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Characterization of a New Peripheral Painful Neuroma Model in Göttingen Minipigs

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Introduction

Preclinical research on peripheral nerve injury and repair has primarily focused on rodent models, with limited studies in larger animals. However, a suitable large-animal model is crucial for the translational evaluation of new technologies. Göttingen Minipigs (GMP) were selected due to their physiological similarity to humans in terms of peripheral nerve structure, function, and repair, their acceptability in toxicological studies, and their suitability for long-term follow-up due to slower growth rates.

Methods

Male and female GMPs underwent peroneal nerve dissection (>2 cm; Figure 1) and were followed for one year. Some female animals received Integra tube implants for nerve repair. Functional and sensory assessments included computerized gait analysis, tactile and heat sensitivity tests, electrophysiology (cMAP and DSNAP), locomotor activity (open field), leg functional scoring, and behavioral assessments.

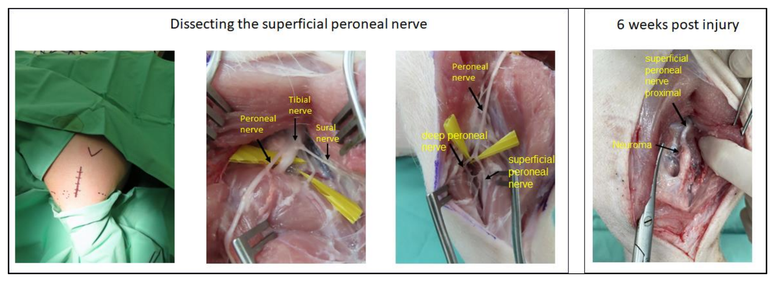


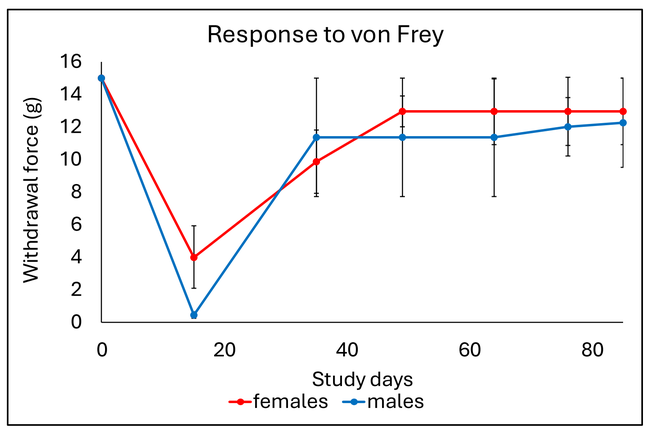
Figure 1: Postmortem images of GMP hind leg innervation. Right: Neuroma developed at the dissected peroneal nerve site.

Conclusions

- The pig neuroma model closely resembles the human condition, particularly in that not all animals develop pain—mirroring the variability observed in humans. The anatomical size of pigs allows for the creation of critical nerve gaps ranging from 4–7 cm, and even exceeding 7 cm.
- Behavioral assessments, including both spontaneous (non-evoked) and stimulus-evoked responses, indicate persistent thermal hyperalgesia in the subset of animals that do develop pain. Despite this, the animals retain functional mobility, making them suitable for evaluation through locomotor behavior assays.
- While rabbits remain the most widely used large-animal model for peripheral nerve injury, the pig model supports a broader range of assessments for both data collection and functional analysis.

Results

Response to Evoked Stimulation



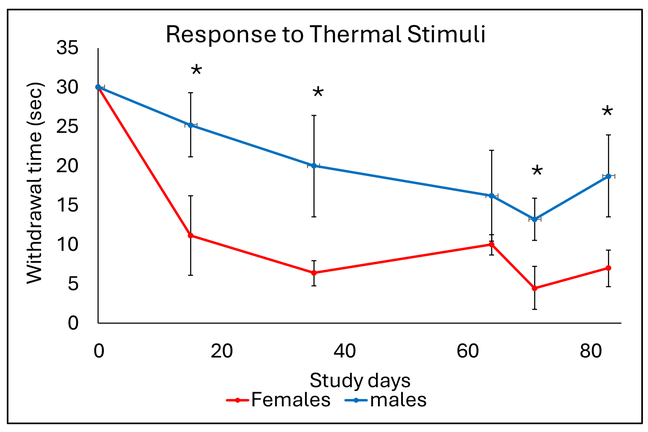
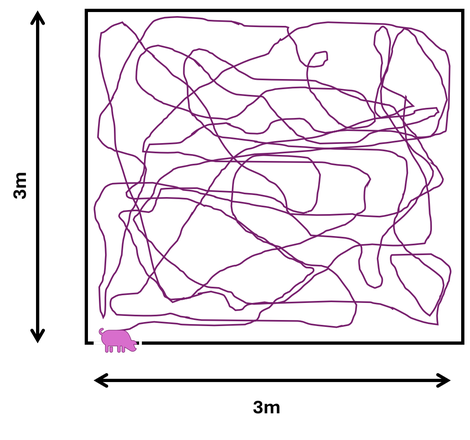


Figure 2: Response to von Frey and Thermal Stimuli. Left: Mechanical sensitivity. Transient tactile allodynia was observed, with full recovery by 1.5-2 months post-injury. **Right**: Thermal sensitivity. Females exhibited persistent heat hyperalgesia, indicated by reduced withdrawal times. A sex difference was observed across multiple time points, with males showing higher thermal withdrawal times compared to females.

Locomotor Activity



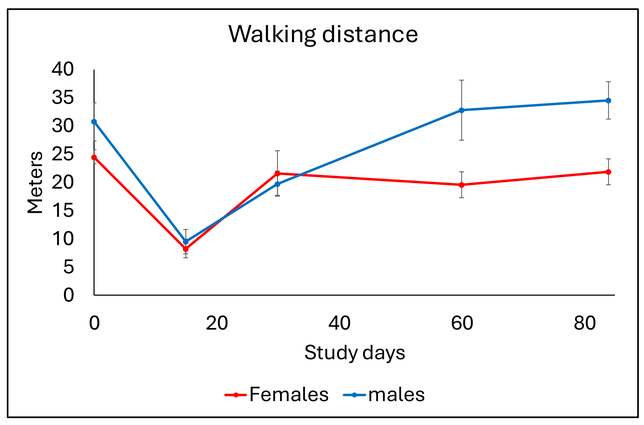
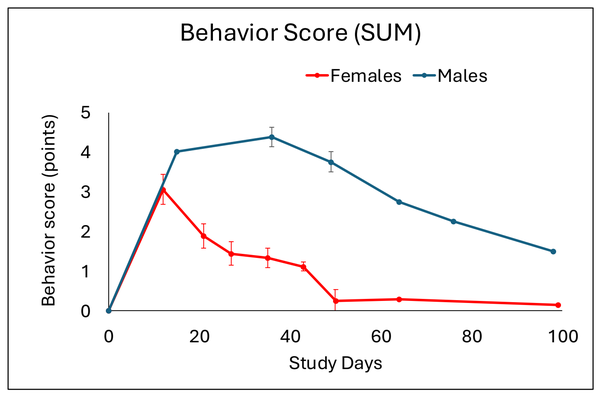
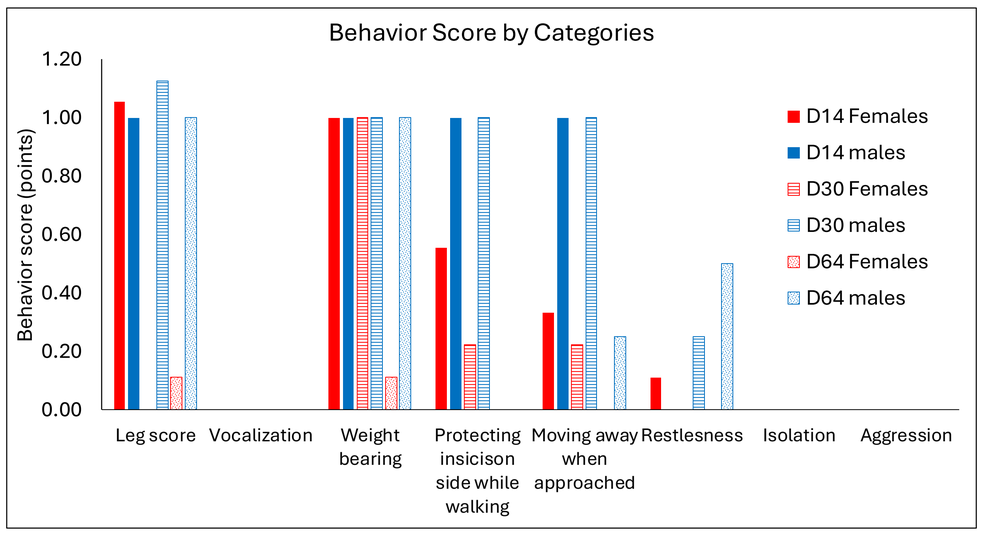


Figure 3: Locomotor Activity Assessed by Open Field Assay. Left: Schematic of a typical walking pattern in pigs without pain or dysfunction, showing unrestricted movement throughout the arena. **Right:** Total walking distance over a 5-minute period. Animals regained locomotor function by 3–4 weeks post-injury.

Behavior Score and Body Weight Changes





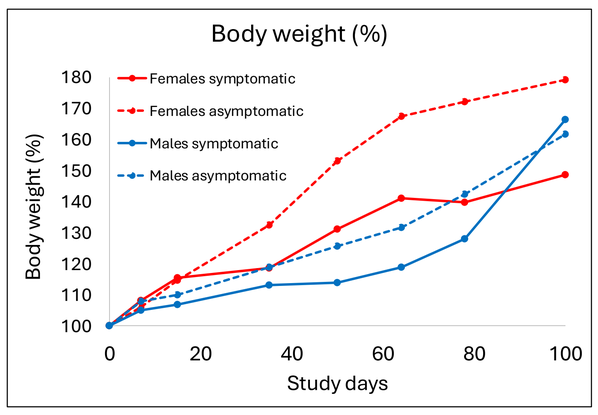
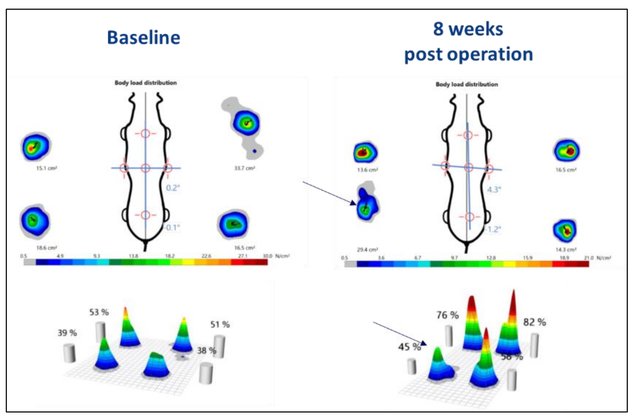


Figure 4: Behavior Scores and Body Weight. Top left: Mean group behavior scores. Female animals recovered faster than males. (Graphs include only symptomatic animals.) **Bottom left:** Weight gain differences between symptomatic and asymptomatic animals. Asymptomatic animals gained more weight than symptomatic animals in both sexes, with a more pronounced difference in females. **Right:** Individual behavior score components. By study day 14, all animals showed changes in posture or behavior of the operated leg. These resolved in females later in the study, while males continued to display in leg score. A similar pattern was observed in weight-bearing. Male animals also showed more anxiety-related behaviors, including guarding the operated side and avoiding contact, along with higher restlessness scores.

Non-Evoked Outcome Measure



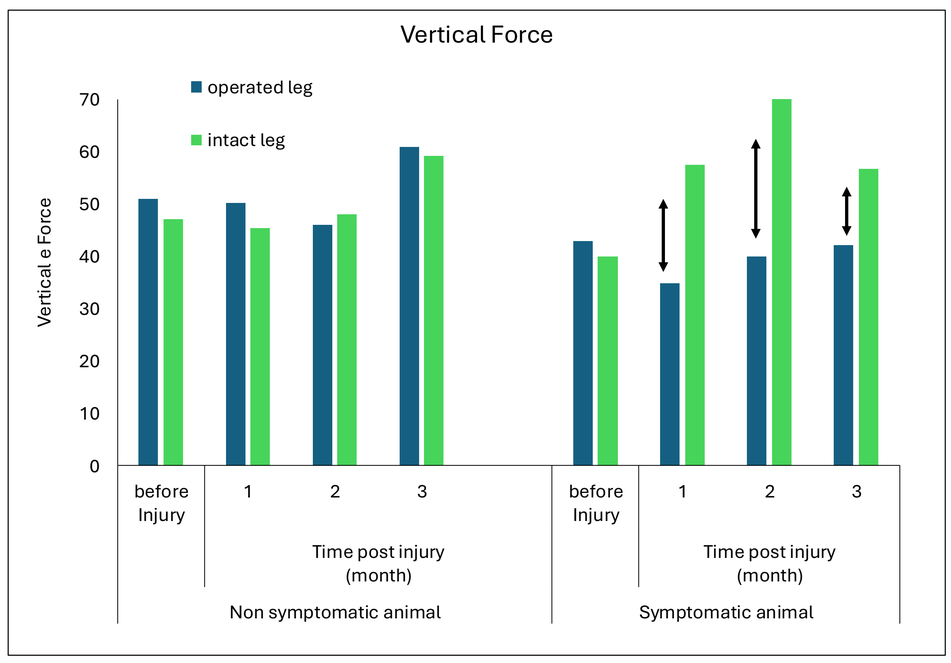


Figure 5: Gait Analysis and Vertical Force. Left: Schematic of computerized gait analysis using the Zebris Medical system. **Right:** Vertical force applied by the hind legs of symptomatic female animals. A clear difference was observed between the operated leg (blue column) and the intact leg (light green column), with animals shifting body weight to the intact, healthy leg to avoid carrying weight on the injured, operated leg (black arrows). No consistent differences were observed between male and female animals, and this parameter was found to be inconsistent.