Functional Differences in Cutaneous Afferents and Thermomechanical Integration in Fibromyalgia

Fibromyalgia (FMS) is an inflammatory chronic pain condition characterized by intermittent fatigue, brain fog and sleep disturbance (Wolfe, 2017). The aetiology is currently unknown and approximately ninety-percent of those with a fibromyalgia diagnosis are female, and (Bennet, 2007). While there are no known effective treatments, fibromyalgia patients often report increased pain severity during cold winter months, which is alleviated in summer (Bennet, 2007; Macfarlane et al., 2010; Russell, 1989). The thermal modulation of pain in fibromyalgia may suggest an integration between sensory modalities, which is supported by reports of skin cooling, often being perceived as pressure or pain (Kosek, 1996). Whether this integration occurs at the central or peripheral level is currently contested.

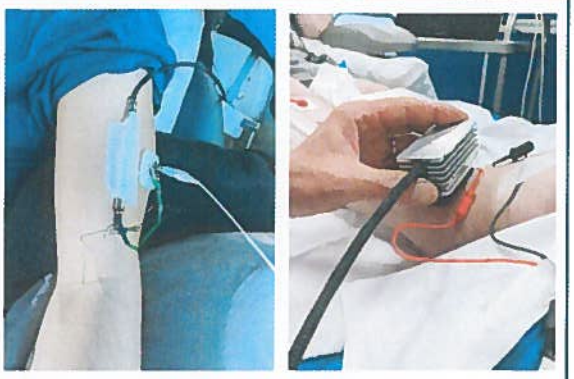

Figure 1 Microneurography setup (left) and thermode setup (right).

Thermomechanical integration is demonstrated by the Silver Thalar (coin) illusion, which was observed by Weber in the 19th century (Buckingham, 2014), establishing that objects (coins) of the same weight are perceived as heavier when cooled. While multimodal sensations were thought to be integrated centrally, evidence suggests that the Silver Thalar illusion results also from integration at the peripheral level (Buckingham, 2014). Animal electrophysiological recordings of cutaneous nerve fibres in the ducks suggest the Merkle Cell, specifically the PIEZO2 ion channel, mediates the potentiation of moderately cold temperatures (Zheng, 2019). The PIEZO2 ion channel is a logical mechanism here as it responds to both cooling and indentation of the skin, where cooling increases firing to touch, thus improving touch acuity (Zheng, 2019). While the physiological relevance of increased touch acuity in cold conditions for the duck may be explained by the foraging habits involving immersion of the duck's bill in cold water, functional relevance in humans is unclear. In relation to fibromyalgia, it is unknown whether the cold potentiated response of Merkle Cells contribute to cold potentiated pain in fibromyalgia. To answer this question, in experiment one microneurography recordings of peripheral nerve responses during cooling of the skin in fibromyalgia patients and healthy controls.

Experiment One: Merkle Cell response differences between fibromyalgia and Healthy Controls

Microneurography is an electrophysical technique facilitating the recording of a single cutaneous nerve fibres in awake human participants (Vallbo & Johansson, 1978; Vallbo et al., 2004). During microneurography a high-impedance amplifier is taped to the participant's skin and reference and active electrodes are inserted percutaneously (Figure 1). Once the electrode penetrates the outer nerve layer (myelin sheath) the electrode enters a bundle of nerve fibres (fascicle) with the uninsulated electrode tip pressing up against a single nerve fibre. Finally, the area of skin (receptive field) innovated by the nerve fibre is mechanically, thermally and electrically stimulated and the responses are digitally recorded via Lab Chart (PowerLab 16) software (Holwerda et al., 2018). It is a difficult procedure,

requiring technical expertise, specialised equipment, with a low data yield (Mano et al., 2006). Figure 2 shows the response of the Merkle Cell to cooling of the skin. Interestingly, the results indicate that thermal thresholds of the Merkle Cell is significantly lower in fibromyalgia patients, meaning that the Merkle Cells begin firing sooner thus suggesting they are more sensitive to cooling in fibromyalga patients. While this finding suggests a functional difference in A-fibre periferal nerves and a sensitive to cold in fibromyagia, in isolation it does not explain whether innocuous cold sensitivity is related to exacerbated cold-modulated pain in fibromyalgia.

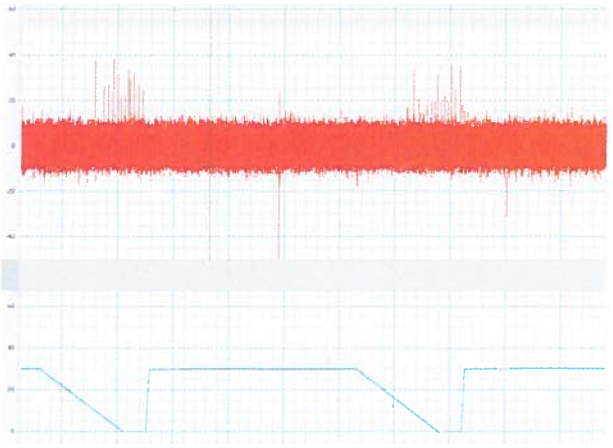

Figure 2 shows the response of an SA2 unit (red) to cooling of the skin from 30 to 0°C (blue line).

Experiment Two: Silver Thaler Illusion between fibromyalgia and healthy controls

A second experiment will be conducted investigating perceptual differences between fibromyalgia and healthy controls in response to the Silver Thaler Illusion. This will help to understand whether temperature modulates pressure sensing differently in fibromyalgia. To test this, a warm and cool 500g weight is alternatively placed on the skin and the participant will report which weight is perceived as heavier, the first one or second one. Data collection is ongoing for experiment two, it is anticipated data collection will be complete June 2024.

Experiment Three: Silver Thaler Illusion In Defined Neuropathy Patients

While the Silver Thaler Illusion is thought to be mediated by Merkle Cells (large A-fibre), it is currently unknown whether other nerve fibre types may contribute to this phenomenon. This prompts the research question: Does the Silver Thaler Illusion require simultaneous input from small (c-fibre) and medium (Aδ) diameter fibres? Patients will be recruited who have undergone unilateral cordotomy for alleviation of cancer-related pain, which entails surgically lesioning the spinothalamic pathway. This pathway contains small and medium diameter nerve fibres, which encode, temperature and pain signalling. Lesioning of the spinothalamic pathway on the left side reduces pain and temperature perception on the right side of the body, while sensation on the left side remain intact. Therefore, allowing for comparison of lesioned and intact sides. This experiment will replicate the Silver Thaler Illusion on both the lesioned and intact sides. Therefore, providing a comparison of how skin cooling increases sensitivity to indentation force with and without small and medium diameter fibres, within the same participant. Data collection is for experiment three is anticipated to end September 2024.

Holwerda, S. W., Luehrs, R. E., Gremaud, A. L., Wooldridge, N. A., Stroud, A. K., Fiedorowicz, J. G., Abboud, F. M., & Pierce, G. L. (2018). 50 Years of Microneurography: Insights into Neural Mechanisms in Humans: Relative burst amplitude of muscle sympathetic nerve activity is an indicator of altered sympathetic outflow in chronic anxiety. *Journal of neurophysiology, 120*(1), 11.

Mano, T., Iwase, S., & Toma, S. (2006). Microneurography as a tool in clinical neurophysiology to investigate peripheral neural traffic in humans. *Clinical neurophysiology, 117*(11), 2357-2384.

Vallbo, A., & Johansson, R. (1978). The tactile sensory innervation of the glabrous skin of the human hand. *Active touch, 2954*, 29-54.

Vallbo, A. B., Hagbarth, K.-E., & Wallin, B. G. (2004). Microneurography: how the technique developed and its role in the investigation of the sympathetic nervous system. *Journal of applied physiology, 96*(4), 1262-1269.