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RESPONSE TO LETTER

Impact of Electroacupuncture on the Expression Profile of the Anterior Cingulate Cortex in a Rat Model of Irritable Bowel Syndrome Based on Transcriptome Sequencing and Bioinformatics Analysis [Response to Letter]

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Dear editor

We sincerely appreciate your meticulous reading and highly constructive comments on our work. The questions you raised from the perspectives of neuroanatomical basis and cellular heterogeneity are both precise and insightful, providing significant inspiration for us to deepen this research. We extend our heartfelt gratitude for your valuable input.

Regarding the first point raised in your letter, the lack of direct experimental evidence for the distinct pathways through which ST25 (Tianshu) and ST36 (Zusanli) exert their effects, we fully understand your concern. The discussion in the original article suggesting that "ST36 acts via the vagal-adrenal axis while ST25 acts via spinal-brainstem ascending projections" was indeed proposed as a hypothesis for discussion, based on existing literature and the differential gene expression profiles observed between the two acupoints, rather than an established conclusion. Your identification of a key break in the chain of argumentation is both accurate and important. Currently, our laboratory fully recognizes this methodological limitation and is actively employing techniques such as viral tracing, activity-dependent labeling, and chemogenetic ablation approaches to directly validate and distinguish the specific ascending anatomical pathways and ACC neuronal subpopulations activated by ST25 and ST36 stimulation. We aim to provide more robust experimental evidence for acupoint specificity at the neural circuit level in future studies.

Regarding the second point, the inability of bulk RNA-seq data to resolve cell-type specificity, we likewise concur with your observation. The pronounced cellular heterogeneity of the ACC region means that averaged transcriptomic signals inevitably obscure the true landscape of responses across distinct cell subpopulations. Your expert analysis of the differential cellular distributions of GRM2, PDK4, and SGK1 highlights precisely the blind spot in our current data interpretation. Inspired by your comments, we will prioritize the use of single-cell RNA sequencing or multiplex in situ hybridization in subsequent experimental designs to re-evaluate electroacupuncture-induced transcriptomic remodeling at single-cell resolution, thereby clarifying the specific cellular vehicles through which these key genes are regulated. Concurrently, we will seek further evidence at the molecular and protein expression levels to investigate the fundamental connections between relevant signaling pathways and the visceral hypersensitivity and anxiety-like behaviors observed in IBS.

In summary, we regard the study as a preliminary transcriptomic atlas for exploring the central mechanisms of electroacupuncture. The two methodological limitations you identified represent the core directions for our future

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research. Your critique does not diminish our enthusiasm; rather, it provides us with a clear roadmap for progressing from correlational description to causal mechanism. If these gaps can be filled by integrating neural circuit tracing, cell-type-specific manipulation, and clinical cohort validation, we believe it will significantly advance acupuncture research from empirical medicine toward precision medicine.

Once again, thank you sincerely for the time and profound insights you have devoted to this work.

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Disclosure

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