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). Ninety-percent of those with a fibromyalgia diagnosis are female, and the aetiology is currently unknown (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 modalities, which is supported by reports of cooling of the skin, often being perceived as pressure or pain (Kosek, 1996). Whether this integration occurs at the central or peripheral level is currently contested.

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, such as object wetness, a combination of thermal and pressure encoding, evidence suggests that the Silver Thalar illusion results also from integration on 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, experiment one consisted of a thermode to cool the skin of fibromyalgia patients and healthy controls during microneurography, and nerve responses were recorded and compared among different nerve fibre types.

Figure 1 Microneurography setup.

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,

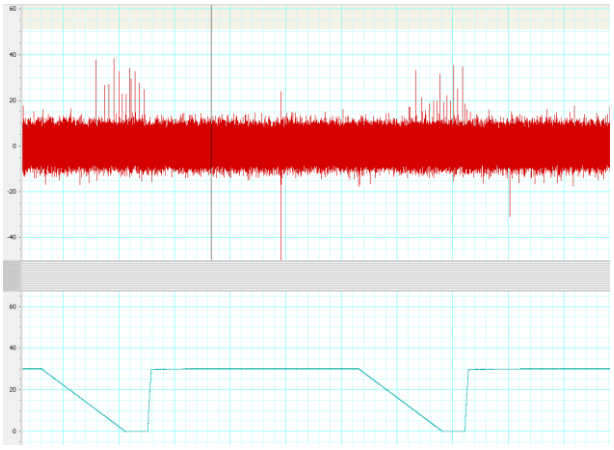

Figure 2 shows the response of an SA2 unit (red) to cooling of the skin from 30 to 0°C (blue line).

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. Data collection is ongoing for experiment one, it is anticipated data collection will be complete towards the end of 2023.

Experiment Two: Silver Thaler Illusion between fibromyalgia and healthy controls

A second experiment will be conducted involving the Silver Thaler Illusion and both fibromyalgia patients and healthy controls. In response to cooling reportedly increasing pain in fibromyalgia and cooling increasing the sensitivity of the Merkle Cells to touch, the research question here is: Do Merkle Cells contribute to temperature dependent fibromyalgia pain?

To test this, both fibromyalgia patients and healthy controls will experience the Silver Thaler Illusion. This consists of a warm and cool 500g weight being placed on the skin consecutively and the participant will report which weight was heavier, the first one or second one. A comparison will be made between the responses of fibromyalgia patients and healthy controls, to understand whether a function difference exists. Data collection is ongoing for experiment two, it is anticipated data collection will be complete towards the end of 2023.

Experiment Three: Weber's Illusion with patients following unilateral cordotomy

While the Silver Thaler Illusion is likely to be mediated by Merkle Cells, it is still yet to be confirmed. Therefore, experiment three aims recruit healthy controls to map the magnitude of sensitivity increase to indentation force in Merkle Cells among a range of cool temperatures. A tactile stimulator will control the downwards force of an attached QST.Lab thermal probe (figure 3), facilitating stimulation across a range of temperatures. Furthermore, the Silver Thaler Illusion will be repeated using the thermal probe in order to replicate the findings with more precision and at varying temperatures. Data collection for experiment three is anticipated to begin in July 2023.

Figure 3 QST.Lab Thermode

Experiment Four: 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 following a unilateral cordotomy, 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 opposite side of the body, while sensation on the same 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 four is anticipated to begin in June 2023.

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.