

Classification of neural activity patterns observed by phMRI upon pharmacological interventions in rats

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Background - Pharmacological fMRI (phMRI) in animals has been successful in demonstrating distinct changes in neural activity prompted upon pharmacological challenges. Yet, consistent cross-study characterisation and quantitative interpretation in terms of neuro-circuitry have received only very limited attention^(1,2). In the present study we aimed at closing this gap by a systematic and quantitative analysis of neural activation patterns elicited by pharmacological interventions with an extensive set of neuroactive reference compounds related to the domains of anxiety and depression. Neural activity patterns observed by perfusion-based phMRI in Fisher rats were subjected to principal component analysis (PCA) in order to yield specific signatures for the drugs' modes-of-action and objective measures of dose-effect and treatment duration-effect relationships.

Methods - phMRI in rats was performed on a Bruker BioSpec 4.7T/40cm instrument equipped with a 7cm transmit resonator and a receive-only head coil. Perfusion-based functional images were obtained with continuous arterial spin labelling (CASL) with TR/TE = 3000ms/5.5ms, RARE factor = 32, FOV = 4cm x 4cm, 128 x 64 matrix, 1mm slice thickness, 8 slices, 2 averages, 2.5s labelling, and 0.4s post labelling delay^(3,4). The central effects of different pharmacological interventions were tested at 1-3 doses in naive F344 Fischer rats (n>=8 per condition) after acute and 21-day repeated dosing. For phMRI, animals were kept freely breathing under isoflurane anaesthesia (2% in O₂/air). Changes in neural activity versus control (vehicle) in more than twenty anatomically-defined brain regions were quantitatively investigated by PCA with the different brain regions spanning a high-dimensional feature space. The scores on the principal components found to be significant were used to provide a quantitative characterisation of the drugs' effects.

Results and Discussion - Neural activity patterns elicited by pharmacological interventions with reference drugs targeting the serotonergic, GABAergic, dopaminergic and glutamatergic systems were characterised with PCA. Parallel analysis yielded a set of two orthogonal activity patterns (significant principal components) that best described the differences between the drugs under investigation. Figure 1 shows an excerpt of the scores obtained for the effects of selected drugs after acute administration. Drugs having the same mechanism-of-action such as benzodiazepine agonists (bluish symbols) or selective biogenic amine reuptake inhibitors (greenish symbols) clustered together while drugs belonging to different classes remained clearly separated. This segregation was further supported by dose-dependent changes in brain activity patterns. Increasing drug doses generally moved the respective patterns further away from the point of no change, i.e. the origin. Repeated versus acute treatment with classical antidepressants also moved the activity patterns from virtually no effect to a full-fledged response as is expected due to their well documented lag in treatment response. Moreover, compounds with opposing, e.g. stimulating effects (reddish symbols), revealed virtually inverted activity patterns. Repeated studies with the same drug-dose combinations yielded consistent outcomes in that the respective activity patterns came to lie within close proximity. The activity patterns used for classifying the drugs comprised brain structures such as medial prefrontal cortex, nucleus accumbens, and periaqueductal gray which are well known network nodes implicated in depression and anxiety, hence strongly supporting the analysis' rationale from a neurobiological stance.

Conclusions - We have demonstrated that a systematic and quantitative analysis of neural activity patterns revealed by phMRI in rats upon pharmacological interventions with reference drugs impacting on the domains of anxiety and depression has yielded signatures for the drugs' modes-of-action and objective measures of the differential drug-induced effects including dose-effect and time lag-effect relationships. The robustness of the present analysis approach supports the notion that preclinical phMRI will be used beyond empirical analysis of neural activity and may serve as a means for characterising and classifying novel pharmacological treatment options.

References

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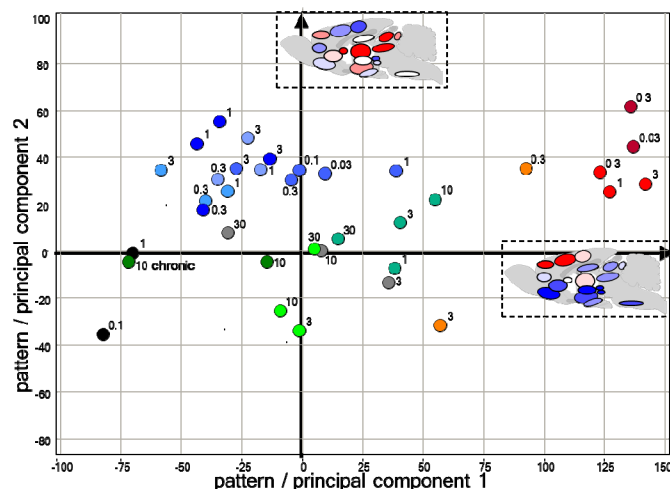


Fig. 1 ● diazepam ● fenobam ● yohimbine
● alprazolam ● paroxetine ● amphetamine
● lorazepam ● fluoxetine ● benzo inv. ago.
● zolpidem ● pregabalin ● haloperidol