Ipsilateral deficit revealed by operant conditioning following right middle cerebral artery occlusion in mice

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Middle cerebral artery occlusion is an animal model of brain stroke that consistently leads to a striatal infarction [1]. The striatum is involved in several aspects of cognition, including behavioural flexibility (i.e., the ability to adapt behaviour in a changing environment) [2].

Alongside basic sensorimotor testing, we propose an operant-based task requiring flexibility in response orientation, in order to clarify the cognitive impairments following experimental stroke.

Animals and surgery. MCAo (N=5) or sham surgery (N=5) were performed on adult C57Bl/6H mice (N=5). Under isoflurane anaesthesia, right middle cerebral artery were occluded for 30 minutes. Functional testing began 3 weeks after surgery.

Grip-strength test. Forepaw grip-strength was measured over five trials using a dedicated apparatus (Bioseb©).

Open-field locomotion. Animals were placed in a transparent cage equipped with photoreceptors. The number of beam crossings provides a locomotion measure during an one hour session.

Behavioural flexibility. Conditioning took place in boxes equipped with two levers and a food-tray (Med Associates©). Following instrumental response shaping, behavioural flexibility was assessed in 8 sessions during which the two levers were available, but only one was associated with food reinforcer under a fixed-ratio 5 schedule; after each reinforcement, the active lever changed.

Histological analysis. Deeply anaesthetised mice were transcardially perfused with 4% paraformaldehyde. 50µm brain sections were incubated overnight with mouse Anti-NeuN (1:1000), then in secondary antibodies horse Anti-Mouse (1:400). After amplification with ABC reagent, cell nuclei were revealed, using DAB as chromogen. Lesion extents were estimated under microscope with Nikon NIHID software.

Statistics. Grip-strength data were treated with a non-parametric Mann-Whitney tests; a repeated measures ANOVA was applied to the measures of locomotion and operant learning.

If motor abilities and global learning performance were not affected per se, analysis of responses pattern revealed that MCAo caused an elevation of perseverative errors in the ipsilesional hemifield only, suggesting the existence of a lateralised flexibility deficit.

This finding could be explained either by a contralateral sensory neglect or by an inhibition deficit related to the ipsilesional side. Previous animal and human studies favour the contralateral sensory neglect hypothesis [4,5]. It is not excluded however that both mechanisms could be involved at different levels.