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SUDEP: The Worst in Epilepsy and the Hardest to Image

Altered Brain Connectivity in Sudden Unexpected Death in Epilepsy (SUDEP) Revealed Using Resting-State fMRI

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The circumstances surrounding sudden unexpected death in epilepsy (SUDEP) suggest autonomic or respiratory collapse, implying central failure of regulation or recovery. Characterization of the communication among brain areas mediating such processes may shed light on mechanisms and noninvasively indicate risk. We used rs-fMRI to examine network properties among brain structures in people with epilepsy who suffered SUDEP (n = 8) over an 8-year follow-up period, compared with matched high- and low-risk subjects (n = 16/group) who did not suffer SUDEP during that period and a group of healthy controls (n = 16). Network analysis was employed to explore connectivity within a "regulatory subnetwork" of brain regions involved in autonomic and respiratory regulation and over the whole brain. Modularity, the extent of network organization into separate modules, was significantly reduced in the regulatory subnetwork, and the whole-brain, in SUDEP and high-risk groups. Increased participation, a local measure of intermodular belonging, was evident in SUDEP and high-risk groups, particularly among thalamic structures. The medial prefrontal thalamus was increased in SUDEP compared with all other control groups, including high-risk group. Patterns of hub topology were similar in SUDEP and high-risk groups but were more extensive in low-risk patients who displayed greater hub prevalence and a radical reorganization of hubs in the subnetwork. Sudden unexpected death in epilepsy is associated with reduced functional organization among cortical and subcortical brain regions mediating autonomic and respiratory regulation. Living high-risk subjects demonstrated similar patterns, suggesting such network measures may provide prospective risk-indicating value, though a crucial difference between SUDEP and high-risk groups was altered connectivity of the medial thalamus in SUDEP, which was also elevated compared with all subgroups. Disturbed thalamic connectivity may reflect a potential noninvasive marker of elevated SUDEP risk.

Commentary

Sudden unexpected death in epilepsy (SUDEP) is the most devastating consequence of this debilitating disorder. It is sadly not uncommon, particularly in young individuals with drug-resistant epilepsy who experience generalized seizures. Estimates begin at approximately 1 death per 1000 person-years but range up to 10 times that number in high-risk patients who are candidates for epilepsy surgery.[1] The pathophysiology of SUDEP remains poorly understood and is exceedingly difficult to study because we do not prospectively know which patients will succumb to it. Therefore, human investigations of brain networks involved in SUDEP are very rare, and the few neuroimaging studies of patients who have died largely consist of retrospective identification of structural magnetic resonance imaging (MRI) data collected during clinical evaluation.

In the highlighted manuscript, Allen and colleagues report the first, to my knowledge, functional MRI (fMRI) study of resting state networks in patients who died of SUDEP. The authors have led a long-standing simultaneous fMRI-electroencephalography study examining interictal discharges in epilepsy and have collected data on many high-risk patients using consistent imaging techniques.[2] By searching databases for deaths among patients they had imaged over 8 years, the investigators identified 8 patients who likely died of SUDEP, including 4 "definite" cases and 4 "probable" cases. These patients had a mean age in the mid-20s and included 4 females, and 6 patients had focal epilepsy while 2 suffered from juvenile myoclonic epilepsy. All individuals experienced approximately one or more generalized seizures per month. The patients were studied with a 10-minute resting state fMRI scan, utilizing relatively common data collection and preprocessing protocols. Importantly, the authors also identified 2 other groups of 16 patients deemed to be high or low risk for SUDEP, as well as a healthy control group for comparison.

In their analyses, Allen and colleagues focused on regions in the "regulatory subnetwork" which play an important role in cardiovascular and respiratory control. This subnetwork included structures in the medial/orbitofrontal cortex, insula,

cingulate cortex, mesial temporal lobe, basal ganglia, and thalamus. Various graph theory measures were utilized to compare connectivity in this network and across the whole brain between subject groups. The authors found reductions in modularity but increases in participation in the subnetwork in patients with epilepsy, which was most marked in the SUDEP and high-risk patient groups. This may suggest that high-risk patients have impaired subnetwork organization but also an increased diversity of nodes which are more likely to participate in other modules. The abnormal increase in participation was most apparent in medial thalamic nuclei with prefrontal connections, where altered connectivity was more specific to patients who suffered from SUDEP. Also, both SUDEP and high-risk cases demonstrated similar alterations in degree centrality of several subnetwork nodes, some of which correlated with baseline frequency of generalized seizures.

The authors argue that their results suggest impaired communication in regions involved in respiratory and cardiovascular regulation that may shed light onto processes underlying SUDEP. Most of the largest network alterations were seen in both patients who died and those in the high-risk group, which raises the question of whether these changes are more simply related to a higher frequency of generalized seizures. However, alterations in the intermodular properties of the medial thalamus were larger in patients who died, even when compared to high-risk individuals. The present authors and others have also previously described volumetric and functional changes in the thalamus in patients with drug-resistant epilepsy who may be at high risk for SUDEP.[2,3] Next, the investigators found connectivity alterations in bilateral medial amygdala in SUDEP and high-risk individuals. This is an important observation given that stimulation of the medial amygdala has been shown to produce apnea in patients with epilepsy,[4] and seizure spread to amygdala may correlate with ictal apnea.[5] These findings raise hope that neuroimaging biomarkers of SUDEP risk may one day be achievable, in order to identify patients who require the closest monitoring.

One important limitation of this work by Allen and colleagues is that the brainstem was not included in the functional imaging. Evaluation of brainstem networks will likely be critical to better understand SUDEP mechanisms because of both autonomic and respiratory centers in the lower brainstem and the ascending arousal pathways in the upper brainstem. It is possible that SUDEP involves not only seizure-induced hypoventilation but also a subsequent failure of normal arousability from hypercapnia, which requires in part the brainstem ascending reticular activating system (ARAS).[6] Previous MRI work has uncovered brainstem atrophy in patients with focal epilepsy who died of SUDEP,[7] which may lead to destabilization of functional interactions between the brainstem and neocortex.[8] Furthermore, both functional and structural connectivity decreases have been described in brainstem ARAS nuclei in patients with drug-resistant temporal lobe epilepsy, and some of these changes may be related to seizure generalization and disease severity.[9] Finally, the central nucleus in the medial amygdala, which may play a role in ictal apnea, has dense projections to brainstem ARAS and autonomic nuclei.[10] Evaluation of brainstem functional connections will be an important goal in future neuroimaging studies of SUDEP.

Despite these limitations and the understandably small sample size, the study by Allen and colleagues marks a critical first step to uncovering the potential network underpinnings of SUDEP in humans. With an increasing number of centers pursuing functional neuroimaging studies of patients with epilepsy, it will be important for the community to identify a larger number of data sets belonging to individuals who ultimately succumb to this horrible fate. Sudden unexpected death in epilepsy truly represents the worst in epilepsy, but stopping it must begin with understanding it.

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