Fuzzy Cluster Analysis of Galantamine Effects on fMRI

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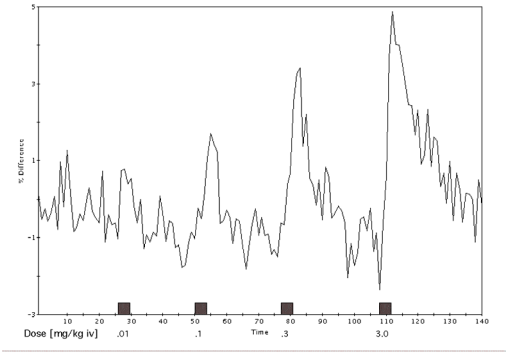
Synopsis: Investigation of drug effects by fMRI is limited by the knowledge of time course required by traditional analysis methods. We here report successful application of a new technique, Fuzzy Cluster Analysis (FCA), which is free of this limitation. Complex pharmacological experiments were performed in anesthesized rats to evaluate the hypothesis of a nicotinic mechanism of action for a new drug, galantamine. FCA (implemented in EvIdent), was successful in detecting pharmacological events, even when complex or at very low doses, without requiring prior phrmacokinetic knowledge or even the time of injections. Evidence of allosteric nicotinic potentiation was observed.

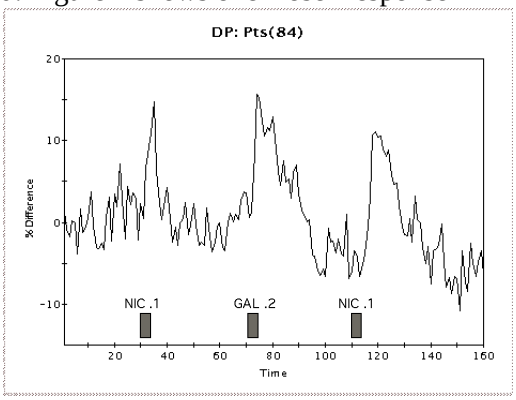
Introduction: Fuzzy Cluster Analysis (FCA) is an exploratory, paradigm-independent method of partitioning the total dataset into membership classes by assigning 'soft' coefficients, rather than binary assignments[1]. The algorithm attempts to group similar temporal responses so as to maximize the dissimilarity between the resulting group averages, and yields both the average time course and the topographic weight distribution of each group. In other words, it identifies both the topographical and chronological distributions of significant events. Because it is blind to the experimental design, it can reveal both expected and unexpected patterns; further, it can separate clusters by magnitude, as well as timing, of signal. It can also be applied recursively, as secondary clustering of already-defined clustering, to elicit more finely-divided features (for example, it may be possible to separate arterial from capillary sources within an area of interest). These properties make it highly suitable for exploratory data analysis and hypothesis generation.

Galantamine (GAL) is an Acetylcholinesterase Inhibitor (AChEI) recently approved for the treatment of Alzheimer's Disease. Its mechanism of action is still not entirely understood. Its clinical efficacy is equal or superior to other AChEI's, but its in vitro inhibition appears weaker. One hypothesis of its efficacy suggests that it is an allosteric modulator of the nicotinic receptor. The current experiment was aimed at investigating this hypothesis.



Methods: 17 adult Sprague-Dawley rats, 200-300 g, anesthetized with urethane (1g/kg i.p.), were administered various combinations of pharamcological agents during fMRI monitoring. All scans were performed at 200 MHz on a 30 cm bore 4.7 T MRI. BOLD contrast was obtained in 8 64x64 coronal slices of 1 mm thickness (gap .25 mm, GE, TR/TE 320/15 ms, FOV 30 mm), yielding a resolution of about .5x.5x1 mm. Anatomical images, blood flow, and others were also obtained. pCO2, temperature, blood pressure and heart rate were monitored. All drugs were administered iv. FCA was performed by EvIdent.

Results: In all animals, pharmacological activation was easily detected. Figure 1 shows one Dose-Response experiment (011802), where the rat was injected GAL at the following doses and times (mg/kg iv /image numbers): .01/26-29, .1/50-54, .3/78-81 and 3/108-112. Figure 2 shows an example (051002) of the main result. The second injection of nicotine (0.1 mg/kg) which followed GA (0.2 mg/kg) caused a much greater cerebral response than the first, identical dose of nicotine.



Discussion: This study provides the first in-vivo evidence that galantamine can potentiate the cerebral reponse to nicotine. It also provides data on the spatial and temporal distribution of cerebral responses to galantamine, mecamylamine and donepezil.

Methodologically, this study provides compelling evidence of the ability of FCA and EvIdent to locate phramacologically-induced efefcts in BOLD data, in both space and time. While powerful and effective, this analytic strategy is not yet free of ambiguity. Residual issues include statistical significance levels, group data analyses, and the effects of various techniques for frequency filtering and detrending.

References:

1. Jarmasz M & Somorjay RL, Artificial Intelligence in Medicine 2002;25:45-67