

Summary

Our neuroscience-specific translational tools like biomarkers, behavioral and cognitive testing, electrophysiology, and modern neuroimaging methods, can dramatically increase the efficiency of choosing a lead candidate for your program by offering more predictive data than traditional measures.



DISCOVERY

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Neuroscience Translational Tools

Fine Motor Kinematic Analysis

In order to be able to evaluate the effects of pharmacological treatment on motor capabilities, a proper tool should be used. Conventional motor tests, such as rotarod or open field, are often inadequate to capture any notable treatment effects on motor performance. [Fine motor kinematic analysis](#) can investigate subtle, yet highly significant, changes of gait and movement details in rodents. Its sensitivity provides a wide therapeutic window for possible treatment candidates, and also enables assessing pharmacological disruption of motor function.

Many [pharmacological studies](#) with multiple mechanisms of action have been shown to induce motor impairment in mice. More traditional measures tend to evaluate gross motor function and not fine movements. Moreover, the clinical utility of the traditional assays has been questioned, increasing the need to create novel assays that are more sensitive to subtle deficits in motor function.

In the high precision kinematic assay, a mouse is placed on a runway and allowed to walk from one end to the other. The movement of the animal is recorded with a high-speed camera, assessing multiple body parts from three angles allowing for a comprehensive analysis of the motor function. The analysis provides detailed information (e.g, changes in joint angles, trajectories and the acceleration rates of selected body points and their relation to each other, interlimb coordination, etc.). We've shown that, with a number of known psychoactive compounds, the kinematic analysis is more sensitive than traditional motor assays to subtle motor deficits. In addition, by breaking the [behavior](#) into components, we're able to provide a much richer characterization of motor changes.

Assay Principle

The anatomical landmarks of the mouse are marked and followed in freely moving animals as they traverse a brightly illuminated corridor. The movement is recorded with a high-speed camera with a simultaneous recording of three different views. Full-body tracking will be performed with 31 markers in tail, paws, joints, trunk, and head. The analysis of the trajectories will be performed for a number of full gait cycles (i.e., the periods between two consecutive left hind limb floor contacts). For each automatically detected gait cycle, a large number of parameters are determined to characterize the gait properties. In addition, the data are analyzed by principal component analysis to compact the information, identify correlations between original variables, and create a small set of new and more sensitive, uncorrelated parameters.

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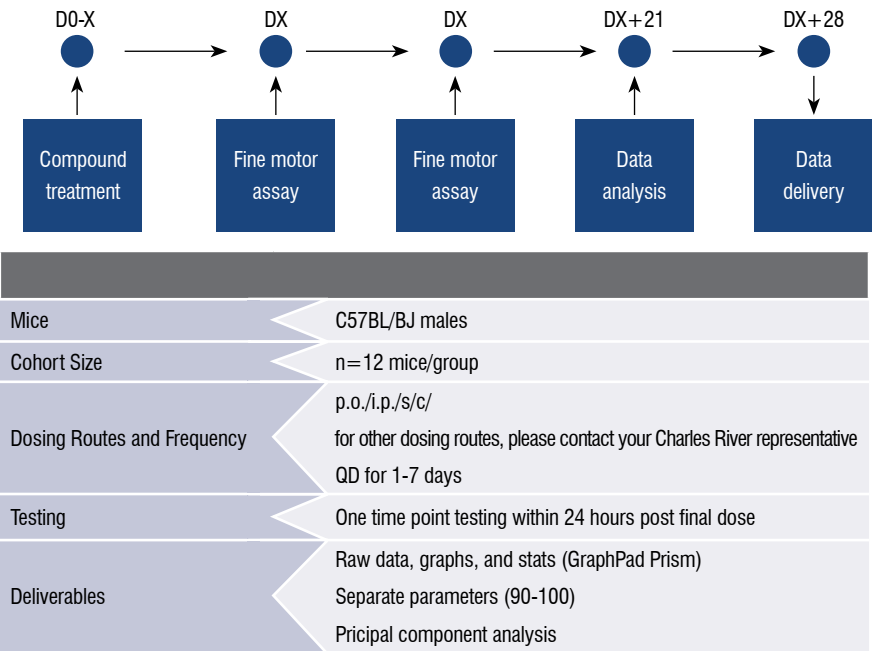
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EVERY STEP OF THE WAY

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Assay Setup



Assay Performance

Performance of C57BL/6J male mice was validated using three psychoactive compounds – amphetamine, morphine, and pregabalin. Each of the compounds had a very distinctive and significant effect on the gait features (Figures 1 and 2).

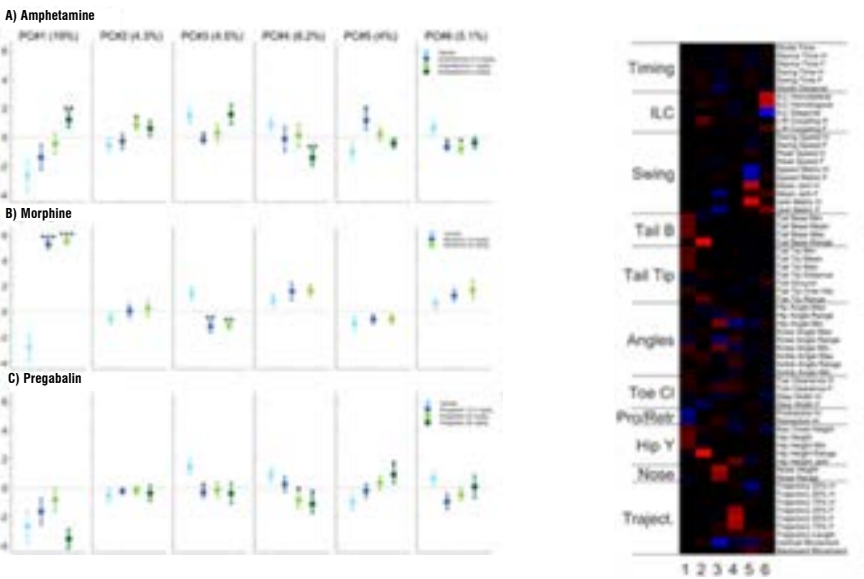


Figure 1. Fine motor and gait profiles of C57BL/6J mice treated with amphetamine (A), morphine (B) and pregabalin (C). Principal component scores (PC #1-6) on the left, and the corresponding principal component vectors (eigenvectors) shown as heat map on the right, describing mutually correlating gait parameters within each PC (red = positive correlation, blue = negative correlation). Numbers in the horizontal axis of the heat map indicate the PC number. The percentage in each panel describes the proportion of variation in the whole data set that each PC comprises. Data are presented as mean ± SEM (* p<0.05, **, p<0.01, ***p<0.001, compared to vehicle treated mice, unpaired t-test). Abbreviations: H – hind limb, F – fore limb

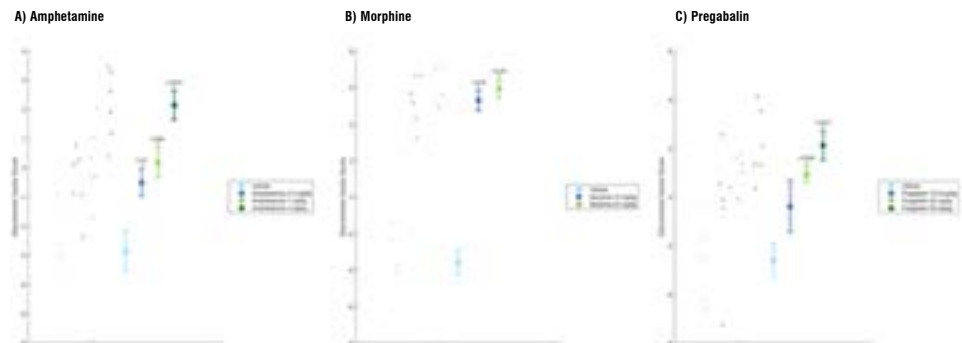


Figure 2. PCA-discriminant vector scores for different groups of C57BL/6J mice treated with amphetamine (A), morphine (B), and pregabalin (C). The score is based on differences between vehicle and drug-treated groups in all the PC scores, giving an overall fine motor kinematic score for each individual and group (* $p < 0.05$, versus vehicle, unpaired t-test).

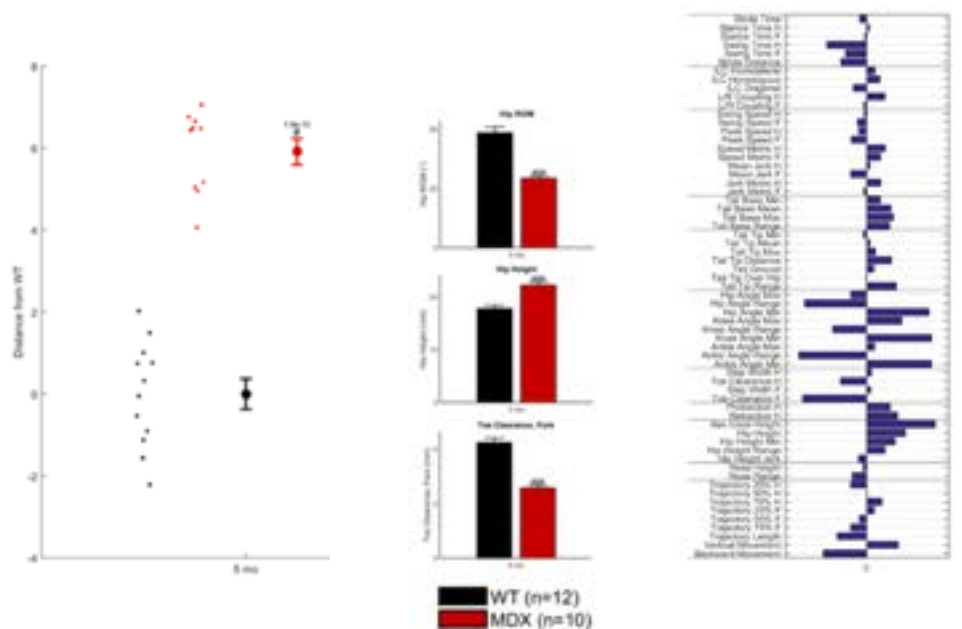


Figure 3. Five-month-old MDX male mice (C57BL/10ScSn-Dmdmdx/J) with progressive muscular dystrophy. This shows strong alterations in lower body posture, which can be seen in increased hip, knee, and ankle extensions, and also in increased overall hip height and decreased fore limb toe clearance, when compared to control mice (C57BL/10ScSnJ). The overall "distance from WT" score separates the groups with a clear margin (on left). The kinematic "fingerprint" (discriminant vector) of an MDX is shown right (middle figure, with most distinct alterations marked in orange). Individual parameters of hip range of movement (ROM), hip height, and toe clearance (fore) are shown on the far right (### $p < 0.001$ unpaired t-test).

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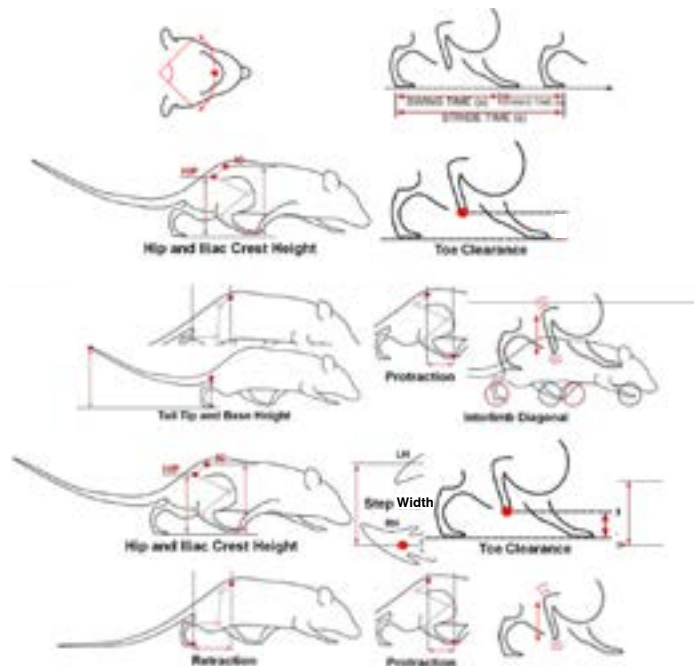


Figure 4. Examples of different kinematic gait parameters offered. Total number of different parameters is over 100. A) General spatio-temporal parameters: stride distance, duration, speed, stance time, and swing time. B) Inter-limb coordination: diagonal cadence, left/right alternation rhythm. C) Swing phase and paw trajectory: swing speed, smoothness, trajectory shape, and abnormality. D) Body posture and joint angles: hip height, tail, head, limb function, gait variability, and deviations.

Summary

[Fine motor kinematic analysis](#) is able to differentiate subtle yet very significant changes induced by pharmacological treatment. As an example, when using reference test articles, the changes are very distinctive for each of the drugs. For amphetamine, the most prominent features were elevated back body posture and decreased horizontal extension of the hind limbs, as well as subtle changes in the shape of paw trajectories. Morphine induced very high and forward tail positioning, but lower positioning of the nose. Pregabalin induced changes in paw trajectory and unstable acceleration of the paw during swing phase.

These results give more information of the fine motor changes induced by psychoactive treatments in mice. Moreover, the data provide further support for using a high precision kinematic assay as a tool for assessing pharmacological disruption of motor function that provides a more sensitive and comprehensive measure than traditional [pharmacological studies](#).

Get actionable data four weeks after the *in vivo* phase of the study.

This specific analysis of rodent movements improves the statistical power for therapeutic studies and detects early gait changes more sensitively than conventional motor testing. Our exclusive motor test uses data from spontaneous locomotion, and doesn't require extensive training or pharmacological induction to use.