

1. **PUBLISHABLE SUMMARY**

**Dopamine and immunity**

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Despite its elusive nature, the potency of placebo is recognized in modern medicine. Over the past 50 years, clinical trials have routinely included a placebo group to control for non-specific effects such as statistical errors, disease ontology and patient expectations. This expectation of the patient for clinical improvement plays a key role in the placebo effect, but it is not known how it affects recovery. Deciphering the neuronal mechanism underlying such mind-body interactions, harbors the potential to utilize the curative capacity of the brain. We focus on the effects of the brain on the immune system, the body’s central mechanism for protection. Our aim is to understand which neuronal networks in the brain affect immunity, how the signal is transmitted to the immune system, and how the neuronal activity is manifested in the cellular and molecular functions of the immune cells. We focus our research on the dopaminergic reward-regulating system because it has been previously implicated in immune function, and it is considered to play a key role in the placebo effect. To achieve these objectives, we utilize state of the art technologies both in neuroscience and in immunology. We applied pharmacogenetics (DREADDs; Designer Receptors Exclusively Activated by Designer Drugs) to directly manipulate the activity of the reward circuits and to analyze the subsequent effect on the immune response. To analyze the effects on the immune system, we used a novel mass cytometry-based technology (CyTOF), which enables simultaneous analysis of tens of parameters, providing a bird's-eye view of the immune system. The combination of a precise manipulation of the brain with a broad screen to identify effects on the immune system, turned out to be exceptionally effective. We found that activation of the ventral tegmental area (VTA), a key component of the reward system, boosts the anti-bacterial immune response. Activation of the VTA prior to bacterial (*E. coli*) exposure increased the antibacterial activity of monocytes/macrophages manifested by increased phagocytic activity of these cells and increased their ability to kill the bacteria. We also found that VTA activation prior to the initial exposure to the pathogen resulted in increased immunological memory for the pathogen. Thus, re-exposure to the same pathogen, 30 days later resulted in an increased immune response. These findings may be especially relevant for the development of more effective and durable vaccinations. We then used chemical ablations the sympathetic nervous system to partially address the question of which neuronal pathways mediate the effects from the VTA to the immune system. We demonstrate that these effects are mediated, at least in part, via the sympathetic nervous system (SNS). Taken together, these findings are the first to establish a causal relationship between the activity of the VTA and anti-bacterial protective immunity, offering a new mechanistic insight into the association between psychological and physical well-being. The contribution of the potential findings to current research is also manifested in its potential to shift the current perception of the immune system as an autonomous entity. These findings have diverse potential implications on future research directions. Understanding communication mechanisms between the brain and immune system suggest the potential opportunity to harness the body’s endogenous mechanism of protection. Boosting the immune response to pathogens will provide new therapeutic approaches to develop more effective vaccination strategies and fight infection, which can potentially reduce the use of antibiotics.

The study summarizing these results was published in ***Nature Medicine*** ***(Ben Shaanan et al., 2016)***

I have been involved with extensive public outreach programs including public talks for Technion alumni, talks given to senior populations across the country (at least two talks each year), a yearly talk for high school students, and participation in the education program for science teachers at middle schools and high schools. In addition, I participated in the brain awareness week in 2016 at Haifa University, and in 2017 at the Carmiel campus, Israel. Moreover, most of the students in my lab participate in voluntary activities in elementary and high schools through which they expose these students to modern neuroscience.

In another aspect of our outreach activities to bring neuroscience to the public, my group was involved as part of the FENS Kavli network, in the organization of public talks at local pubs during the FENS meeting at Copenhagen in June 2016. Following the success of this activity I plan to participate again in this forum in Berlin in 2018.

Moreover, I was in close contact with the media and our work was reported by the major news outlets across the world including: Wall Street Journal, Scientific American, Yahoo! News, The Straits Times, The Japan Times, Haaretz, voice of Asia, Daily Nation (Kenya), Breitbart News Network, Medindia, MarketWatch, Daily News & Analysis, Health Medicinet, Global Post, Health24, Emirates 24/7, China Post, Science and Life Russia, Nature Asia, The Economic Times and others. Finally, we routinely report our scientific achievements to the global community through my Twitter account and the Technion Facebook and Twitter accounts.

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