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*"Common sense is not so common."*

Voltaire

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# Scalp-recorded slow EEG responses generated in response to hemodynamic changes in the human brain

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**Abstract**

**Objective**: To study whether hemodynamic changes in human brain generate scalp-EEG responses.

**Methods**: Direct current EEG (DC-EEG) was recorded from 12 subjects during 5 non-invasive manipulations that affect intracranial hemodynamics by different mechanisms: bilateral jugular vein compression (JVC), head-up tilt (HUT), head-down tilt (HDT), Valsalva maneuver (VM), and Mueller maneuver (MM). DC shifts were compared to changes in cerebral blood volume (CBV) measured by near-infrared spectroscopy (NIRS).

**Results**: DC shifts were observed during all manipulations with highest amplitudes (up to 250 μV) at the midline electrodes, and the most pronounced changes (up to 15 μV/cm) in the DC voltage gradient around vertex. In spite of inter-individual variation in both amplitude and polarity, the DC shifts were consistent and reproducible for each subject and they showed a clear temporal correlation with changes in CBV.

**Conclusions**: Our results indicate that hemodynamic changes in human brain are associated with marked DC shifts that cannot be accounted for by intracortical neuronal or glial currents. Instead, the data are consistent with a non-neuronal generator mechanism that is associated with the blood–brain barrier.

**Significance**: These findings have direct implications for mechanistic interpretation of slow EEG responses in various experimental paradigms.



*Keywords:* DC-EEG, DC shift; Slow potential; Cerebral blood flow; Blood–brain barrier; Near-infrared spectroscopy

## 1. Introduction

Conventional EEG techniques record events with frequencies of 0.5 Hz and higher. Detection of slower potential changes requires a direct current EEG (DC-EEG) technique (Speckmann and Elger, 1999). DC potential changes (or DC shifts) refer to slow EEG responses measured by a DC-EEG amplifier with a bandwidth starting from 0 Hz (Caspers et al., 1987; Speckmann and Elger, 1999). Pronounced DC shifts are observed in humans under many conditions, for example during epileptic seizures (Chatrian et al., 1968; O'Leary and Goldring, 1964; Caspers et al., 1987; Vanhatalo et al., 2003a), during changes in vigilance states (Wurtz, 1967; Wurtz and O'Flaherty, 1967; Marshall et al., 1998), during changes in brain $CO_2$ levels (Caspers et al., 1987; Lehmenkuhler et al., 1999; Voipio et al., 2003), and spontaneously in premature brain (Vanhatalo et al., 2002). Slow EEG responses are well documented also during cognitive or motor tasks (contingent negative variation and Bereitschaftpotential, respectively, Birbaumer et al., 1990).

According to the currently prevailing view (Caspers et al., 1987; Birbaumer et al., 1990; Speckmann and Elger, 1999), DC shifts are mainly attributable to electrical responses generated by cortical neurons and glial cells. However, several lines of evidence suggest an essential role for an intracranial, non-neuronal generator. For example, voluntary hyperventilation in humans provokes millivolt-scale DC shifts (Voipio et al., 2003), which are far too large to be accounted for by a purely neuronal generator. Invasive recordings in experimental animals (Wurtz, 1967; Wurtz

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and O'Flaherty, 1967; Caspers et al., 1987; Amzica et al., 2002) show that slow DC shifts are often not associated with intracortical current loops that are responsible for EEG signals at higher frequencies. Instead, slow voltage shifts recorded in the brain correlate strikingly well with changes in cerebral blood flow (CBF) (Besson et al., 1970; Woody et al., 1970; Cowen, 1974; see also Voipio et al., 2003). There is also solid evidence for a large pH-sensitive transendothelial potential gradient between the cerebrospinal fluid (CSF) and blood both in humans and in many animal species (Loeschcke, 1971; Tschirgi and Taylor, 1958; Held et al., 1964; Hornbein and Sorensen, 1972; Sorensen et al., 1978; Revest et al., 1993). A recently proposed volume-conduction model accounts for the generation of significant DC potential gradients on scalp by the blood–brain barrier (BBB; Voipio et al., 2003), thus providing a novel mechanistic basis for the interpretation of DC shifts.

In the present study, we examined the possibility that acute manipulations of intracranial hemodynamics would produce DC shifts that could be recorded on the human scalp. We measured DC-EEG during various non-invasive manipulations, which elicit changes in pressure gradients between different intracranial compartments. All these manipulations are in routine clinical use: Bilateral jugular vein compression (JVC), head-up tilt (HUT), and head-down tilt (HDT), Valsalva (VM) and Mueller maneuvers (MM). JVC, VM, and MM exert their intracranial effects mainly via the vascular route, while HUT and HDT act mainly by a hydrostatic pressure mechanism. We also studied the dependence of the DC shifts on the changes in cerebral blood volume (CBV) and/or CBF (CBV/F) detected by near-infrared spectroscopy (NIRS), in order to find evidence for a possible causal relationship between DC shifts and intracranial hemodynamics.

## 2. Subjects and methods

### 2.1. Subjects and overview of experiments

Twelve healthy subjects (8 males; age 25–43 years) were recruited for the study. The first ($n = 6$) part of the study consisted of JVC, HUT, HDT, VM, and MM with DC-EEG recordings only, and the second part ($n = 8$) of CBV/F measurement by NIRS simultaneously with DC-EEG recording. All measurements were done in supine position, and all maneuvers were performed 3–7 times, each followed by a recovery of at least 60 s (except in the experiment shown in Fig. 2D). This study was approved by the Ethical Committees of both the University Hospital of Helsinki, as well as the Harborview Medical Center, University of Washington. All subjects gave informed consent under a protocol approved by the University Hospital of Helsinki and by the University of Washington Human Subjects Committee.

### 2.2. Recording techniques

#### 2.2.1. DC-EEG recording

Six-channel recordings (Fz, Cz, Oz, T3, T4, and the right mastoid) were performed using a custom-designed DC-EEG amplifier (long-term stability better than 1 μV/h, bandwidth DC—160 Hz, high input impedance differential preamplifiers equipped with circuits for automatic electrode offset voltage compensation and testing of electrode–skin contact impedance) and sintered Ag/AgCl electrodes with 12 $mm^2$ of active area (type E220N-LP; In Vivo Metric, Ukiah, CA, USA). A separate electrode holder lifted the Ag/AgCl electrode 6 mm above the skin, forming a closed space that was filled with electrode gel (Berner Ltd, Helsinki, Finland). The large volume of the electrode gel in the electrode cup and holder, and the airtight contact of the holder with the skin beneath, prevented electrode gel from drying to avoid drifts generated by changes in electrode potentials (Geddes and Baker, 1968). Amplitudes of the DC shifts were quantified with reference in mastoid, while off-line re-referencing was employed to verify the intracranial topography of the DC potentials (Section 2.3.4). Signals were acquired at 500 Hz by a 12 bit data acquisition card and computer (amplitude resolution 2.4 μV). The software for data recording and analysis was programmed under Labview (National Instruments, Austin, TX, USA). Respiration pattern was monitored with a capnograph (Capnomac, Datex, Helsinki, Finland) in those trials where DC-EEG responses to apnea were studied.

#### 2.2.2. Near-infrared spectroscopy

Measurement of relative changes in CBV/F was determined with NIRS, which essentially measures intracranial absorbance of near-infrared light (wavelengths 780 and 840 nm) by deoxy-hemoglogin (deoxy-Hb) and oxyhemoglobin (oxy-Hb) (Obrig and Villringer, 1997; Villringer et al., 1997). The sum of these two parameters, total Hb (tHb), gives a fairly good estimate of total CBV. It is notable, however, that NIRS measures blood volume in both arterial and venous vascular beds (Watzman et al., 2000), and the signals may be altered independently by both CBV and CBF (Hoshi et al., 2001). A close correlation between changes in actual flow of cerebral blood and the volume of cerebral blood (tHb signal) has been shown in numerous other situations (Toronov et al., 2001; Villringer et al., 1997; Hoshi et al., 2001; Smielewski et al., 1997; Al Rawi et al., 2001). The design of the head cap used in the present study (i.e. distance between the emitters and detectors; see Ichikawa et al., 1999) does minimize, if not exclude, the possible signal from scalp vasculature. We measured the tHb signal with a sampling rate of 2 Hz using a 24 channel NIRS device (ETG-100, Hitachi Medical Corporation, Tokai, Japan; Ichikawa et al., 1999). Channels were placed symmetrically over the frontal–parietal regions. For analysis, we chose one representative channel to compare tHb changes with the simultaneous DC-EEG recordings.

The overall waveform of the tHb response was similar in the majority (usually >20 out of 24 channels) of the channels, reflecting a near global change in tHb signal during these maneuvers.

### 2.3. Experiments

We chose experimental manipulations, which act in the cranium mainly through an intravascular (JVC, VM, and MM) or an extravascular (HDT and HUT) route. Mechanical obstruction of venous outflow by JVC results in intracranial venous congestion with little effect on the arterial side (Iwabuchi et al., 1983; Grady et al., 1986; Buchvald et al., 1999), while changes in the intrathoracic, and hence in the central venous pressure during expiratory (VM) or inspiratory (MM) strain result in abrupt hypertension (VM) (Hamilton et al., 1944; Williams, 1981; Glaister and Jobsis-VanderVliet, 1988; Tiecks et al., 1995) or hypotension (MM) (Morgan et al., 1993; Virolainen et al., 1995; Reinhard et al., 2000) within both intracerebral arteries and veins. Tilt tests (HDT and HUT), in turn, mediate their effects primarily via extravascular changes in CSF hydrostratic pressure within the craniospinal cavity (Magnaes, 1976; Chapman et al., 1990; Caprihan et al., 1999; Shakhnovich et al., 1999).

#### 2.3.1. Compression of the jugular vein

JVC was performed by the subject him/herself lying in supine position with the neck slightly extended in order to facilitate bilateral occlusion (Buchvald et al., 1999). The occlusion was performed by gentle compression 2–3 cm beneath the angle of the lower jaw with the middle and index fingers. After a few trials the subjects learned to compress their jugular veins strongly enough to cause a clear change in CBV/F (as seen in the tHb signal) without causing movement artefacts in the DC-EEG. Compression lasted for 20 s, and trials were accepted only if they produced a clear change in the tHb NIRS signal.

#### 2.3.2. Head-down and head-up tilts

Tilt-table tests ($n = 6$) began with a baseline measurement in supine position for at least 5 min. Subsequently, the table was tilted either 30 ° head down or 20 ° head up for 20 s. Recordings from 4 subjects were analyzed due to motion artefacts with the other two subjects. Simultaneous recording with DC-EEG and NIRS was performed on 3 subjects.

#### 2.3.3. Valsalva and Mueller maneuvers

The subjects ($n = 6$) performed VM by expiring through a closed mouthpiece attached to a barometer they could read (Virolainen et al., 1995; Pott et al., 2000). They were requested to generate and hold a predetermined (20, 40, or 60 mmHg) positive pressure for 15–20 s. The MM consisted of inspiring at functional residual capacity through a mouthpiece attached to the barometer and holding a predetermined negative pressure (−20, −40, or −60 mmHg) for 15–20 s. During MM there was a minute air leak in the mouthpiece to prevent closure of the glottis (Reinhard et al., 2000), hence ensuring transmission of the negative mouth pressure into the thorax. Subjects often reported increased dizziness towards the end of the stronger strains (−40 and −60 mmHg), providing a subjective indicator of transiently compromised cerebral circulation. In the experiments with simultaneous DC-EEG and NIRS measurements strain pressure was not measured, but subjects were required to generate a pressure that produced a clear change in CBV/F as observed by the tHb signal. Only trials with a clear CBV/F response and without movement artefacts were included.

#### 2.3.4. Controls

All trials with artefacts caused by movements of body or head were excluded from analysis. Skin-borne electrical potentials (Picton and Hillyard, 1972; Wallin, 1981; Grimnes, 1984) were short-circuited by scratching the skin through basal lamina with a tiny needle (Picton and Hillyard, 1972; Cowen, 1974). Artefacts caused by ocular movements during MM and VM were avoided by requesting the subjects to keep their gaze fixed onto the barometer. During HDT and HUT the subjects were instructed to fixate onto a point that moved together with the bed. Possible ocular artefacts were also inspected from the EEG traces during analysis. The possibility that apnea during VM and MM would cause a DC shift by a $CO_2$-dependent mechanism (Voipio et al., 2003) was evaluated by

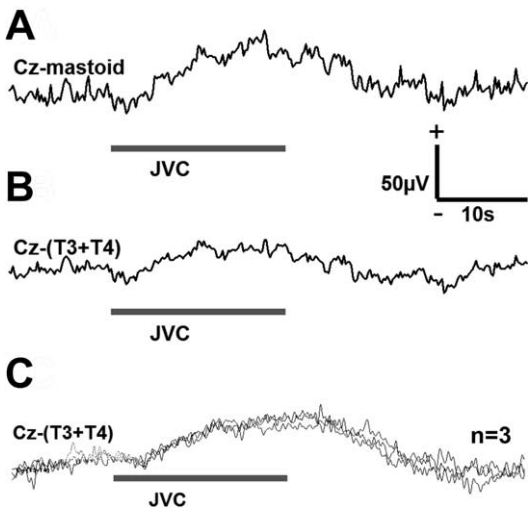


Fig. 1. A single trial of JVC induces a prominent DC shift at Cz. Off-line digital re-referencing of the response at Cz vs. mastoid (A) to linked temporal derivations (B) causes only a small decrease in the amplitude of the DC shift, which suggests an intracranial voltage source. Reproducibility of the response within the same subject is shown in (C). All DC-EEG traces in every figure (except in Figs. 7 and 8A, B) depict single trials. All traces were first low-pass filtered at 4 Hz and then averaged over every 0.5 s in order to facilitate the visual distinction of the slow DC shifts from background EEG activity. Negative is downwards in all figures.

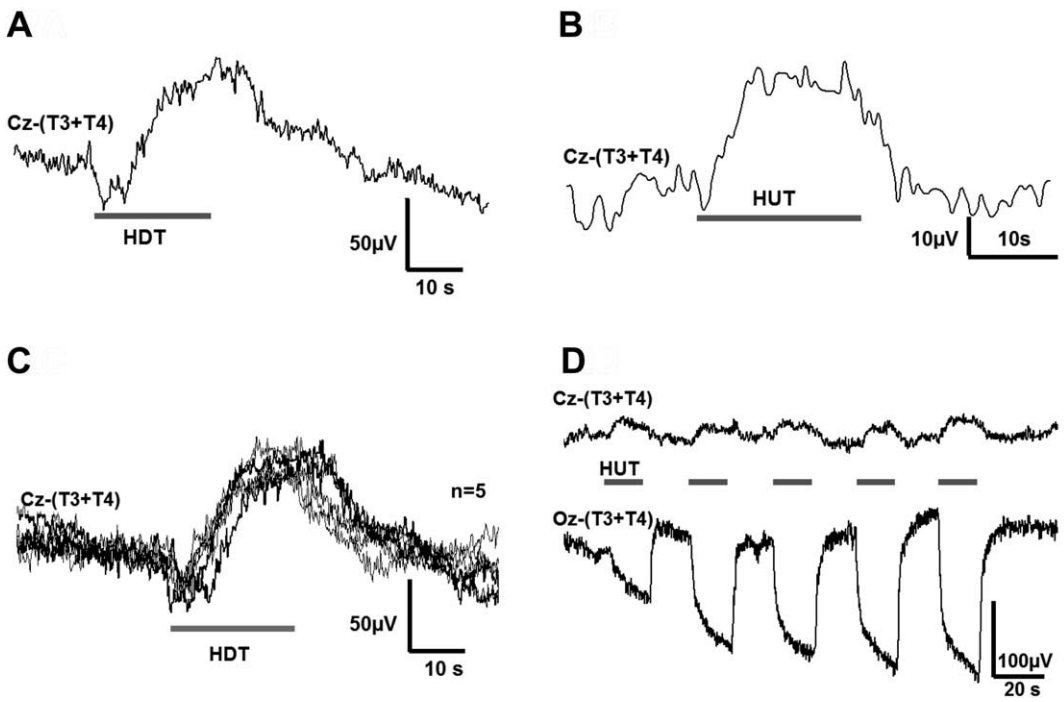


Fig. 2. DC shifts associated with HDT or HUT. Single trials of 30 ° HDT and 20 ° HUT are shown in (A) and (B), respectively. The responses were reproducible within each individual, as illustrated in recordings for HDT in (C). (D) A trial of subsequent HUTs with intervals shorter than the standard >60 s resulted in increasing DC shifts at Oz while the shifts at Cz were still quite reproducible. All traces in (A)–(D) are from the same individual.

performing a 20 s apnea with normal intrathoracic pressure. The possibility of glossokinetic artefacts (Jaffe and Brown, 1983; Vanhatalo et al., 2003b) causing the observed DC shifts was tested by performing voluntary, maximal back-and-forward movement of the tongue. We found that the time course of tongue response was always immediate as opposed to the slow (tens of seconds) recovery observed after our straining maneuvers, and that the amplitudes of tongue-movement artefacts were always smaller than the DC shifts (data not shown). Also, DC deflections caused by tongue movement were markedly reduced or absent in differential signals between midline and temporal electrodes.

## 3. Results

### 3.1. Jugular vein compression

In order to test the hypothesis that changes in CBV/F are associated with DC shifts, we first carried out experiments with a 20 s period of decreased cerebral venous outflow brought about by JVC. Bilateral JVC consistently resulted in a significant DC shift at the midline electrodes (Fig. 1A) that began within seconds after the onset of compression and often reached a stable level before the end of the JVC. Recovery to baseline was similar or slightly faster than the build-up of the shift. Off-line digital re-referencing of the data to a calculated

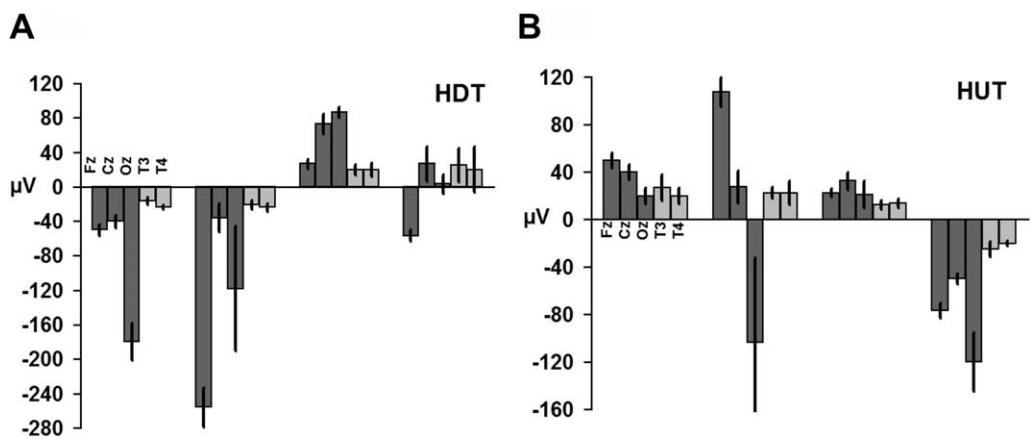


Fig. 3. Topography of DC shifts during HDT (A) and HUT (B) in 4 subjects. Bars represent the mean (± SEM) of peak amplitudes for each electrode derivation from all trials on one subject. Note that the highest amplitudes are seen at the midline electrodes, and the polarity may be reversed between different electrodes.

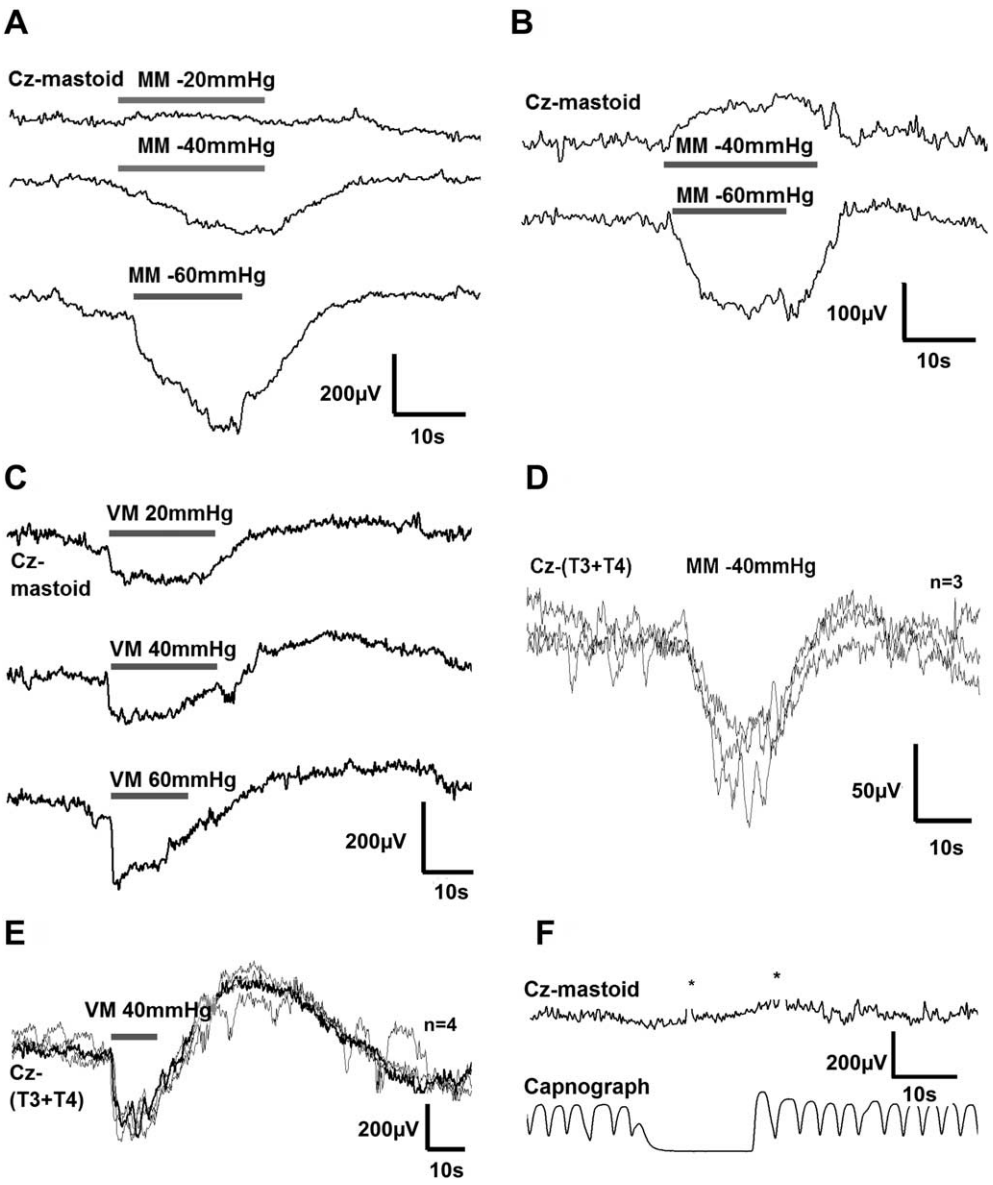


Fig. 4. DC shifts associated with MM and VM. During MM (A and B, data from two different individuals) the DC shift began and recovered gradually, while during VM (C) the DC shifts started with a rapid change from the baseline level and showed a much slower recovery back to baseline (Fig. 5B). Note the clear pressure-dependence of the DC shift (A–C). In some subjects the polarity of response varied between the lower (−20 or −40 mmHg) and higher (−60 mmHg) pressure strain (B). Note the reproducibility in recordings of the MM (D) and VM (E) responses within a single individual. Fig. 4F demonstrates a DC shift caused by voluntary apnea, with the 20 s respiratory pause indicated by the capnograph signal (lower trace). Apnea-related DC shifts developed very slowly, and they did not reach an amplitude that could significantly contaminate the responses upon MM and VM. Eye blink artefacts have been removed and marked with an asterisk.

linked temporal signal (T3 + T4) decreased the DC shift amplitudes at midline derivations but indicated the generation of significant DC gradients (shifts up to 15 μV/cm) on scalp above the temporal level (Fig. 1B). Successive JVCs with 1–2 min intervals showed that the DC shifts were highly reproducible within each of the 6 subjects tested (Fig. 1C). However, a large inter-individual variation was observed with peak amplitudes of the JVC-induced shifts ranging from −60 to +150 μV at Cz against (T3 + T4) (negative in 4 and positive in two subjects; see also Fig. 7 that shows responses from a different series of JVC experiments). The negative shifts were monophasic whereas the positive ones were often biphasic with an initial negative shift followed by a reversal of polarity taking place within a few seconds. It is worth pointing out that this type of a response is not inconsistent with a single generator underlying the observed DC shifts (see also Woody et al., 1970).

### 3.2. Effect of HDTs and HUTs

Next we examined whether DC shifts could also be caused by changes in extravascular pressure via a hydrostatic

mechanism. Both HDT and HUT resulted in slow DC shifts (Fig. 2A, B) in all of the 4 subjects analyzed. The responses varied from rapid shifts that reached their peak in 10 s to shifts that developed at a constant rate throughout the 20 s tilt period. The highest amplitudes were seen at the midline derivations (Fig. 3A, B) indicating again the presence of significant DC gradients on scalp above the temporal level. As with JVC, both the amplitudes and polarities of the DC shifts varied between subjects (Fig. 3A, B), but the responses were quite reproducible within each subject (Fig. 2C). When subsequent HUTs were occasionally carried out with intervals much briefer than the standard $>60$ s, the resulting DC shift was increased at some electrode derivations (Fig. 2D). Again, some of the positive shifts were biphasic with an initial negative deflection lasting up to 10 s (Fig. 2A, C).

### 3.3. Valsalva and Mueller maneuvers

The above results suggest that intervention in brain hemodynamics and/or intracranial pressure (ICP) might cause DC shifts on scalp. Therefore, we next recorded DC-EEG during VM and MM, which are routine manipulations in clinical work. An abrupt increase (VM) or decrease (MM) in thoracic pressure, and thereby in ICP, resulted in a rapid DC shift in each of the 6 subjects (MM Fig. 4A, B and VM Fig. 4C). The responses were reproducible within every subject (Fig. 4D, E) in spite of inter-individual variation in amplitude and polarity. The observed time courses varied from very fast shifts from baseline to peak amplitude (typical to VM), to slowly levelling or linearly increasing responses (typical to MM). Again, some of the initially negative responses were biphasic with partial recovery or reversal of polarity by the end of the maneuver. After MM, the recovery of the DC shift had a time course similar to that of its development, whereas after VM the recovery was often prolonged by a positive overshoot before returning back to baseline (Figs. 4C, E, and 5B).

The amplitude of the DC shift correlated with the pressure, but the dependence was not always monotonic. As shown in Fig. 4A, B, a positive shift that was observed upon MM at low pressure levels could be converted to a negative one during subsequent MM trials at higher straining pressures (Fig. 6C). This behavior was seen in two subjects at midline derivations upon MM (Fig. 6C). With VM, higher straining pressures resulted consistently in higher amplitudes of the DC shift (Figs. 4C and 6D).

The topography of the DC shift was similar in both straining maneuvers: the highest amplitude was observed at the midline derivations (Fig. 6A, B). Off-line digital re-referencing to a calculated linked temporal reference (T3 + T4) highlights that the observed shifts were generated around midline (Fig. 5).

We then tested the possibility that the DC shifts during MM or VM would be caused by the respiratory pause (i.e. apnea) during these maneuvers. As expected (Voipio et al., 2003), voluntary apnea resulted in a positive DC shift, which was highest at the Cz derivation (up to 15–33 μV, referred to mastoid; Fig. 4F). However, the very slow time course and the low amplitude of apnea-related DC shifts indicate that respiratory pause is not responsible for the DC shifts observed during the manipulations described above.

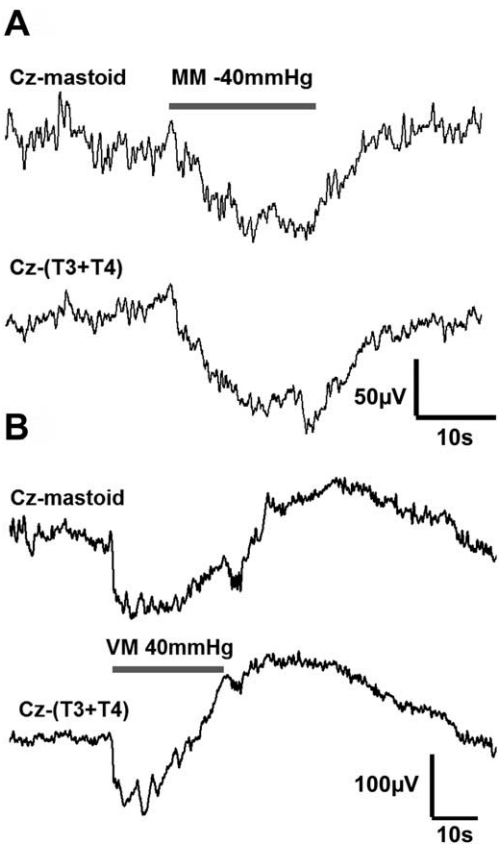


Fig. 5. During MM (A) and VM (B) the differential signal between Cz and T3 + T4 was very similar to the one obtained with a mastoid reference. This supports the idea that DC shifts are not dependent on mastoid electrodes, and hence their voltage source likely resides within the cranium. Note also that after VM (B) there is a very slow recovery and a marked overshoot before returning to baseline.

### 3.4. DC shifts vs. NIRS signal

All the results presented so far are consistent with the idea of a causal link between DC shifts and changes in CBV/F. To characterize this further, we determined the temporal correlation of DC shifts with changes in CBV/F by simultaneous recording of both signals. We started these experiments with JVC, since this manipulation gave the most consistent DC shifts. As shown with the specimen traces in Fig. 7A, JVC gave rise to a prompt positive shift at Cz that was paralleled by a strikingly similar tHb signal. In subjects with negative JVC-induced shifts at Cz, the similarity in the shape of the NIRS and DC-EEG responses was preserved although the tHb shift did not reverse (Fig. 7B). In order to unravel such correlations in each individual from the inter-individual variability of the DC

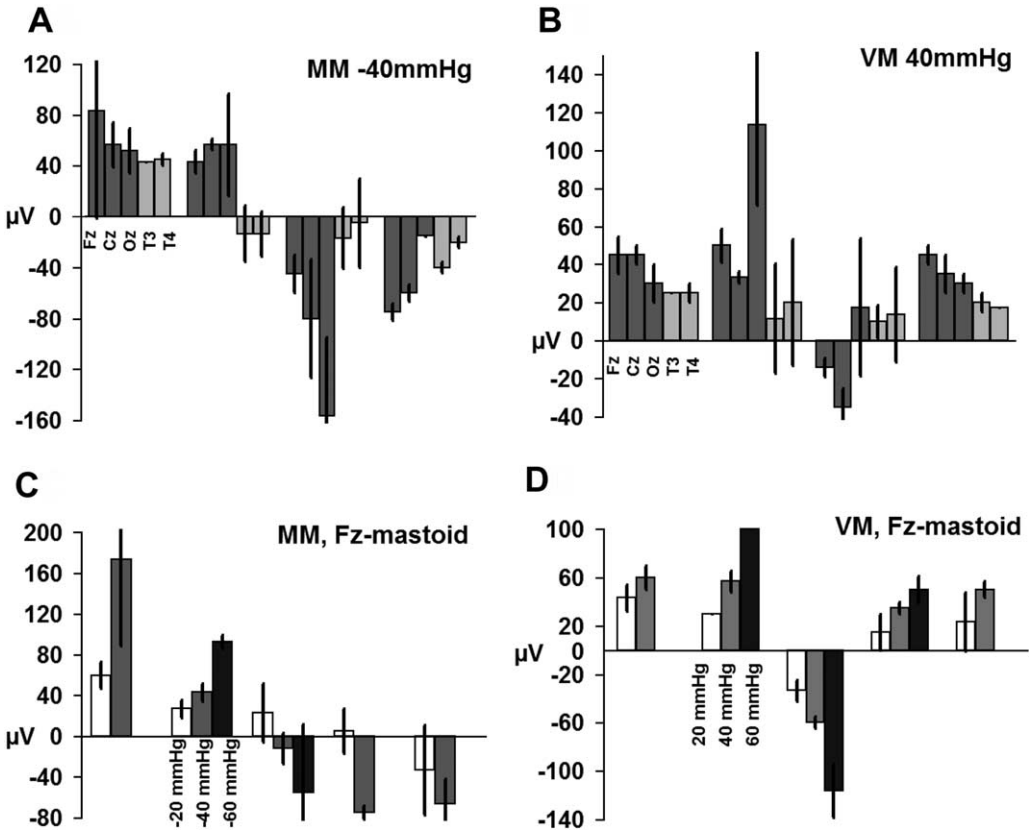


Fig. 6. Topography and pressure dependence of the DC shifts during MM (A,C) and VM (B,D) in 4 subjects. Each bar represents the mean (± SEM) of peak amplitudes from all trials in one derivation. The amplitudes are highest at the midline electrodes (A,B), and they are clearly augmented by increasing the straining pressure (C,D). All amplitude measurements are referred to mastoid.

shifts, we carried out experiments of this type on 6 subjects with 4–6 JVCs in each. Both the tHb signals and the DC shifts at Cz with respect to (T3 + T4) were averaged within each subject, and the gradually changing DC signal during both JVC and the recovery phase has been plotted against the simultaneous tHb signal in Fig. 7C. It is evident that the JVC-induced DC shift and the change in CBV/F are tightly linked in each of the 6 subjects studied.

We extended the results obtained with JVC using the other manipulations on 4–6 subjects. Straining maneuvers caused a consistent increase (VM) or decrease (MM) in CBV/F (tHb signal), which showed a close temporal correlation with DC shifts (Fig. 8A, B). During the tilts (HUT and HDT) the time course of the DC shift and of the change in tHb was essentially the same, although tHb often returned back to baseline somewhat earlier than the DC shift (Fig. 8C, D).

## 4. Discussion

The present study demonstrates marked DC shifts during 5 different, routine physiological maneuvers known to affect intracranial hemodynamics, adding to earlier findings (Besson et al., 1970; Woody et al., 1970; Cowen, 1974) by demonstrating a tight link between DC shifts and changes in CBV/F.

Due to the very small compliance of the cranium, rapid changes in ICP and CBV/F have direct effects on each other (Kety et al., 1948; Greenfield and Tindall, 1965; Czosnyka et al., 1999). All manipulations in this study thus affect both ICP and CBV/F, although by different routes (Section 2.3). Limited spread of intravenous pressure in the vascular bed due to obstruction of bridging veins (Oka et al., 1985) by increased ICP (Numoto and Donaghy, 1970; Nakagawa et al., 1974; Laas and Arnold, 1981) might partly explain the observed topography with highest DC shifts typically over the midline. Such a topography is also consistent with our recently proposed BBB-driven volume conduction model of DC shift generation (Voipio et al., 2003), which predicts largest shifts at areas around vertex for a uniformly distributed signal generated by the BBB. Regional variation of ICP (Bundgaard and Cold, 2000) makes it likely that the changes in ICP elicited by the present maneuvers may not be homogeneously distributed. The observed inter-individual differences in the polarities and the amplitudes of the DC shifts (Woody et al., 1970; Somjen and Tombaugh, 1998) might be related to differences in the time course,

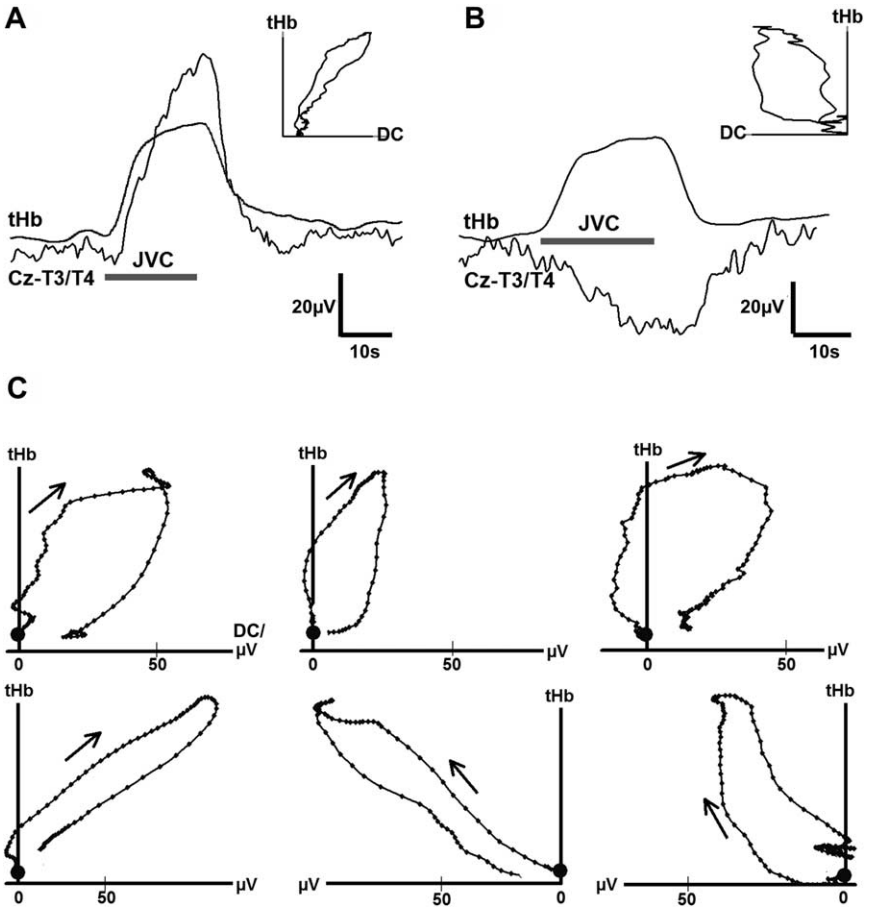


Fig. 7. DC shifts induced by JVC are paralleled by tHb responses. During both positive (A) and negative (B) DC shifts (two different subjects; Cz vs. T3 + T4), NIRS records a monophasic tHb response with a time course similar to that of the DC shift. The traces shown (A–C) are averages of 3–5 subsequent responses and the semiquantitative tHb signal is shown on a relative scale. Plotting the tHb responses against the DC shifts as continuous $x$–$y$ plots starting at the beginning of JVC (insets in A and B) illustrates the subject-specific relationship of the two signals. (C) Plots of tHb against DC shifts (Cz vs. T3 + T4) during JVC and recovery in 6 subjects. The baseline level of the DC-EEG signal at the beginning of JVC is taken as 0 μV (closed circle), and the tHb signal is shown in a normalized scale to aid comparison.

anatomical distribution, and the relative contribution of ICP and CBV/F changes induced by these maneuvers.

It is likely that the DC shifts described in our study are caused by changes in intracranial transepithelial potentials. Several intracranial epithelial or endothelial layers, especially those associated with the BBB, are known to possess relatively large transcellular electric potentials (Tschirgi and Taylor, 1958; Held et al., 1964; Loeschcke, 1971; Hornbein and Sorensen, 1972; Sorensen et al., 1978; Revest et al., 1993). Animal experiments have clearly demonstrated that these DC potentials are readily altered by changes in CBF, pH, and/or by ionic trafficking (Loeschcke, 1971; Hornbein and Sorensen, 1972; Somjen et al., 1991), and the latter is sensitive to changes in transepithelial pressure gradients (Cutler et al., 1968; Lyons and Meyer, 1990; Albeck et al., 1991). DC shifts are also associated with transient changes in the gross permeability properties of the BBB (Somjen et al., 1991; Amzica et al., 2002). A leakage of BBB during a rapid increase in intracarotid pressure (Hardebo and Nilsson, 1981; Ziylan, 1984; Iijima et al., 1994) may thus contribute to the DC shifts observed during VM. In cats and monkeys, $CO_2$-induced brain potential shifts can have a biphasic shape, and their polarity can be reversed by hypoventilation or by manipulation of ICP. Based on simultaneous measurements of CBF, pH, and brain potential, such effects were taken to result from a change in the relative roles of two factors associated with CBF and brain pH with different time courses and opposite effects on the BBB potential (Woody et al., 1970). These earlier observations suggest that all the DC shifts observed in our study (including the variability between, and hysteresis within subjects) can be explained by changes in BBB potentials.

There is increasing evidence pointing to a tight link between neuronal activity and CBF (Rees et al., 2000; Logothetis et al., 2001), which has been utilized in functional imaging techniques, such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI) and NIRS. Our findings (this study and Voipio et al., 2003) raise the intriguing possibility that slow EEG events

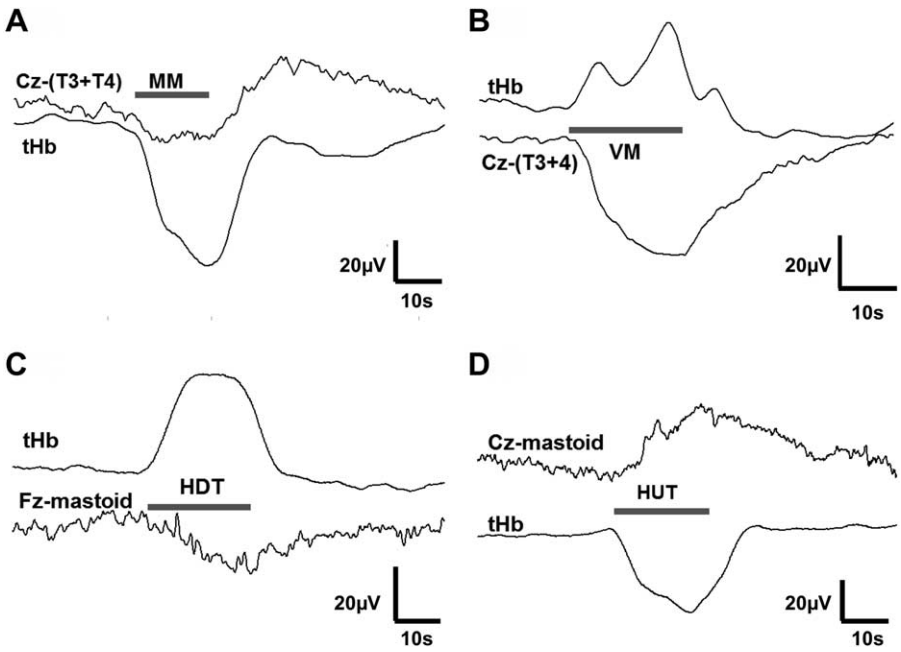


Fig. 8. Simultaneous recording of DC shift and changes in CBV/F during MM (A), VM (B), HDT (C), and HUT (D) maneuvers. Note the strikingly similar time course of the DC shifts and the changes in tHb during all these manipulations. Traces in (A) and (B) are average responses of 2–5 trials, and traces in (C) and (D) demonstrate single trials. Because of its semiquantitative nature, the tHb signal is given on a relative scale.

might reflect activity related changes in CBF (cf. Lang et al., 1988; Uhl et al., 1991; Oishi and Mochizuki, 1998; Lamm et al., 2001; Vanhatalo et al., 2003a).

Finally, it is obvious that even a modest change in respiratory pressure can generate DC shifts comparable to the few microvolt scale changes seen during cognitive paradigms (e.g. contingent negative variation (CNV) or Bereitschaftspotential; Birbaumer et al., 1990; Pihan et al., 2000; Roberts et al., 1989). Thus, studies on DC shifts related to cognitive tasks should include adequate controls or direct monitoring of the subjects respiration patterns.

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