Glial glutamate regulation, critical determinant of whole brain physiology: a computational study

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Introduction:

Glutamate is the chief excitatory brain neurotransmitter and its extracellular concentration is tightly regulated by many synaptic processes mainly involving glia (mostly astrocytes) and neurons [1]. Perturbations to this regulatory system, e.g. due to deficient glial glutamate uptake, have been shown to cause noxious effects: e.g. the excess glutamate release which can induce hyperexcitability in post-synaptic neurons to the point of excitotoxicity and cell death [1]. So far, the mechanisms through which such glutamate injuries modulate neuronal activity have been experimentally and theoretically detailed mostly at the microscopic brain scale, mainly because experimental data are challenging to obtain and analyse [2]. Hence, what remains poorly known to date is which of these inferred mechanisms lingers at the macroscopic scale. In addition, the mechanisms through which glutamate injuries could modulate the large-scale neuronal networks activity remain totally unexplored. In this study, we propose a step forward by introducing a whole brain biophysically plausible network model of neuron-glia mass models (NNGMM) to generate working hypotheses of the effect of glutamate injuries on the large-scale neuronal networks activity.

Methods:

The NNGMM was built out of three main elements (Fig. 1 A-B): (a) a NGMM (extending [3]) ascribed to each network node to represent the collective dynamics of a population of neurons and glia, (b) a realistic human brain structural connectivity for coupling the populations of neurons, and (c) a glial connectivity for coupling the populations of glia. The 3T magnetic resonance imaging data of one subject of the WU-Minn HCP [4] was used to define the network nodes (cortical parcellation of ~500 regions, following [5]), and the network edges, by estimating the structural connectivity with a probabilistic tractography method [6] and the glial connectivity from a geodesic distance matrix between cortical regions mass centers. To investigate the effects of deficient glial glutamate uptake, first we simulated whole brain activity for 3 min, for three glial network coupling strengths (ω: 0.01, 3.8, 4.4), for which every time at 80 s, we blocked the glutamate receptors of the glia population of the left inferior parietal (Fig. 1 C) preventing further glial glutamate uptake and resulting in increased extracellular glutamate concentration in that region. We then quantified the resulting change of neuronal activity for each brain region by comparing the greatest change in local field potentials (LFPs) amplitude between a post- and pre-injury temporal window (Fig. 1 D).

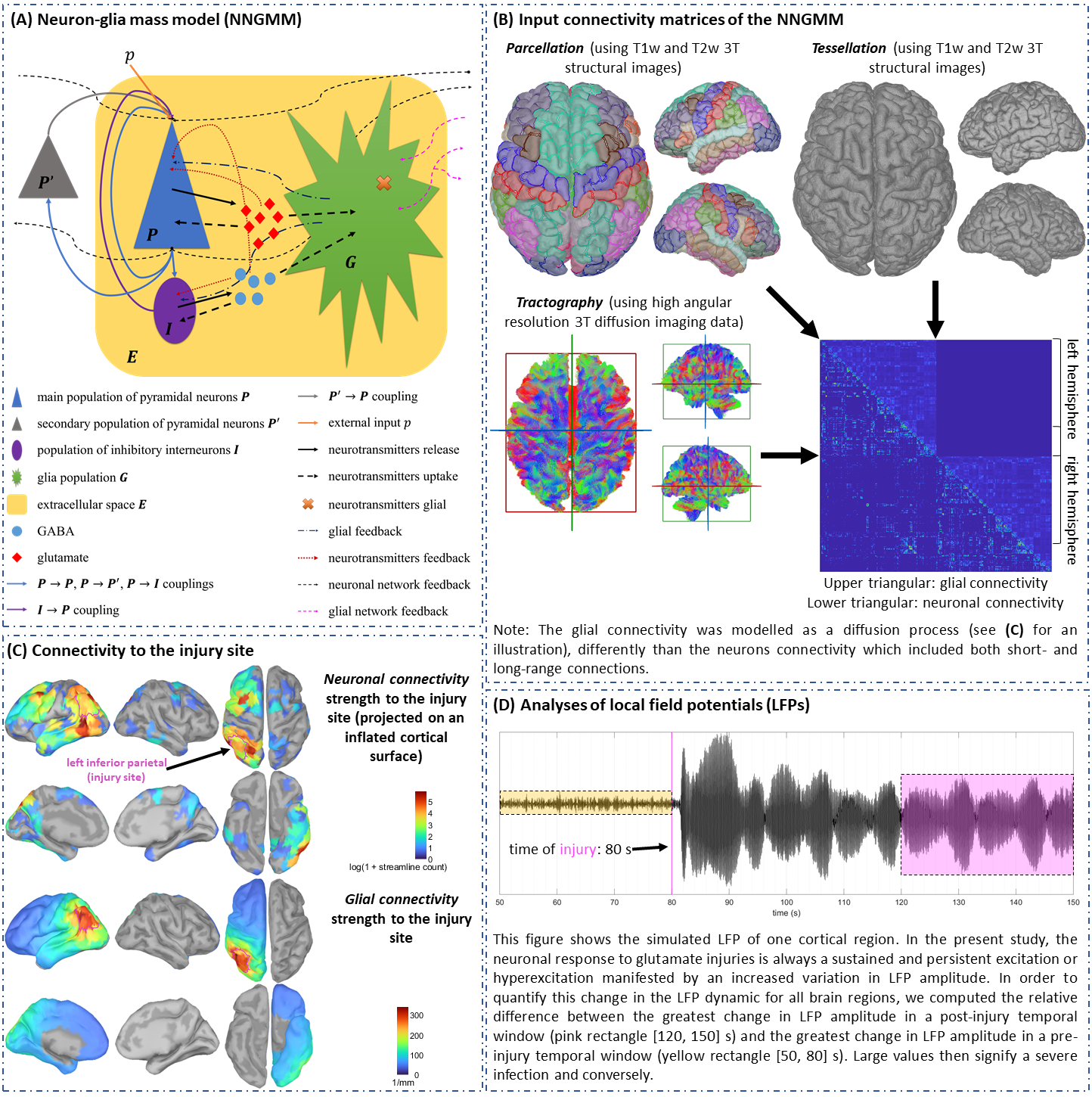
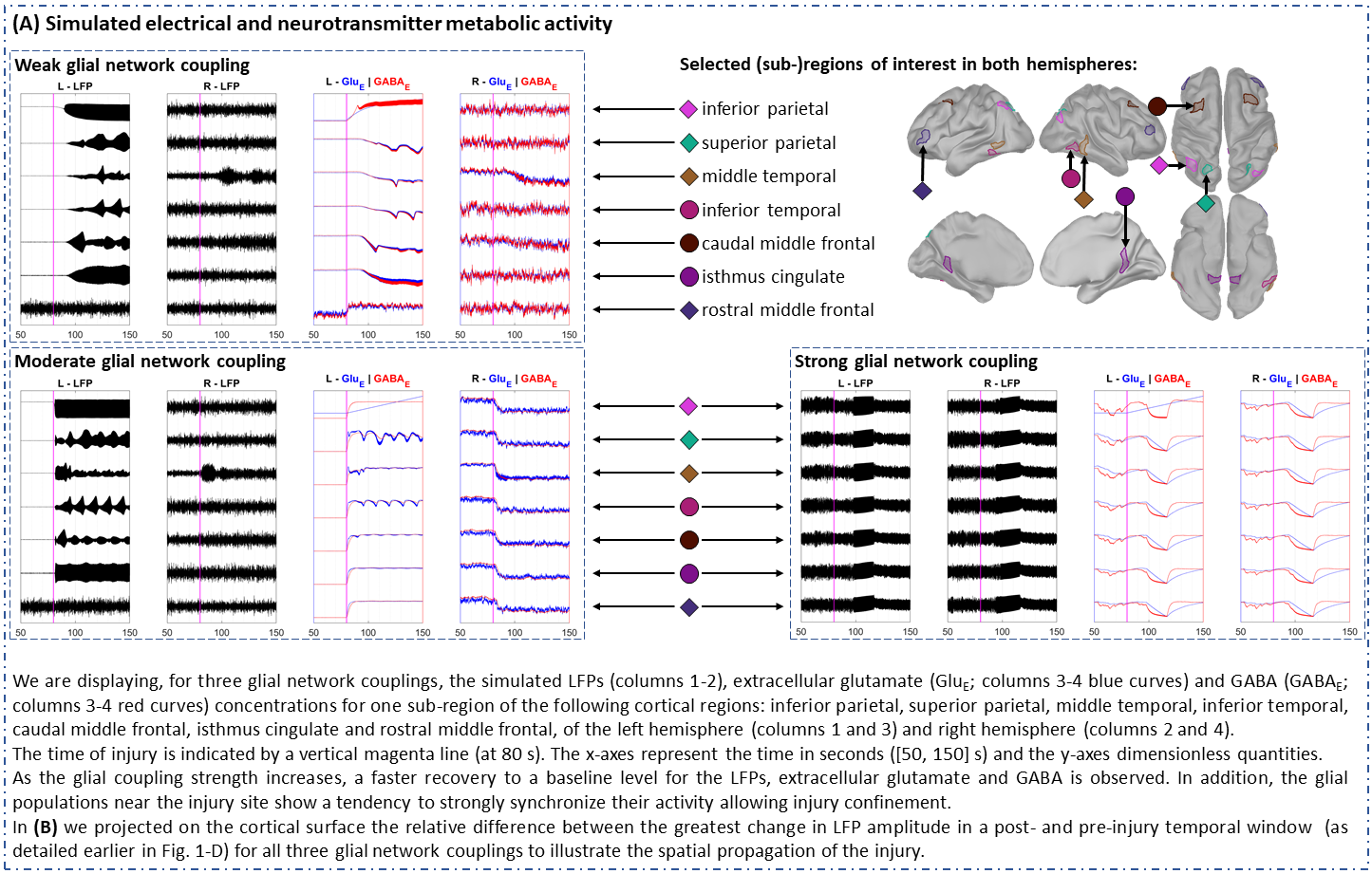


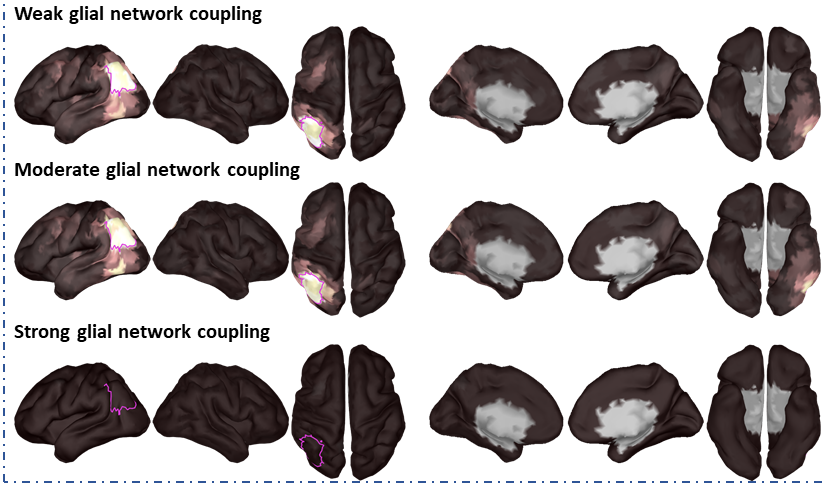
Figure 1: (A) Neuron-glia mass model (NNGMM) – (B) Input connectivity matrices of the NNGMM – (C) Connectivity to the injury site – (D) Analyses of local field potentials (LFPs)

Results:

For weak and moderate ω the injury propagated through both the neuronal and glial pathways infecting nearby and distant regions (e.g. left caudal middle frontal or left and right middle temporal; Fig. 2-A) by affecting persistently their LFPs but only transiently affecting their neurotransmitter metabolism for which a recovery to a new baseline level was observed. For strong ω, the injury only transiently affected both the LFPs and neurotransmitter metabolism, and the networks effectively quickly recovered to their pre-injury baseline.



We are displaying, for three glial network couplings, the simulated LFPs (columns 1-2), extracellular glutamate (Glu_E; columns 3-4 blue curves) and GABA ($GABA_E$; columns 3-4 red curves) concentrations for one sub-region of the following cortical regions: inferior parietal, superior parietal, middle temporal, inferior temporal, caudal middle frontal, isthmus cingulate and rostral middle frontal, of the left hemisphere (columns 1 and 3) and right hemisphere (columns 2 and 4).
The time of injury is indicated by a vertical magenta line (at 80 s). The x-axes represent the time in seconds ([50, 150] s) and the y-axes dimensionless quantities.
As the glial coupling strength increases, a faster recovery to a baseline level for the LFPs, extracellular glutamate and GABA is observed. In addition, the glial populations near the injury site show a tendency to strongly synchronize their activity allowing injury confinement.
In **(B)** we projected on the cortical surface the relative difference between the greatest change in LFP amplitude in a post- and pre-injury temporal window (as detailed earlier in Fig. 1-D) for all three glial network couplings to illustrate the spatial propagation of the injury.



These figures show the relative difference between the greatest change in LFP amplitude in a post-injury and pre-injury temporal window as explained in Fig. 1-D and correspond to the cases presented in **(A)**. We can observe that the site of injury becomes darker (meaning the brain networks better contain the injury) as the coupling strength between glial populations is increased. Moreover, as the glial network coupling increases, for instance comparing weak and moderate glial network couplings, we can observe how nearby regions are more strongly recruited (with for instance an increased brightness for the left middle temporal and decreased brightness for the left caudal middle frontal) and how an injury confinement starts to appear (for instance increased homogeneity of semi-bright colors around the injury site as well as for distant regions such as the left caudal middle frontal).
The neuronal pathway taken by the injury to reach the other hemisphere can be observed by looking at the internal and external views (columns 4 and 5) .

Figure 2: (A) Simulated electrical and neurotransmitter metabolic activity – (B) Short- and long-range propagation of injury through neuronal and glial networks

Conclusions:

Our preliminary results suggest that glial networks may both alleviate or accentuate glutamate injuries, confirming their pivotal role in modulating brain physiology [7]. The present study only considered the scenario where the neuronal responses to glutamate injuries are either persistent neuronal excitation or hyperexcitation, or transient neuronal excitation followed by recovery to a new regime close to the initial baseline regime. However, glutamate injuries may also induce periodic or persistent neuronal inhibition [4] due to the interplay with the counteracting effect of increased extracellular GABA concentration, and so we plan to include this

scenario in further analyses. Our model includes the unique opportunity to investigate the dialogue mechanisms between glial and neuronal networks at the macroscopic brain scale.

Keywords:

Computational Neuroscience

Electrophysiology

GABA

Glia

Glutamate

Modeling

Neuron

Neurotransmitter

Resting state (Healthy subjects)

Methods used in the study: Structural MRI 3.0T**,** Diffusion MRI 3.0T**,** Computational modeling

Processing packages : FSL,TractoFlow, Scilpy, Brainstorm, Easy Lausanne

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