Title: Cortisol Response to Standardized Pain and Sensory Examinations in Rett Syndrome

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Introduction: Mutations of the methyl-GpG-binding protein 2 (MECP2) gene account for most cases of Rett syndrome (RTT). Several studies in animal models of RTT have shown abnormal stress responses, characterized by excessive cortisol responses to stress, potentially implicated abnormal programming of the hypothalamic-pituitary-adrenal (HPA) axis in development of some characteristics of RTT, particularly mood disturbance and sleep problems. There is limited information on stress responses in this population, however. This lack of research is potentially attributable, in large part, to difficulties in identifying stress paradigms that can be used in this population due to ethical and practical limitations. In the current study, we investigated cortisol responses to two standardized designed to investigate musculoskeletal pain status and somatosensory function, respectively.

Method: Data from 14 participants with clinical diagnoses of RTT (aged 4-38 years) have been analyzed to date. Each research visit followed a standard sequence: informed consent, a 5-minute baseline period, a standardized range of motion exam designed to evaluate musculoskeletal pain, a 5-minute recovery period, a modified standardized quantitative sensory test (mQST) testing somatosensory function, and a final 5-minute recovery period. Saliva samples were collected at three timepoints throughout the visit: immediately following informed consent (T1), immediately following the sensory exam (T2), and at the end of the visit (approximately 5-10 minutes after T2; T3). Based on the known time course of cortisol responses to stress, the timing of the samples was designed such that T2 should reflect primarily the response to the range of motion exam, and T3 should reflect the response to the mQST. Linear mixed models were used to determine whether there were significant changes in cortisol across the three samples, and to evaluate differences in patterns based on age and parent-reported mood and sleep problems.

Results: The results showed that, on average, there were significant two-way interactions between sample time and mood problems and age. There were no significant effects of sleep problems. Post-hoc analyses showed that individuals with more parent-reported mood symptoms had marginally higher cortisol levels at T1, and although there was a trend towards increasing levels across the three timepoints, these differences were not statistically significant. In contrast, individuals with lower mood symptoms showed a significant increase in cortisol levels from T1 to T2, followed by a drop at T3. The results for age suggested that younger individuals showed significant increases from T1 to T2, and from T2 to T3, whereas older individuals showed an increase from T1 to T2, followed by a decrease from T2 to T3, although none of these changes were significant.

Discussion: These results show that both the standardized range of motion exam and the mQST protocol produce significant changes in cortisol concentrations among individuals with RTT, although the specific patterns differ based on both age and mood problems, although we did not observe any relations with parent-reported sleep problems. Preliminary evidence suggests that younger individuals may respond more to the mQST protocol than older individuals, which is consistent with our observations of behavioral responding, and may suggest a loss of tactile sensitivity over time in this population. Overall, these findings suggest that these assessments may be feasible and useful in the assessment of stress reactivity among individuals with RTT. Subsequent analyses will include assessment of relationships between cortisol responses and behavioral reactivity during each protocol.

References/Citations: