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Differential gene expression analysis in treatment of Parkinson's disease using the moduli space of triangles

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The long-term utility of levodopa (l-dopa) treatment against PD is known to be limited by its subsequent induction of dyskinesia (l-dopa-induced dyskinesia or LID). Up to now, few treatment strategies have been identified to reverse LID and restore l-dopa efficacy in dyskinetic patients. Among various mechanisms, l-dopa sensitization ("priming") may play an important role in the development and maintenance of LID. Disregulation of dopamine (DA) synthesis, release and clearance of extracellular DA (due to DA neuronal death and consequent "ectopic" synthesis and release by 5-HT terminals) is thought to lead to exaggerated fluctuations in the synaptic DA concentrations and consequent neurobiological alterations during chronic intermittent l-dopa treatment. These fluctuations, in turn, induce long-term, synaptic alterations in the striatum and other brain areas comprising the basal ganglia. Previous studies have shown that long-term sensitization to cocaine can be reversed by injecting a dopamine receptor agonist, followed by a 5-HT2 or 5-HT3 antagonist approximately 3.5 hours later [1,2]. To the extent that cocaine addiction may share similar neurobiological mechanisms with LID, it is reasonable to examine a regimen of the DA agonist pergolide followed by the 5-HT2 antagonist ketanserin at the peak of acute withdrawal over a treatment period and reverse sensitization to l-dopa. Based on our previous finding that this specific drug combination regimen can reverse previously-established behavioral and molecular markers of cocaine or methamphetamine sensitization in rats [3], we determined the striatal mRNA expression profiles associated with l-dopa-induced dyskinesia in rats and its reversal by the pergolide-ketanserin regimen. 6-Hydroxydopamine (6-OHDA)-lesioned rats were treated with l-dopa twice a day for 21 days (days 1 – 21) to induce abnormal involuntary movements (AIM), a model of LID. Subsequently, they were treated subcutaneously once a day for 2 weeks with one of the following. Group A received pergolide followed by ketanserin; Group B received pergolide followed by saline; Group C, the control group, received saline on both occasions. The expression levels of mRNA were measured for 27,342 genes. The normalized values provide triplets of positive numbers $D = \{ (A(n), B(n), C(n)) : n = 1,2,... 27342\}$. This paper reports progress in application of new mathematical methods for exploring this genome-scale gene expression data. The main geometric idea is to represent the data as a collection of points in a space that parameterizes congruence classes of triangles in the plane. The distinguishing advantage of this approach is in extracting significant (biological) features and patterns of triangle shapes that are not typically discernible by commonly used statistical analyses. This method is applied to the data set **D**, where a relatively small group of genes are identified and tabulated.

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