

Review of: "From Psychostasis to the Discovery of Cardiac Nerves: The Origins of the Modern Cardiac Neuromodulation Concept"

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Potential competing interests: No potential competing interests to declare.

This interesting article reviews the evolution of social and scientific conceptions of cardiac structure and function through time, starting with discoveries of the ancient Egyptians, moving to medieval conceptions of the heart as the seat of the soul, emotion, intelligence, and as an important religious and spiritual symbol, then highlighting Renaissance anatomical studies that facilitated significant advances in understanding of cardiac structure and pumping function, and ending with modern conceptions of cardiac physiology with a focus on cardiac innervation and neural control of cardiac function.

I have only a few comments, as follows:

1. In the section describing the evolution of understanding of cardiac physiology through history, some segments are quite vague and may benefit from additional references. The revolutionary work and contribution of William Harvey should be specifically cited, e.g., Aird WC. Discovery of the cardiovascular system: from Galen to William Harvey. *J Thromb Haemost.* 2011 Jul;9 Suppl 1:118-29. doi: 10.1111/j.1538-7836.2011.04312.x. PMID: 21781247.

For a detailed historical outline of research on the heart, I would also recommend referring to e.g., Roberts et al., *Across the centuries: Piecing together the anatomy of the heart*, Translational Research in Anatomy, Vol 17, 2019, 100051, ISSN 2214-854X, <https://doi.org/10.1016/j.tria.2019.10005>.

2. The section describing the electrophysiological properties of the SAN and cardiac rhythmicity is very lean, without any references to convey the current understanding of the concept. For example, please refer to the extensive work of Lakatta or DiFrancesco and colleagues and others, e.g.:

Lakatta et al., *Circ Res.* (2010) 106:659–73. 10.1161/CIRCRESAHA.109.206078;

Tsutsui et al., *Sci Signal.* 2018 Jun 12;11(534). doi: 10.1126/scisignal.aap7608. PMID: 29895616; PMCID: PMC6138244

Lakatta & DiFrancesco, *J Mol Cell Cardiol* (2009) 47:157–70. 10.1016/j.yjmcc.2009.03.022

3. The section describing cardiac innervation and neuromodulation is heavily focused only on the research and important contributions of groups associated with the University of Padua. Perhaps a more inclusive attempt should be made to include and recognize the contribution of others, for example, the great work and contribution of Armour and Ardell, specifically their conception of “the little brain on the heart.”

Armour JA. The little brain on the heart. *Cleve Clin J Med*. 2007;74(suppl 1):S48–S51.

Armour J. A. (2008). Potential clinical relevance of the 'little brain' on the mammalian heart. *Exp. Physiol.* 93, 165–176.
10.1113/expphysiol.2007.041178

Ardell JL, Armour JA. Neurocardiology: Structure-Based Function. *Compr Physiol*. 2016 Sep 15;6(4):1635-1653. doi:
10.1002/cphy.c150046. PMID: 27783854

Hanna et al., Innervation and Neuronal Control of the Mammalian Sinoatrial Node a Comprehensive Atlas. *Circ Res*. 2021
Apr 30;128(9):1279-1296. doi:10.1161/CIRCRESAHA.120.318458.

It may also be appropriate to recognize the new concept of the brain-like cytoarchitecture of the SAN: Bychkov et al., The Heart's Pacemaker Mimics Brain Cytoarchitecture and Function: Novel Interstitial Cells Expose Complexity of the SAN. *JACC Clin Electrophysiol*. 2022 Oct;8(10):1191-1215. doi: 10.1016/j.jacep.2022.07.003.