Interoceptive Technologies. New Technological Solutions for Stress Management and Human Neuroenhancement.

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ABSTRACT

Traditionally, neuroscience and psychology have studied the body from the outside, i.e. how the external senses (vision, hearing etc.) affect our behaviour, cognition and health. This approach misses a crucial aspect of the experience, which is 'interoception', defined as the sense of the physiological state of our inner body. The interoceptive system represents a core component and a gateway to our health. Interoceptive inputs underpin unconscious, basic, adaptive responses at the homeostatic, endocrinal and immunological levels. Similarly, dysfunction of the interoceptive system has been identified in conditions ranging from acute and chronic stress; depression; anxiety; post-traumatic stress disorder, to less obviously related difficulties, such as insomnia; chronic pain; and addiction. In this context, the development of a scientifically-grounded technology, capable of accessing and manipulating this system would be a breakthrough, with unprecedented potential to promote human health and wellbeing. However, despite increasing evidence of the fundamental role interoceptive processing plays in every aspect of our life, there have been almost no attempts to develop scientifically-grounded, interoceptive technologies, that can manipulate the interoceptive system and thus enhance human wellbeing. In this contribution, we will first review the most recent technological developments in terms of interoceptive stimulation, ranging from virtual reality to neurostimulation. Then we will introduce technological breakthroughs in terms of interoceptive devices and non-invasive interoceptive neuromodulation, describing the developing of new instruments and preliminary data regarding the effectiveness of these technologies in promoting wellbeing, reducing stress, fatigue, and pain, and enhancing human performances. We expect that this technology will apply to a broad range of different contexts, including clinical and subclinical settings, improving mood regulation, impulse control, enhancing cognitive, autonomic and stress adaptive responses through a non-pharmacological solution that does not require medical regulation nor prescription.

***Keywords**: interoception, interoceptive technologies, stress, neuroenhancement, neuromodulation*

1.0 BACKGROUND

Traditionally, neuroscience and psychology have studied how the external senses, such as vision and hearing, contribute to our mental and physical health. However, this misses perhaps the most crucial aspect of our wellbeing, which is the experience of our body from within – known as **interoception**.

Interoception is defined as "the process by which the nervous system senses, interprets, and integrates signals originating from within the body, providing a moment-by-moment mapping of the body's internal landscape across conscious and unconscious levels" [1]. Interoceptive inputs underpin unconscious, basic, adaptive responses at the homeostatic, endocrinal and immunological levels [2, 3], but research is rapidly uncovering their crucial contribution to: autonomic balance [1]; emotion recognition and regulation [4]; and coping strategies [5]. Moreover, dysfunction of the interoceptive system has been identified in conditions [6] ranging from: acute and chronic stress [7]; depression [8, 9]; anxiety [10, 11]; post-traumatic stress disorder [12]; and obsessive-compulsive disorder [13], to less obviously related difficulties, such as insomnia [14]; chronic pain [15]; eating disorders [16]; and addiction [17].

The interoceptive system represents a core component and a gateway to our health, therefore the development of scientifically-grounded technology, capable of accessing and manipulating this system would be a breakthrough, with unprecedented potential to promote human health and wellbeing. However, despite increasing evidence of the fundamental role interoceptive processing plays in every aspect of our life, this understanding has not been followed by the development of viable interoceptive, technological solutions.

To address this challenge, we developed a first-iteration prototype of a portable (Fig.1) interoceptive stimulator (iStim) [18, 19]. This solution is based upon the concept of **interoceptive neuromodulation**, namely the stimulation of the peripheral interoceptive nervous afferents with a series of non-invasive tactile inputs that are directly processed by the interoceptive cortex, providing a variety of psychobiological effects.

Specifically, the interoceptive system is composed of small unmyelinated polymodal C-fibres that collect sensory, endocrine, immunological and autonomic information from all over the body [20]. C-fibres differentiate in free tactile arborizations on the skin creating a **secondary touch system** that is specifically processed by the interoceptive cortex [21]. Importantly, human and animal models indicate that **interoceptive touch** stimulation **neuromodulates** the brain's cortical activity and can reduce chronic and acute stress, enhancing stress resilience [22]; enhance autonomic response [23]; modulate the endogenous u-opioid and oxytocin systems [24, 25]; reduce anxiety [26]; and pain [27-30]; promote social and emotional bonding [31]; mitigate social exclusion feelings [32]; and reduce arousal (separation anxiety) in infants [33].

The iStim prototype can precisely stimulate the interoceptive tactile system, inducing maximum firing frequency in the peripheral C-Tactile nervous afferents (Fig.2). In the past years, we performed and published several experiments to evaluate the effectiveness of interoceptive tactile stimulation on different dimensions, namely; autonomic stress reduction, chronic pain reduction, and emotion recognition enhancing. Our results demonstrate that interoceptive neuromodulation delivered with iStim can manipulate both low-level responses – enhancing heart rate variability [18] – and reducing chronic pain [34] and higher-level cognitive processes enhancing emotions recognition processing. We also recently won a competitive Novel Technology Grant that will allow us to take this technology to the next level by miniaturizing the iStim technology into a wearable, interoceptive, wrist device that the user can activate to self-administer the interoceptive tactile neuromodulation, providing a personalized stimulation that can enhance wellbeing, reduce stress and pain and enhance both autonomic and cognitive responses throughout the daily life, in real-time.

Figure 1 (left): Interoceptive stimulator. Figure 2 (right): Interoceptive stimulation on a patient (image reproduced from Di Lernia, Lacerenza [35])

1.1 Conceptual Research Approach

How interoception impacts on health and wellbeing is at the centre of the current debate in neuroscience and psychology. A major limitation on research has been the difficulty of developing technologies able to access and modulate the interoceptive system, in order to promote health and enhance wellbeing. Current attempts have either used invasive means such as: direct brain stimulation [36]; transcranial deep magnetic stimulation [37, 38]; and transcranial direct current stimulation [39]; or require complex, fixed lab setups, without ecological applicability [40-43].

To address this challenge, we have been testing the effectiveness of a **non-invasive neuromodulation technique that targets the interoceptive touch afferent system.** Interoceptive touch has a wide range of potential applications and, even though the mechanisms underpinning its effects have not yet been fully elucidated, evidence indicates that they are probably connected to a neuro-modulatory inhibitory effect in the dorsal horn, with concomitant release of TAFA4 protein, that has analgesic and calming effects [29, 30] in synergy with autonomic parasympathetic [23] and endocrine down-regulatory effects [24, 25]. The iStim prototype has successfully demonstrated the effectiveness of interoceptive tactile stimulation in neuromodulating both autonomic parasympathetic activity, enhancing the rMSSD and High-Frequency HRV components in healthy participants [18], and high-order conscious perceptions and processes such as pain perception [34] and emotion recognition processing. We will review these results in the following sections.

2.0 SCIENTIFIC EVIDENCE

In the following section we will present evidence of the effectiveness of our interoceptive technology in:

- Enhancing hearth rate variability promoting wellbeing and reducing stress at the autonomic level, published in Di Lernia, Cipresso [18].
- Reducing chronic pain in chronic pain patients, published in Di Lernia, Lacerenza [35]
- Neuro-enhancing emotion cognitive processing.

2.1 Heart rate variability enhancement

2.1.1 Methods

13 healthy participants were recruited through consecutive sampling [8 females; mean age = 38.09 years, SD = 18.53; BMI mean = 22.57, SD = 1.91]. The study design was a single-blind between-subjects. Participants were randomly assigned to control (SHAM) condition or to experimental (EXP) condition. In EXP condition subjects received interoceptive tactile stimulation through the iStim prototype for approximately 11 minutes. Conversely, in SHAM condition subjects received proprioceptive static pressure tactile stimulation for the same length of time. Participants were connected to a BioSignalPlux Bluetooth ECG device with Ag/AgCl electrodes sampling at 1000Hz to collect heart-rate variability measures. A 5 minutes resting baseline was recorded before the experimental procedure.

2.1.2 Results

Participants who received interoceptive tactile stimulation delivered with the iStim prototype showed an enhancement of the parasympathetic heart rate variability component. Specifically, they had higher RMSSD (a vagally mediated index) and enhanced power in the High-Frequency band (a specific parasympathetic index) (Fig. 3 and 4).

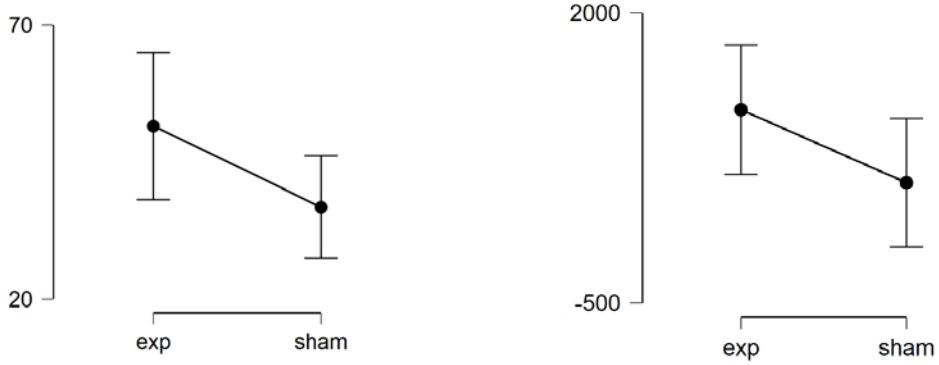


Figure 3 (left): Interoceptive touch enhanced the RMSSD component (ms).

Results indicated a significant effect of Group on rMSSD after controlling for rMSSD at baseline [$F(2, 10) = 7.024$, $p = .024$, $\eta^2 = .413$]. Post-hoc test using Bonferroni indicated that Interoceptive touch in the experimental group [mean = 51.57; SD = 14.44] enhanced the rMSSD vagally mediated component, compared to the control group [mean = 36.83; SD = 8.88].

Figure 4 (right): Interoceptive touch enhanced the HF component (mV).

Results indicated a significant effect of Group on HF power after controlling for HF power at baseline [$F(2, 10) = 5.919$, $p = .035$, $\eta^2 = .372$]. Post hoc test using Bonferroni indicated that Interoceptive touch in the experimental condition (exp) significantly enhanced the power of the High Frequency parasympathetic band [mean = 1164.86; SD = 602.69] compared to the control group [mean = 536.17; SD = 527.43]. Images reproduced from Di Lernia, Cipresso [18]

2.1.3 Significance

Overall, this study confirms the possibility of artificially enhancing the parasympathetic heart rate variability component, utilizing the stimulation of interoceptive tactile peripherical afferents. According to the

literature, activation of the peripheral interoceptive afferents is directly connected to the left insula and through this to the descending parasympathetic system. These results confirm the possibility of using this method and the potential of the prototype (iStim) as a non-invasive neuromodulation device able to produce alteration at the autonomic level.

2.2 Analgesia induced in chronic pain patients, across different kind of pathologies

2.2.1 Methods

Chronic pain is a complex pathological condition that responds poorly to pain management treatments and therapies. It is often untreatable and deeply compromises the quality of life of over 500 million people around the world. Here we present data from a novel potential interoceptive treatment using a non-invasive method to induce analgesia through interoceptive stimulation of the C-Tactile afferents in the skin with the iStim prototype. This study employed a single-blind, between-subject design, in primary (PP), secondary musculoskeletal (SMP), and neuropathic (NP) chronic pain, to test the ability of specific CT interoceptive stimulation to reduce pain perception. Forty-nine chronic pain participants were recruited [39 women; Age M = 57.92, SD = 14.48; BMI M = 23.90, SD = 4.33; Pain at baseline_NRS M = 4.89, SD = 2.24; BDI_depression M = 18.06, SD = 11.05; STAI_State M = 42.17, SD = 13.23]. There were 19 PP participants, 13 SMN and 17 NP participants. The experiment followed a single-blind, between-subjects design. CP participants were randomly assigned to the experimental condition [N = 24] in which they received interoceptive CT stimulation, or to the control condition [N = 25] where they received control stimulation with non-interoceptive tactile pressure, both conditions lasted approximately 11 minutes.

2.2.2 Results

Results indicated that there was a significant reduction in perceived pain following the interoceptive stimulation (Fig. 5). In summary, results indicate that CP subjects who received interoceptive C-Tactile interoceptive stimulation reported a pain reduction of 22.58% in average, compared to baseline values [Pain at baseline NRS, M = 4.25, SD = 2.13; Pain Post stimulation_NRS, M = 3.29, SD = 2.27; ΔPain , M = -0.958, SD = 1.268] after approximately 11 minutes of stimulation. Conversely, CP subjects who received control stimulation did not exhibit any pain reduction compared to baseline values [Pain at baseline_NRS, M = 5.52, SD = 2.22; Pain Post stimulation, M = 5.56, SD = 2.32; ΔPain, M = 0.040, SD = 0.889].

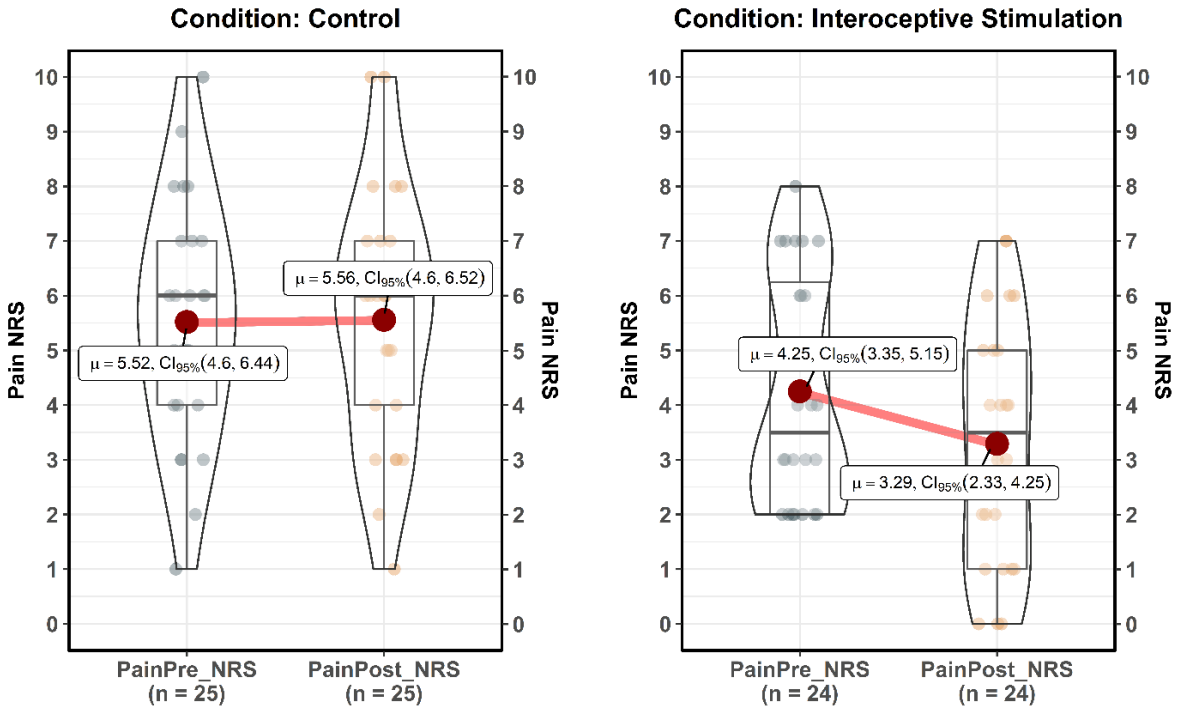


Figure 5: Interoceptive touch reduces Chronic pain.

Linear mixed models parameters indicated a significant main effect of Time [F (1, 47) = 8.6796, p = 0.005, η_p^2 = 0.148, Cohen's f = 0.417] and a significant main effect of Condition [F (1, 47) = 8.1159, p = 0.006, η_p^2 = 0.140, Cohen's f = 0.403]. More importantly, the interaction effect of Time x Condition was significant [F(1,47) = 10.2577, p = 0.002, η_p^2 = 0.170, Cohen's f = 0.453]. Post hoc analyses indicated that the Experimental group that received the interoceptive stimulation reported a significant reduction of pain [EMM estimate = -0.958, SE 0.223, p_b < .001] between pain before the stimulation [PainPre_NRS EMM = 4.25, SE = 0.457] and pain after the stimulation [PainPost_NRS EMM = 3.29, SE = 0.457]. No significative differences in perceived pain were found in the Control group following the stimulation [EMM estimate = 0.040, SE = 0.218, p_b > .05]. No significative differences were found on pain at baseline between Control and Experimental group [EMM estimate = 1.270, SE = 0.640, p_b = .315] as well. Image reproduced from Di Lernia, Lacerenza [35]

2.2.3 Significance

Chronic pain is a complex pathology that is extremely difficult to treat, and it is usually resistant to medications. Interoceptive tactile stimulation delivered with the iStim prototype was able to reduce pain severity in terms of statistical and clinical relevance, after only 11 minutes of stimulation. The interoceptive stimulation was effective independently from the physical conditions (neuropathic pain, musculoskeletal pain, fibromyalgia, mixed pain, etc) suggesting trans-diagnostic effectiveness due to cortical, autonomic, and endocrine analgesic effect. To the best of our knowledge, this is the first evidence that interoceptive tactile neuromodulation can be used as an effective treatment for complex, medication-resistant conditions.

2.3 Emotion recognition augmentation

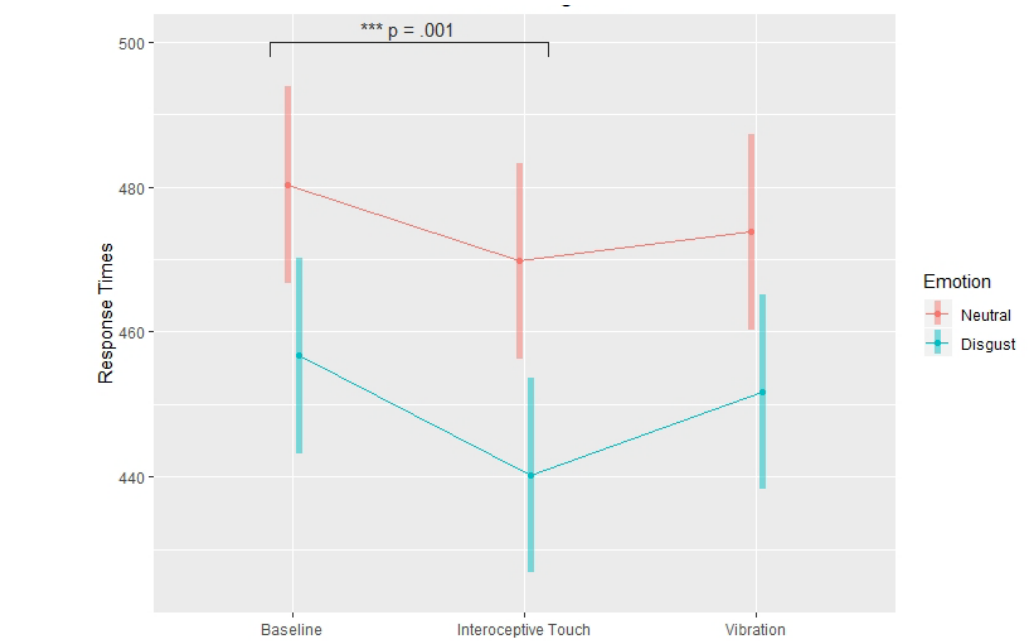
2.3.1 Methods

Interoceptive touch is primarily processed by the left insula [21]. In this study, we tested the effect of

interoceptive touch on motor response inhibition in an emotional go/no-go task (GNG). Considering a previous finding that GNG performance is linked to activity in the left brain hemisphere [44] we expected that interoceptive touch would improve the performance on a GNG task; facilitate the recognition of the emotions presented (lower response times); and reduce misses and false alarms. 45 participants (Mean Age 23.64, SD 2.32, 34 females) performed an emotional GNG task [45]. The task assesses participants' ability to withhold prepotent behavioural responses (requiring cognitive control) when faced with potentially interfering emotional information (requiring emotion regulation). Importantly, the task measures the ability to correctly and rapidly discriminate the emotionally relevant stimuli (requiring emotion recognition), which serves both the cognitive control and the emotion regulation processes. 120 images of neutral and disgusted facial expressions from the FACES database (half males, half neutral) (Ebner et al. 2010) were used in the task. The task consisted of two emotional conditions (neutral/disgust): in one, participants were instructed to respond as quickly as possible with a keypress only to neutral faces (GO stimuli) and to ignore disgust faces (NoGO stimuli). In the other emotional condition, participants had to respond to disgust faces (GO stimuli) and ignore the neutral faces (NoGO stimuli). Each condition consisted of 40 trials (70% Go trials). Each participant completed three runs of the task. The study always began with the baseline run in both emotional conditions. Next, participants underwent 2 tactile stimulation conditions (iStim/Vibration) either with interoceptive touch (iStim) or with vibrational stimulation as a control condition, following Triscoli, Croy [23]. The order of the task conditions (Go neutral and Go disgust) was counterbalanced between runs and individuals. The order of the stimulation (interoceptive touch or vibration) was also counterbalanced. In both conditions, participants received the stimulation for approximately 6 minutes.

2.3.2 Results

Interoceptive touch reduced response times [RTs Mean 454.96, SD 48.38] in discriminating both the emotions (neutral and disgust) compared to the baseline [RTs Mean 467.22, SD 41.99]. Following the interoceptive stimulation delivered with iStim, participants were faster in recognizing the facial emotion displayed during the task, independently of which emotion was the target (neutral/disgust). This result suggests a neurocognitive effect of the interoceptive stimulation which resulted in improvement of the emotion recognition processing. Moreover, both types of bodily stimulation (interoceptive touch and vibration) reduced the percentage of missing (i.e., failures to respond to the Go stimulus), indicating enhanced attention following either type of physical stimulation. However, vibrational stimulation had no significative effect on response times [RTs Mean 462.70, SD 49.14] suggesting no neurocognitive effect for the control condition. Results in Fig. 6.



(a)

(b)

Figure 6: Neuroenhancement emotion recognition

(a). Linear mixed model's total explanatory power was substantial (conditional R2 = 0.90). Analysis of variance (ANOVA) on linear mixed model parameters indicated a significant main effect of the Stimulation [F (1, 44) = 6.5662, p = 0.001]. Post hoc analyses indicated that interoceptive tactile stimulation [RTs after interoceptive touch EMM = 455 SE = 6.22] was able to augment emotion recognition processing reducing response times (RTs) [EMM estimate = -13.51, SE 3.75, $p_b < .001$] independently from the displayed emotion (neutral or disgust) compared to baseline [RTs at baseline EMM = 468 SE = 6.24]. There were no significative differences between the control (vibration) condition and other conditions [RTs after vibration EMM = 463 SE = 6.22]. (b). Raw data plots divided by emotion.

2.3.3 Significance

Emotion recognition is a fundamental cognitive process connected to several aspects of our daily life, including empathy, prosocial behaviour, emotion regulation and mood dysregulation. It is also relevant in clinical conditions, such as alexithymia which is a trans-diagnostic component of various pathologies (e.g., depression, autism etc.). In this study, interoceptive touch was able to artificially augment emotion recognition processing, facilitating the participants' ability to perceive and discriminating emotions in others. To the best of our knowledge, this is the first evidence that interoceptive tactile neuromodulation can augment cognitive processes. This suggests a potential use in improving mood regulation and as a non-invasive treatment in conditions characterized by impaired emotional processing.

3.0 CONCLUSION AND FUTURE WORK

Mechanisms of interoceptive stimulation are still to be understood, nevertheless, several hypotheses can be formulated. Recent evidence from animal models indicated that C-Tactile stimulation can suppress pain through a modulatory inhibitory effect in the dorsal horn with a concomitant release of protein TAFA4 that has analgesic and anti-stress effects [29, 30]. Similar results have been found for acute thermal pain in humans, where C-Touch was able to modulate thermal pain intensity in healthy subjects [27, 28]. Moreover, as demonstrated in a previous study [18], interoceptive tactile stimulation can enhance HRV and specifically the HF band, suggesting a direct effect upon the parasympathetic system with a possible concomitant reduction of the sympathetic stress-related activation. Likewise, evidence from literature suggested that interoceptive touch may mediate oxytocin release [25], and several studies demonstrated that oxytocin has a direct effect upon several domains modulating pain intensity, anxiety, and depressive symptoms, thus expressing a defined analgesic effect [46, 47]. Lastly, interoceptive tactile stimuli are primarily processed by the left insula [21] and, according to Craig's emotional asymmetry proposal [48], a left insula activation could have reduced the contralateral co-activation of the right insula, which is primarily involved in sympathetic (e.g., stress) processing. Notwithstanding, it is probable that effect of interoceptive stimulation cannot be ascribed to a single mechanism, but it is likely to be fostered by a synergy of different processes at autonomic, endocrine, and cortical level.

Interoceptive stimulation may also show direct applications to addiction and drug abuse. In a wider perspective, the interoceptive network is a central hub implicated in the craving sensations [49] behind addictive behaviours and addictions [50]. Moreover, recent evidence pinpointed the insular cortex as a promising target for the treatment of addictions [51]. Behavioural studies identified a deep relationship between interoception and addiction, suggesting that impaired interoception may actually contribute to drug abuse [17]. Previous studies reported how social (interoceptive) touch was able to modulate the opioid system [24]. Likewise, C-Tactile stimulation may mediate oxytocin release [25] and oxytocin has emerged as a promising candidate in the modulation of addictive behaviours, due to its ability to interfere with the neural substrates of addiction, providing treatment targets for substance-use disorders [52]. All this considered, interoceptive treatments based upon C-Tactile stimulation, may also provide a viable answer to address addictions and the current opioid crisis. Future steps include assessing the long-term effects of the tactile interoceptive stimulation, and clarifying possible mechanisms mediated by the interoceptive system (blood biomarkers, cortical activity, autonomic activity). The presented studies provided valuable outcomes suggesting new perspectives, notwithstanding, more research is needed to better comprehend the mechanisms behind these processes.

3.1 Expected Impact and Applicative Potential (even if in the far future)

We are currently developing a **wearable interoceptive device** that will integrate, miniaturize and further develop the iStim technology. The wearable device will utilize a non-invasive tactile probe controlled by a microcircuit. The probe will employ an array of sensors to fine-tuning and optimising the neuromodulation. The wearable device will thus be able to stimulate the interoceptive C-Tactile afferent system with very high

precision, by constantly adapting the stimulation, while also measuring the user's physiological responses (HRV) in real-time thus providing personalized neuromodulation, according to the user's needs.

Despite its clear potential, interoceptive neuromodulation and interoceptive technologies have not yet been clearly developed within the current scientific literature, except for our (iStim) prototype. No wearable interoceptive technologies currently exist that can neuromodulate the cognitive, autonomic, and endocrine systems. Moreover, to the best of our knowledge, non-invasive interoceptive neuromodulation has never previously been applied to enhance wellbeing in ecological contexts, nor have the biomarkers of its effectiveness been explored. Our proposed device is, therefore, an unprecedented innovation, with the potential to provide a scientific advance in the general wellbeing of the population at large, as well as having application in clinical and subclinical settings.

Importantly in this context, given the non-invasive nature of the neurostimulation, the device will not require medical supervision or prescription. The users can thus operate the device themselves to optimise the stimulation and maximally enhance their interoceptive response, in ecological contexts, to promote their wellbeing at cognitive, autonomic and endocrine levels in daily life. Furthermore, there is potential for future sub-clinical and clinical use, where we envision personalized self-administered treatments based on the specific user's needs and condition. Interoceptive dysfunctions have been found in a broad range of conditions (as diverse as PTSD, insomnia, addiction, pain acute and chronic, etc.). Thus, we highlight the potential of our wearable device to prove its high-gain, in both clinical and subclinical settings, providing a non-pharmacological non-invasive treatment.

REFERENCES

[1] Owens, A.P., et al., Investigating the relationship between cardiac interoception and autonomic cardiac control using a predictive coding framework. Auton Neurosci, 2018. **210**: p. 65-71.

[2] Craig, A.D., Interoception: the sense of the physiological condition of the body. Current Opinion in Neurobiology, 2003. **13**(4): p. 500-505.

[3] Craig, A.D., Significance of the insula for the evolution of human awareness of feelings from the body. Annals of the New York Academy of Sciences, 2011. **1225**(1): p. 72-82.

[4] Zamariola, G., et al., Relationship between interoception and emotion regulation: New evidence from mixed methods. J Affect Disord, 2019. **246**: p. 480-485.

[5] Pollatos, O., E. Matthias, and J. Keller, When interoception helps to overcome negative feelings caused by social exclusion. Front Psychol, 2015. **6**: p. 786.

[6] Quadt, L., H.D. Critchley, and S.N. Garfinkel, The neurobiology of interoception in health and disease. Ann N Y Acad Sci, 2018. **1428**(1): p. 112-128.

[7] Schulz, A. and C. Vögele, Interoception and stress. Frontiers in psychology, 2015. **6**: p. 993-993.

[8] Dunn, B.D., et al., Heartbeat perception in depression. Behav Res Ther, 2007. **45**(8): p. 1921-30.

[9] Sprengelmeyer, R., et al., The insular cortex and the neuroanatomy of major depression. J Affect Disord, 2011. **133**(1-2): p. 120-7.

[10] Pollatos, O., et al., Interoceptive awareness mediates the relationship between anxiety and the intensity of unpleasant feelings. Journal of anxiety disorders, 2007. **21**(7): p. 931-943.

[11] Rosso, I.M., et al., Anxiety sensitivity correlates with two indices of right anterior insula structure in specific animal phobia. Depress Anxiety, 2010. **27**(12): p. 1104-10.

[12] Rosso, I.M., et al., Insula and anterior cingulate GABA levels in posttraumatic stress disorder: preliminary findings using magnetic resonance spectroscopy. Depress Anxiety, 2014. **31**(2): p. 115-23.

[13] Schultchen, D., et al., Interoceptive deficits in patients with obsessive-compulsive disorder in the time course of cognitive-behavioral therapy. PLoS One, 2019. **14**(5): p. e0217237.

[14] Chen, M.C., et al., Increased insula coactivation with salience networks in insomnia. Biol Psychol, 2014. **97**: p. 1-8.

[15] Di Lernia, D., S. Serino, and G. Riva, Pain in the body. Altered interoception in chronic pain conditions: A systematic review. Neurosci Biobehav Rev, 2016. **71**: p. 328-341.

[16] Pollatos, O., et al., Reduced perception of bodily signals in anorexia nervosa. Eat Behav, 2008. **9**(4): p. 381-8.

[17] Verdejo-Garcia, A., L. Clark, and B.D. Dunn, The role of interoception in addiction: a critical review. Neurosci Biobehav Rev, 2012. **36**(8): p. 1857-69.

[18] Di Lernia, D., et al., Toward an Embodied Medicine: A Portable Device with Programmable Interoceptive Stimulation for Heart Rate Variability Enhancement. Sensors (Basel), 2018. **18**(8).

[19] Di Lernia, D., G. Riva, and P. Cipresso. iStim. A New Portable Device for Interoceptive Stimulation. 2018. Cham: Springer International Publishing.

[20] Craig, A.D., How do you feel? Interoception: the sense of the physiological condition of the body. Nature reviews. Neuroscience, 2002. **3**(8): p. 655-66.

[21] Gordon, I., et al., Brain mechanisms for processing affective touch. Hum Brain Mapp, 2013. **34**(4): p. 914-22.

[22] Walker, S.C., et al., C-Low Threshold Mechanoafferent Targeted Dynamic Touch Modulates Stress Resilience in Rats Exposed to Chronic Mild Stress. Eur J Neurosci, 2020.

[23] Triscoli, C., et al., Heart rate variability is enhanced by long-lasting pleasant touch at CT-optimized velocity. Biol Psychol, 2017. **128**: p. 71-81.

[24] Nummenmaa, L., et al., Social touch modulates endogenous μ-opioid system activity in humans. Neuroimage, 2016. **138**: p. 242-247.

[25] Walker, S.C., et al., C-tactile afferents: Cutaneous mediators of oxytocin release during affiliative tactile interactions? Neuropeptides, 2017. **64**: p. 27-38.

[26] Vrontou, S., et al., Genetic identification of C fibres that detect massage-like stroking of hairy skin in vivo. Nature, 2013. **493**(7434): p. 669-73.

[27] Liljencrantz, J., et al., Slow brushing reduces heat pain in humans. European Journal of Pain, 2017. **21**(7): p. 1173-1185.

[28] Habig, K., et al., Low threshold unmyelinated mechanoafferents can modulate pain. BMC Neurol,

2017. **17**(1): p. 184.

[29] Lu, Y. and E.R. Perl, A specific inhibitory pathway between substantia gelatinosa neurons receiving direct C-fiber input. Journal of Neuroscience, 2003. **23**(25): p. 8752-8758.

[30] Delfini, M.-C., et al., TAFA4, a chemokine-like protein, modulates injury-induced mechanical and chemical pain hypersensitivity in mice. Cell reports, 2013. **5**(2): p. 378-388.

[31] Olausson, H., J. Wessberg, and F. McGlone, Affective Touch and the Neurophysiology of CT Afferents. 2016: Springer.

[32] von Mohr, M., L.P. Kirsch, and A. Fotopoulou, The soothing function of touch: affective touch reduces feelings of social exclusion. Scientific Reports, 2017. **7**(1): p. 13516.

[33] Manzotti, A., et al., Dynamic touch reduces physiological arousal in preterm infants: A role for c-tactile afferents? Dev Cogn Neurosci, 2019. **39**: p. 100703.

[34] Di Lernia, D., et al., Interoceptive Axes Dissociation in Anorexia Nervosa: A Single Case Study With Follow Up Post-recovery Assessment. Frontiers in Psychology, 2019. **9**(2488).

[35] Di Lernia, D., et al., Altered Interoceptive Perception and the Effects of Interoceptive Analgesia in Musculoskeletal, Primary, and Neuropathic Chronic Pain Conditions. J Pers Med, 2020. **10**(4).

[36] Dimov, L.F., et al., Electrical stimulation of the insular cortex as a novel target for the relief of refractory pain: An experimental approach in rodents. Behavioural brain research, 2017.

[37] Dinur-Klein, L., et al., Smoking cessation induced by deep repetitive transcranial magnetic stimulation of the prefrontal and insular cortices: a prospective, randomized controlled trial. Biological psychiatry, 2014. **76**(9): p. 742-749.

[38] Malik, S., et al., Deep TMS of the insula using the H-coil modulates dopamine release: a crossover [11 C] PHNO-PET pilot trial in healthy humans. Brain imaging and behavior, 2018. **12**(5): p. 1306-1317.

[39] Sagliano, L., et al., Modulating interoception by insula stimulation: a double-blinded tDCS study. Neuroscience letters, 2018.

[40] Ackerley, R., et al., Human C-tactile afferents are tuned to the temperature of a skin-stroking caress. J Neurosci, 2014. **34**(8): p. 2879-83.

[41] Crucianelli, L., et al., Bodily pleasure matters: velocity of touch modulates body ownership during the rubber hand illusion. Front Psychol, 2013. **4**: p. 703.

[42] Ogden, R.S., et al., The effect of pain and the anticipation of pain on temporal perception: A role for attention and arousal. Cogn Emot, 2015. **29**(5): p. 910-22.

[43] Ogden, R.S., et al., Stroke me for longer this touch feels too short: The effect of pleasant touch on temporal perception. Conscious Cogn, 2015. **36**: p. 306-13.

[44] Rubia, K., et al., Mapping motor inhibition: conjunctive brain activations across different versions of go/no-go and stop tasks. Neuroimage, 2001. **13**(2): p. 250-61.

[45] Tottenham, N., T. Hare, and B.J. Casey, Behavioral Assessment of Emotion Discrimination, Emotion Regulation, and Cognitive Control in Childhood, Adolescence, and Adulthood. Frontiers in

Psychology, 2011. **2**(39).

[46] R Goodin, B., T. J Ness, and M. T Robbins, Oxytocin-a multifunctional analgesic for chronic deep tissue pain. Current pharmaceutical design, 2015. **21**(7): p. 906-913.

[47] Tracy, L.M., et al., Oxytocin and the modulation of pain experience: implications for chronic pain management. Neuroscience & Biobehavioral Reviews, 2015. **55**: p. 53-67.

[48] Craig, A.D., Emotional moments across time: a possible neural basis for time perception in the anterior insula. Philos Trans R Soc Lond B Biol Sci, 2009. **364**(1525): p. 1933-42.

[49] Naqvi, N.H., et al., The insula: a critical neural substrate for craving and drug seeking under conflict and risk. Ann N Y Acad Sci, 2014. **1316**: p. 53-70.

[50] Naqvi, N.H. and A. Bechara, The hidden island of addiction: the insula. Trends in neurosciences, 2009. **32**(1): p. 56-67.

[51] Ibrahim, C., et al., The Insula: A Brain Stimulation Target for the Treatment of Addiction. 2019. **10**(720).

[52] Bowen, M.T. and I.D. Neumann, Rebalancing the Addicted Brain: Oxytocin Interference with the Neural Substrates of Addiction. Trends Neurosci, 2017. **40**(12): p. 691-708.

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