To accurately coordinate gastrointestinal (GI) functions more or less independent of the brain, the gut has a nervous system of its own. This so called enteric nervous system (ENS) is embedded in the gut wall and comprises different types of nerve cells which are organized in specialized circuits. Classically, these nerve circuits were considered to be activated in a recurrent fashion by intrinsic sensory neurons that initiate reflex-like activity which underlies the typical GI motor patterns such as peristalsis. Recent evidence however indicates that this circuitry receives alternative sensory input and possesses a high grade of multifunctionality. Its output is largely determined by the integrated activity levels of several cooperative populations of neurons that communicate via many multi-synaptic connections. Therefore, we hypothesized that while previous ENS research was often focused on initiation of motility, modulation of ongoing activity and synaptic communication both by endogenous and exogenous mediators could play a more important role in determining ENS output than generally accepted.

By imaging spontaneous Ca^{2+} spiking and synaptic activity of enteric neurons, we demonstrated that both intrinsic and extrinsic mediators can tilt the activity state of the ENS. Our findings suggest that the bowel is equipped with an intrinsic cannabinoid system that is crucial for processing synaptic communication within enteric nerve circuits. We also found that a member of the neurotrophin family, brain-derived neurotrophic factor, is able to enhance rather than directly activate ENS signaling. This potent modulating role on enteric neuronal activity and synaptic communication is likely to be the reason why GI motility is improved in human subjects treated with neurotrophins. Apart from modulation of ENS function by intrinsic signaling pathways, also herbal compounds can influence ENS signaling, possibly by interacting with members of the TRP family of cation channels. Plant derivatives such as menthol are known to affect GI motility; our data indicate that their action on enteric neurons could be the mechanism behind those changes.

Overall, we conclude that fine-tuning ENS activity by both endogenous and exogenous mediators is critical in determining ENS output. Rigorous future investigations will have to elucidate whether similar modulating mechanisms are present in experimental systems that more closely mimic *in vivo* human GI physiology and whether interfering with these mechanisms may have therapeutic potential for the treatment of GI diseases.