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Infra-slow body-surface potentials show a group-level association with thyroid cancer

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This file contains the supplementary materials cited in the main text, including Materials and methods, Table S1 (analysis conventions and parameters), Table S2 (hardware specifications), Table S3 (quality-control statistics), Table S4 (quality-control sensitivity analysis), and Table S5 (signal-only classification performance).

Materials and methods

Abbreviations used in this supplement: BSP, body-surface potential; DC, direct current; QC, quality control; PSD, power spectral density; SD, standard deviation; IQR, interquartile range; CV, cross-validation; SMOTE, Synthetic Minority Over-sampling Technique; AUC, area under the receiver operating characteristic curve; CI, confidence interval; PHQ-9, Patient Health Questionnaire-9; CMRR, common-mode rejection ratio; RMS, root mean square; ADC, analog-to-digital converter; ML, machine learning.

S1. Analysis conventions and parameters used throughout the study

Table S1 lists the fixed settings used across the manuscript. These values are the single reference for the Methods, Results, and the response letter.

Table S1 Analysis conventions and fixed parameters used

Item	Value/definition
Cohort size (*n*)	*n*=321 recorded; *n*=316 after QC participant exclusion
Groups (thyroid/other)	82/239 recorded; 81/235 after QC exclusion
Depression risk label	PHQ-9 score≥10 (59 positive and 257 negative after QC exclusion)
Protocol structure	3 macro-phases (resting, provocation, recovery); provocation split into three blocks (positive, neutral, negative)
Sampling and filtering	5 Hz sampling; 1.0 Hz analog low-pass; no digital high-pass; no detrending
Band 1	0.025–0.2 Hz
Band 1 energy	Welch PSD integral over Band 1 (Hann, 120 s, 50% overlap)
Tonic baseline	Median DC voltage per block, referenced to resting-block median
QC (segment exclusion)	Clipping (≥3 samples near extremes with <0.01 mV change); step (>5 mV, ±1 sample); motion (10 s window SD>5×session median)
Participant exclusion rule	>40% cumulative segment loss
Primary endpoint	Thyroid group difference in Band 1 energy
Exploratory analysis	Depression-risk classification (BSP-only: AUC≈0.50; null result)
Multiple comparisons	Not used for the primary endpoint; exploratory tests reported with *P*-values
ML evaluation	XGBoost+SMOTE within training folds; repeated outer 5-fold CV (10 repeats; seeds 0–9); fixed model settings
Uncertainty	95% bootstrap CIs (2000 resamples)

S2. Acquisition system hardware specifications

Table S2 summarizes the key parameters of the CTP008 DC-coupled acquisition system.

Table S2 CTP008 acquisition system specifications

Parameter	Value
Input impedance	>100 MΩ
Input voltage range	±20 mV
CMRR	>100 dB
Equivalent input noise	<2.0 μV RMS
Sampling rate (effective)	5 Hz
Analog anti-aliasing filter	Low-pass at 1.0 Hz
Analog-to-digital converter (ADC) resolution	16 bits
Digital high-pass/detrending	None (by design)
Electrode type	Self-adhesive Ag/AgCl pads
Electrode sites	Right middle finger, inner wrist

S3. Signal quality-control pipeline

Prior to automated QC, the clinical team screened recordings for grossly abnormal sessions during visual review. Examples include electrode detachment and overt non-compliance. All 321 patients contributed one usable recording for automated QC. The automated QC pipeline was then applied uniformly to all 321 recordings before feature extraction. Three sequential stages targeted distinct artifact classes:

1. **Clipping / saturation detection.** Segments where the signal remained constant (<0.01 mV change) for ≥3 consecutive samples at the recording extremes (above the 99th or below the 1st percentile of the participant's trace) were flagged, together with a one-sample guard window on each side.
2. **Step-artifact detection.** The absolute sample-to-sample voltage difference was computed. Any point where this difference exceeded a threshold (Default: 5 mV; Strict: 3 mV; Ultra-strict: 2 mV) was flagged as a step-like transient, and a ±1 sample guard window was excluded. These thresholds are physically motivated: typical physiological differences are 0.1–0.2 mV, so a 5 mV jump represents a >25× exceedance of the normal range and is consistent with electrode slippage or abrupt impedance change.
3. **Motion-artifact surrogate.** The local standard deviation was computed in sliding 10-s (50-sample) windows. Windows exceeding a multiple of the session-median standard deviation (Default: 5×; Strict: 3×; Ultra-strict: 2×) were excluded, as sustained high local variability is consistent with movement-related contamination.

After the three stages, any participant with >40% cumulative data loss was excluded from analysis. Table S3 reports the per-stage exclusion statistics across the cohort under the Default threshold set.

Table S3 Per-stage segment-exclusion statistics under Default quality control (QC) (mean±standard deviation (SD) across 321 recordings)

QC stage	Time excluded (%) (mean±SD)	Participants flagged
1. Clipping/saturation	0.3±0.6	154
2. Step artifact (>5 mV)	1.4±7.5	93
3. Motion surrogate (>5×median SD)	1.9±5.4	161
Combined	3.0±8.5	257
Participants removed (>40% loss)		5
Final analytic *N*		316

S4. Sensitivity analysis across QC thresholds

To test whether the reported group effects could be explained by residual artifacts, we repeated the primary analyses under three progressively stricter QC threshold sets (Table S4). If the group-level effects were artifact-driven, stricter artifact removal would attenuate or abolish them. However, we did not observe attenuation. Instead, the thyroid-cancer effect was preserved or slightly strengthened under stricter QC, providing empirical evidence against an artifact-driven interpretation.

Table S4 Sensitivity analysis: thyroid cancer results under three quality-control (QC) stringency levels

Metric	QC-default (step >5 mV, motion >5×)	QC-strict (step >3 mV, motion >3×)	QC-ultra (step >2 mV, motion >2×)
Mean data excluded (%)	3.0%	7.1%	16.2%
n (thyroid/other)	80/234	80/234	80/234
P (Mann–Whitney *U*)	0.0038	0.0031	0.0020
Cohen's *d*	0.318	0.306	0.309

Band 1 energy was recomputed from quality-control (QC)-cleaned raw signals via Welch power spectral density (PSD) integration. Note that the analytic *N* in this table can differ slightly from Table S1 because it is based on raw-file processing and requires valid phase markers and sufficient QC-retained samples for spectral estimation. Here, only participants with valid phase markers are included (*N*=314, thyroid/other=80/234).

S5. Signal-only classification performance

Table S5 Signal-only classification performance in the post-quality-control (QC) cohort (*n*=316)

Task	AUC	Recall	F1
Thyroid vs other (signal-only)	0.508±0.034 (0.442–0.590)	0.230±0.028 (0.081–0.244)	0.242±0.028 (0.102–0.269)
Depression risk (PHQ-9 score≥10; signal-only)	0.507±0.032 (0.427–0.583)	0.169±0.035 (0.063–0.250)	0.179±0.034 (0.082–0.274)

Models used only body-surface-potential (BSP)-derived signal features (no questionnaire-derived inputs). Performance is reported as mean±standard deviation (SD) across 10 repeats of stratified 5-fold cross-validation (CV), with 95% bootstrap confidence intervals (CIs) computed from pooled out-of-fold predictions.