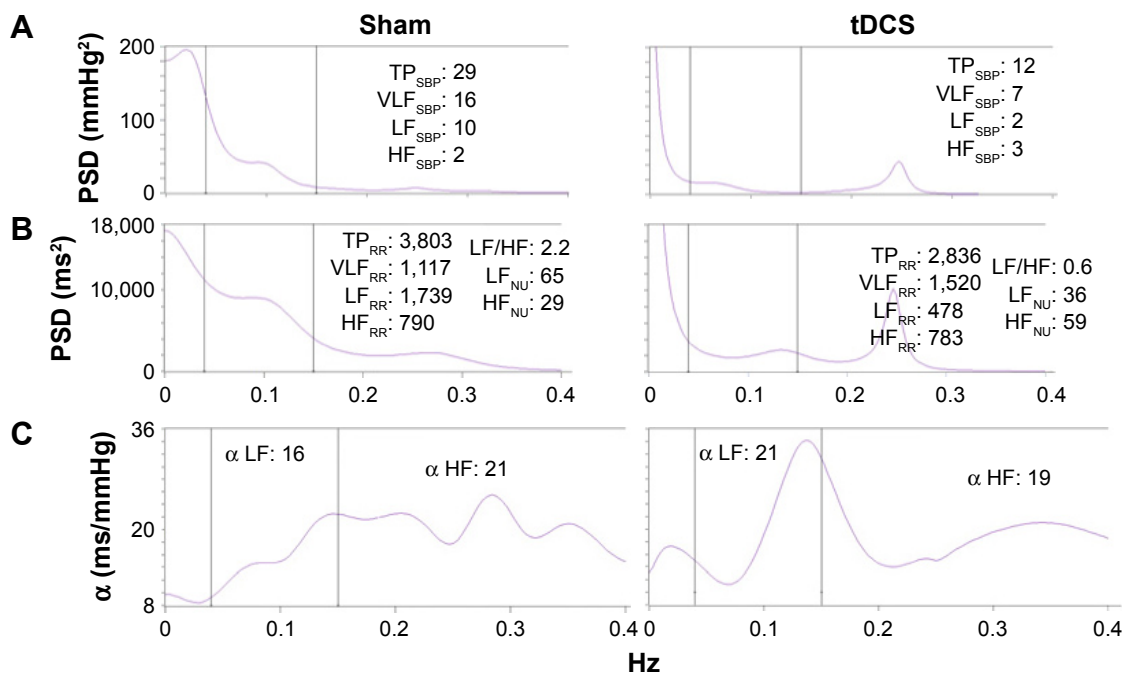


Figure 4 (A) shows the spectrum for SBP, (B) shows the R–R variability spectrum, and (C) shows the index during sham (left panel) or active tDCS (right panel).

Notes: Alpha indexes: the relationship between the square root of a single spectral component of R–R variability (LF or HF) and the square root of the same spectral component for SBP. The (C) shows the three spectral windows considered: a LF power (0.04–0.15 Hz) and a HF power (0.15–0.40 Hz). R–R and arterial pressure variability were recorded simultaneously during controlled breathing. Note the increased HF_{NU} and decreased LF_{NU} and LF: HF during tDCS, a pattern reflecting a sinus vagal increase and sinus sympathetic decrease. LF:HF, ratio between LF and HF.^{30,35}

Abbreviations: SBP, systolic blood pressure; tDCS, transcranial direct current stimulation; LF, low frequency; HF, high frequency; TP, total power; VLF, very low-frequency; NU, normalized units; PSD, power spectral density.

by Kolmogorov–Smirnov test) between the two groups with different age. Paired Student’s *t*-test or Wilcoxon test was used to evaluate differences in the same group during sham or tDCS for the data with normal or non-normal distribution, respectively. Stepwise multiple regression analysis was used to determine the association between the studied variables and age during sham or tDCS. *P*-values ≤ 0.05 were considered statistically significant. All data were analyzed with SPSS-PC+ (SPSS-PC+ Inc, Chicago, IL, USA).

Results

With the exception of age, no other clinical characteristics differed significantly between the two groups (Table 1). The two groups had no differences for number of smokers (three vs two subjects, *P*: nonsignificant) or physical activity levels.

As shown in Tables 2 and 3 in both experimental conditions, elderly participants has lower RR variance ($P < 0.05$), TP_{RR} ($P < 0.05$), LF_{RR} ($P < 0.05$), α LF ($P < 0.05$), stroke volume ($P < 0.001$), cardiac output ($P < 0.001$), and VLF_{RR} ($P < 0.05$) and higher QT variance ($P < 0.05$), QT_e VI ($P < 0.05$; Figure 5), QT_p VI ($P < 0.05$), T_e VI ($P < 0.05$), peripheral resistances, QT, T_e mean, and T_e variance ($P < 0.05$) compared to younger participants.

Compared to sham tDCS, anodal tDCS yielded RR, hemodynamic and repolarization variables changes in the older group only. In detail, QT_e VI, LF_{RR}, LF/HF, and peripheral resistances decreased, whereas QT_e mean, T_e mean, HF_{RR}, and α HF increased. In the younger group, peripheral resistances were significantly lower during active compared to sham tDCS.

Results from the stepwise multiple regression analysis detected a significant positive association between age and QT_e VI (Figure 6), QT_p VI, and T_e VI with similar regression coefficient and significance.

Table 1 Characteristics of the healthy elderly volunteers who underwent transcranial direct current stimulation

Characteristics	Age	Age	P-values
	<60 years	≥60 years	
Patients, n	29	21	
Men/women	12/17	11/10	ns
Age, years	36±11	70±6	<0.0001
Body mass index, kg/m ²	24±3	25±3	ns
Heart rate, beats/min	68±9	66±7	ns
Systolic blood pressure, mmHg	110±17	108±7	ns
Diastolic blood pressure, mmHg	60±10	61±10	ns

Note: Data presented as mean \pm standard deviation unless stated otherwise.

Abbreviation: ns, nonsignificant.

Table 2 RR, QT_e, QT_p, and T_e interval data in the healthy elderly volunteers who underwent sham and active tDCS

Variables	Age		P-values
	<60 years	≥60 years	
Sham tDCS			
Patients, n	29	21	
RR mean, ms	903±126	914±106	ns
RR variance, ms ²	1,552 (1,741)	637 (1,050)	0.014
QT _e mean	334±24	346±24*	ns
QT _e variance, ms ²	6 (6)	14 (17)	0.020
QT _p mean	260±22	267±23	ns
QT _p variance, ms ²	16 (13)	25 (21)	ns
T _e mean	75±11	79±12*	ns
T _e variance, ms ²	21 (20)	36 (34)	ns
QT _e →RR, coherence	0.205±0.030	0.202±0.033	ns
QT _p →RR, coherence	0.223±0.044	0.212±0.032	ns
T _e →RR, coherence	0.206±0.035	0.205±0.029	ns
T _e →QT _p , coherence	0.683±0.199	0.663±0.134	ns
QT _e VI	-1.44 (0.60)	-0.86 (1.15)*	0.004
QT _p VI	-0.95 (0.68)	-0.57 (0.85)	0.007
T _e VI	0.30 (0.70)	0.68 (0.70)	0.004
Anodal tDCS			
Patients, n	29	21	
RR mean, ms	897±125	930±130	ns
RR variance, ms ²	1,543 (1,915)	723 (106)	0.004
QT _e mean	334±28	353±30*	0.032
QT _e variance, ms ²	7 (6)	12 (17)	0.033
QT _p mean	256±24	266±28	ns
QT _p variance, ms ²	16 (23)	23 (21)	ns
T _e mean	78±10	84±11*	0.030
T _e variance, ms ²	22 (24)	35 (27)	0.033
QT _e →RR, coherence	0.213±0.37	0.204±0.32	ns
QT _p →RR, coherence	0.223±0.041	0.211±0.043	ns
T _e →RR, coherence	0.205±0.027	0.202±0.025	ns
T _e →QT _p , coherence	0.726±0.148	0.697±0.129	ns
QT _e VI	-1.70 (0.60)	-1.08 (0.93)*	0.006
QT _p VI	-1.05 (0.58)	-0.55 (0.68)	0.009
T _e VI	0.14 (0.45)	0.69 (0.62)	0.003

Notes: Values expressed as mean ± SD or median (interquartile range 75th percentile to 25th percentile). *P<0.05 sham vs tDCS. QT_e, QT interval (from q to end of T wave); QT_p, QT_p interval (from q to peak of T wave); T_e, T_e interval (from peak to end of T wave).

Abbreviations: tDCS, transcranial direct current stimulation; ns, nonsignificant; SD, standard deviation.

Discussion

The major finding in this study is that in participants older than 60 years anodal tDCS on the left TC reduces QT_eVI, LF_{NU}, LF/HF, and systemic peripheral resistances and increases HF_{NU} and α HF. Thus, it seems that such stimulation improves temporal myocardial dispersion, reduces sympathetic sinus control, and increases vagal and baroreflex activity in elderly subjects.^{29,36}

Present results are in agreement with a previous study, which, using the same stimulation protocol, showed an

Table 3 Power spectral analysis of RR and SBP data in the healthy elderly volunteers who underwent sham and active tDCS

Variables	Age		P-values
	<60 years	≥60 years	
Sham tDCS			
Patients, n	29	21	
LF _{RR'} ln ms ²	6.02±0.89	5.15±1.49	0.014
HF _{RR'} ln ms ²	5.65±1.07	4.32±1.43	0.001
LF _{RR'} nu	51 (22)	63 (25)*	ns
HF _{RR'} nu	42 (24)	26 (24)*	ns
LF/HF _{RR}	1.15 (1.65)	2.6 (3.47)*	ns
LF _{SBP'} mmHg ²	6 (10)	9 (17)	ns
α LF, mmHg/ms	7 (8)	6 (4)	0.020
α HF, mmHg/ms	11 (8)	6 (5)*	0.002
SBP _{finomer'} mmHg	110±17	108±28	ns
DBP _{finomer'} mmHg	52±14	51±15	ns
Stroke volume, mL	69±12	52±14	0.001
Cardiac output, L/m	4.47±0.87	3.45±1.06	0.001
Systemic peripheral resistance, u	1,579 (740)*	2,155 (1,181)*	0.01
Anodal tDCS			
Patients, n	29	21	
LF _{RR'} ms ²	6.25±0.91	5.26±1.32	0.003
HF _{RR'} ms ²	5.64±1.13	4.90±1.71	ns
LF _{RR'} nu	59 (23)	52 (24)*	ns
HF _{RR'} nu	36 (21)	40 (23)*	ns
LF/HF _{RR}	1.67 (2.18)	1.23 (1.70)*	ns
LF _{SBP'} mmHg ²	6 (5)	7 (6)	ns
α LF, mmHg/ms	9 (6)	6 (7)	0.018
α HF, mmHg/ms	13 (10)	8 (10)*	ns
SBP _{finomer'} mmHg	102±14	92±28	ns
DBP _{finomer'} mmHg	45±14	44±15	ns
Stroke volume, mL	72±14	53±16	0.001
Cardiac output, L/m	4.67±0.97	3.44±0.97	0.001
Systemic peripheral resistance, u	1,296 (428)*	1,600 (1,111)*	0.038

Notes: Values are expressed as mean ± SD or median (interquartile range 75th percentile to 25th percentile). *P<0.05 sham vs tDCS.

Abbreviations: SBP, systolic blood pressure; tDCS, transcranial direct current stimulation; LF, low frequency power; HF, high frequency power; ns, nonsignificant; nu, normalized units; DBP, diastolic blood pressure; SD, standard deviation.

increased parasympathetic activity (log of HF) and reduced sympathetic activity (log LF and LF/HF) in athletes but not in untrained subjects.¹¹ Okano et al¹² have replicated these previous results, and both studies speculated about the effects of the stimulation on the ANS in terms of the effects on the IC. Several clinical and experimental observations underline the close link between ischemic lesions in the IC, ANS control, and changes in ventricular repolarization and sudden cardiac death. In particular, acute stroke in the right IC increases plasma norepinephrine, increases the corrected QT interval, and worsens cardiovascular outcome at 1 year after stroke.⁴¹ The right IC therefore seems to play a crucial role in sympathetic activation,^{42,43} in modifying ventricular

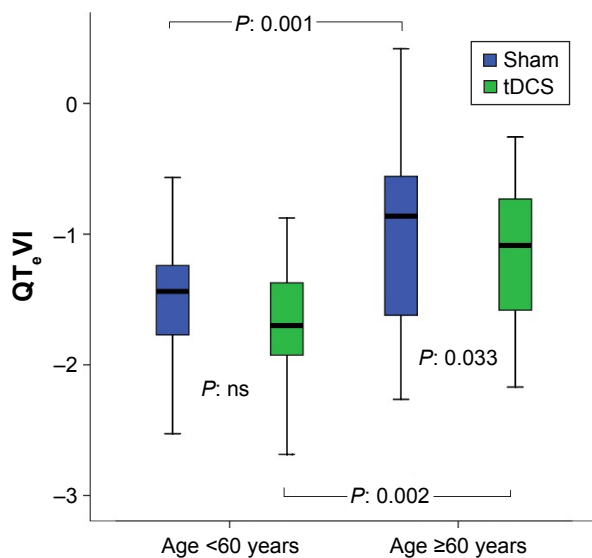


Figure 5 $QT_e VI$ during sham or anodal tDCS in volunteers younger and older than 60 years.

Notes: In the box plots, the central line represents the median distribution. Each box spans from 25th to 75th percentile points, and error bars extend from 10th to 90th percentile points.

Abbreviations: $QT_e VI$, QT_e variability index; tDCS, transcranial direct current stimulation; ns, nonsignificant.

repolarization, and in increasing sudden cardiac death risk. Indeed, sympathetic hyperactivity and increased temporal repolarization dispersion can induce malignant ventricular arrhythmias in patients with structural heart disease.^{22,39} No specific data are available on left insular stroke. Studies on left insular stroke⁴⁴ report conflicting results presumably depending on the subjects' handedness.⁴⁵

A limitation of our study is the relatively low spatial resolution of tDCS.⁴⁶ Therefore, other brain regions besides the IC could also have been modulated. Since adjacent brain areas are also involved in ANS regulation, we cannot determine to which extent a possible adjacent modulation could have influenced the results.⁴⁷

Limitation notwithstanding, a clinically relevant finding in our study is that anodal tDCS over T3 in healthy persons older than 60 years increases sinus parasympathetic activity and baroreflex sensitivity (increased HF_{NU} and αHF power). At the same as these variables change, sympathetic sinus activity diminishes (reduced LF_{NU} and LF/HF power) and so does temporal ventricular repolarization dispersion (reduced $QT_e VI$). This finding could have important clinical applications because it points to the use of tDCS as a potential tool to reduce hypertension in the elderly (via reducing systemic peripheral resistance) and, most important, to prevent malignant ventricular arrhythmias.

For confirming an age-related increase in $QT_e VI$ (Figure 6),⁴⁸ present data suggest that this index may improve during anodal tDCS in the elderly. Such improvement seems to depend mainly on the increased denominator, namely RR variance ($\sim 13\%$) given that concurrent QT_e variance and QT mean increases worsen $QT_e VI$. Hence, rather than depending on a direct improvement in repolarization, $QT_e VI$ seems to improve because of the increased heart rate variability, the exact change causing age-related $QT_e VI$ worsening. The increased heart rate variability during tDCS undoubtedly depends on the increased sinus parasympathetic activity and simultaneous reduction in sympathetic activity, as the spectral data in our study confirm. Whatever mechanism is responsible for the reduced $QT_e VI$, this marker's improvement clearly indicates a degree of clinical improvement in elderly. As well as being a marker of ventricular electrical instability, $QT_e VI$ is also a clinical marker of hemodynamic compensation in the heart failure.^{22,26,34} Even though our data indicate that anodal tDCS may have improved $QT_e VI$ and reduced peripheral resistance in healthy elderly subjects, no specific data on the elderly patients with heart failure with preserved left ventricular ejection fraction.⁴⁹ It is well known that this syndrome,

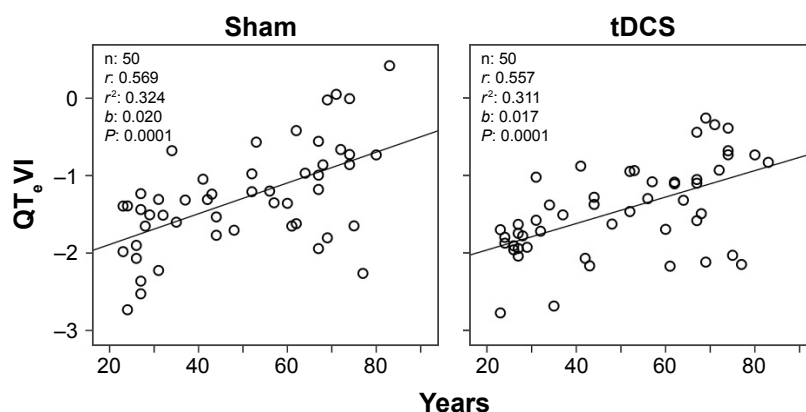


Figure 6 Relationship between QT_e variability index ($QT_e VI$) and age in healthy control subjects during sham or active transcranial direct current stimulation (tDCS).

extremely frequent in the elderly subjects, shows a clinical pattern characterized by normal ejection fraction, high peripheral resistance, and QT_c VI.^{50,51} Moreover, chronic heart failure patients could improve their well known neuroautonomic impairment with this treatment. Therefore, the usefulness of these noninvasive brain stimulation methods as potential treatment for these populations needs to be established with randomized controlled trials. Another point to clarify is how to apply the stimulation: excluding a permanent, invasive stimulation, we could obtain some improvement by cyclic stimulation such as against depression and mania. Although the mechanism is unknown, neuronal plasticity could explain the neuronal lasting changes after brain stimulation.⁵²

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Disclosure

The authors report no conflicts of interest in this work.

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