Cockayne Syndrome-derived neurons display reduced synapse density and altered neural network synchrony.

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Public Summary:
This work described defects in neuronal networks derived from patients with Cockayne syndrome. The cellular and molecular phenotypes described here could be used to screen novel drugs to treat this condition and might be useful to other neurological disorders.

Scientific Abstract:
Cockayne syndrome (CS) is a rare genetic disorder in which 80% of cases are caused by mutations in the Excision Repair Cross-Complementation group 6 gene (ERCC6). The encoded ERCC6 protein is more commonly referred to as Cockayne Syndrome B protein (CSB). Classical symptoms of CS patients include failure to thrive and a severe neuropathology characterized by microcephaly, hypomyelination, calcification and neuronal loss. Modeling the neurological aspect of this disease has proven difficult since murine models fail to mirror classical neurological symptoms. Therefore, a robust human in vitro cellular model would advance our fundamental understanding of the disease and reveal potential therapeutic targets. Herein, we successfully derived functional CS neural networks from human CS induced pluripotent stem cells (iPSCs) providing a new tool to facilitate studying this devastating disease. We identified dysregulation of the Growth Hormone/Insulin-like Growth Factor-1 (GH/IGF-1) pathway as well as pathways related to synapse formation, maintenance and neuronal differentiation in CSB-neurons using unbiased RNA-seq gene expression analyses. Moreover, when compared to unaffected controls, CSB-deficient neural networks displayed altered electrophysiological activity, including decreased synchrony, and reduced synapse density. Collectively, our work reveals that CSB is required for normal neuronal function and we have established an alternative to previously available models to further study neural-specific aspects of CS.