Demyelination in the Forceps Minor contributes to Changes in Social Behavior

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Hypothesis & Aim

Is forceps minor involved in regulation of social behavior?

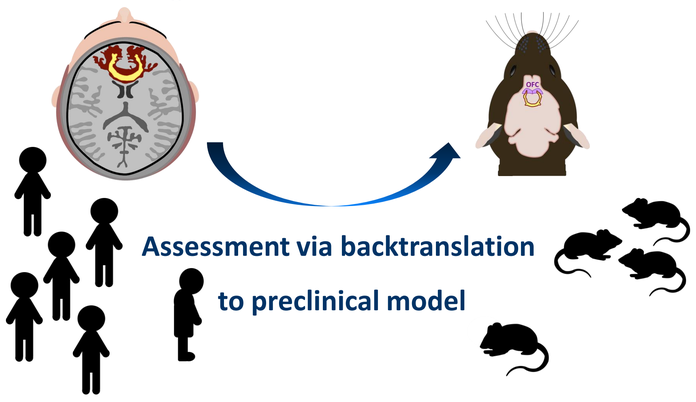


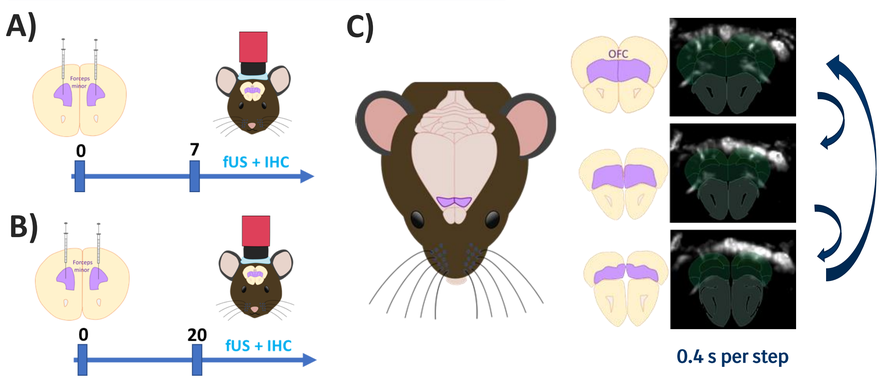
Figure 1: PRISM2-project: biological relationship between forceps minor and social dysfunction; demonstration in animal model

Introduction

Across various neuropsychiatric diseases, **social withdrawal** is often diagnosed as an early symptom and can therefore be considered as a **transdiagnostic marker**. Clinical data suggest that, irrespective of the initial diagnosis, **people exhibiting low social functioning** show **reduced white matter integrity**, specifically in **forceps minor (FM)** a fiber tract connecting both orbital frontal cortices (OFC). As part of the PRISM2 (Psychiatric Ratings using Intermediate Stratified Markers) consortium, we **injected Lysolecithin (LPC)** into FM to induce **focal demyelination** in mice. This technique should allow us to **manipulate interhemispheric connection** via FM, part of the Default Mode Network (DMN), and **back-translate** those **human findings** into **preclinical research**.

Methods

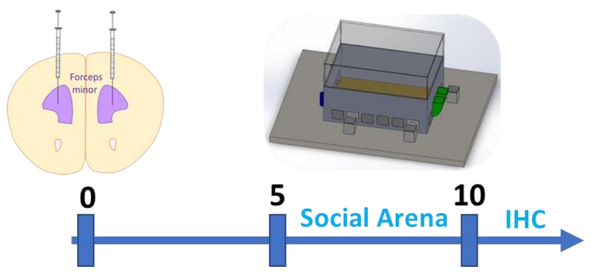
Functional Ultrasound (fUS)



Iconeus One
- LPC: 1% in Saline, 500 nl per hemisphere
- neurovascular coupling – Power Doppler signal
- 2.5 Hz temporal resolution
- 60 min scan, 3 planes
  - demyelination experiment: 11 male mice (6 x Saline, 5 x LPC)
  - remyelination experiment: 11 male mice (5 x Saline, 6 x LPC)

Figure 2: (A-B) Demyelination/remyelination study design: Experimental timeline showing days post injection (p.i.) LPC/Saline injection; (C) Acquisition design

Social Arena



RFID-assisted SocialScan
- synchronization between RFID-data and long-term video tracking
- 16 male mice (8 x Saline, 8 x LPC)
- LPC: 1% in Saline, 500 nl per hemisphere

Figure 3: Experimental timeline showing days after LPC/Saline injection; RFID-assisted 3D Version of Social Arena including three nests, two food hoppers, two water bottles

Results

Demyelination - IHC

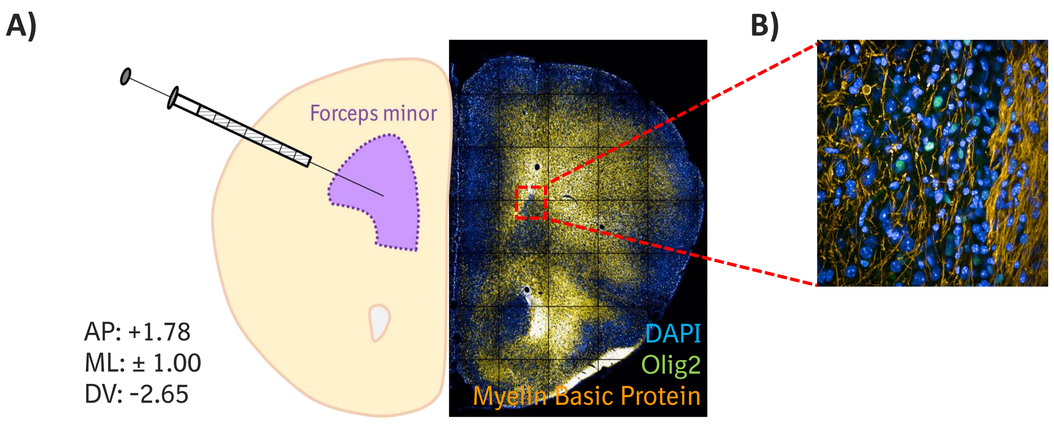


Figure 4: Focal demyelination in FM after Lysolecithin injection; (A) Schematic representation, 20x magnification; (B) 63x magnification

Demyelination - fUS

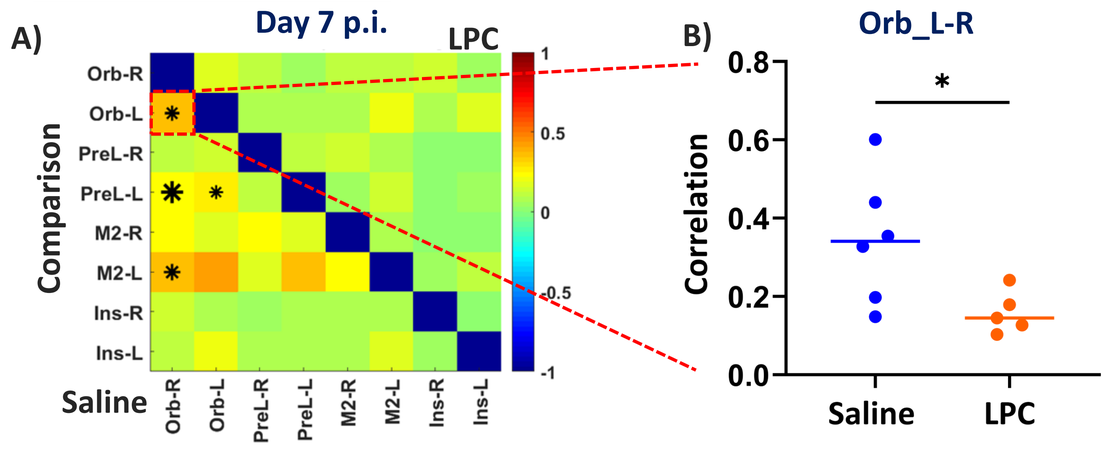


Figure 5: Effects of demyelination on interhemispheric connectivity. (A) connectivity matrix in frontal regions [Orbital area right (Orb-R), Orbital area left (Orb-L), Prelimbic area right (PreL-R), Prelimbic area left (PreL-L), Secondary motor area right (M2-R), Secondary motor area left (M2-L), Insular area right (Ins-R), Insular area left (Ins-L)]; (B) correlation between Orb-L and Orb-R in Saline and LPC group Two-sample t-test, p = 0.0399

Demyelination – Social behavior

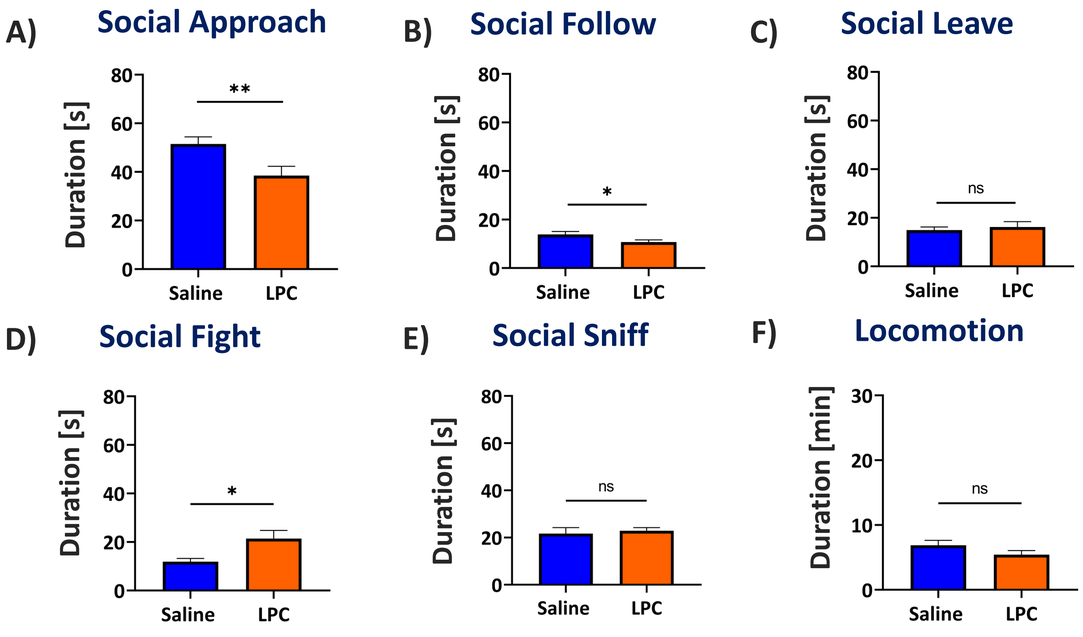


Figure 6: Effects of demyelination on social behavior during night phase (6 p.m.-6 a.m.); (A) social approach p = 0.008 ; (B) social follow p = 0.0407; (C) social leave p = 0.6315 ; (D) social fight p = 0.0101; (E) social sniff p = 0.6703 (F) Locomotion p = 0.1909

Remyelination - fUS

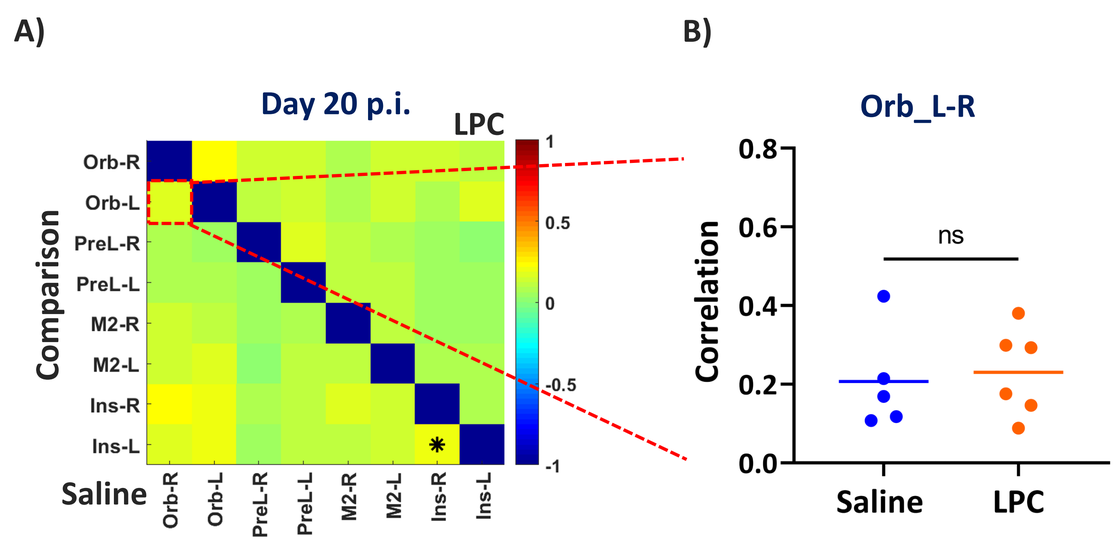


Figure 7: Effects of remyelination on interhemispheric connectivity. (A) connectivity matrix in frontal regions [Orbital area right (Orb-R), Orbital area left (Orb-L), Prelimbic area right (PreL-R), Prelimbic area left (PreL-L), Secondary motor area right (M2-R), Secondary motor area left (M2-L), Insular area right (Ins-R), Insular area left (Ins-L)];(B) correlation between Orb-L and Orb-R in Saline and LPC group; Two-sample t-test, p = 0.7493

Conclusion

Lysolecithin injection into forceps minor results in social behavior impairment and alters functional connectivity of OFC

- **LPC induces focal demyelination**
- **demyelination reduces interhemispheric functional connectivity between orbital areas**
- **demyelination reduces social interaction, in specific approaching and following**
- **indicates involvement of FM, as part of DMN, in social behavior**
- **shows no effect on interhemispheric functional connectivity after remyelination**

In relation to this poster, all authors declare that there are no conflicts of interest