Thinking of epilepsy as a symptom.

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S_dHIELD (Social **d**eterminants of **H**ealth **I**n **E**pi**L**eptic **D**isorders**) Research G**roup*

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Comorbidity as a concept arose in the 1970s as research transitioned from investigating infectious diseases to chronic illnesses. The initial comorbidity definition was "*any distinct additional clinical entity that has existed … during the clinical course of a patient [with] the index disease*".[1] Comorbidity has since become commonplace in medical vocabulary. It encompasses conditions, complications, causes, signs, and symptoms co-occurring with a disorder of interest.[1]

Historically, epilepsy was thought to impact individuals mainly through a predisposition for unprovoked seizures. Recently, ever-increasing evidence has highlighted the high prevalence of numerous comorbidities in epilepsy, to the point that comorbidities have now become a defining feature of epilepsy.[2]

Conceptualising epilepsy as an index disease to various comorbidities has been clinically helpful and has driven research. We now recognise, however, challenges with this conceptualisation. Notably, a narrow focus on seizures oversimplifies epilepsy relationships with co-occurring conditions. Epilepsy is not always "the root of the problem", nor is it an inherently homogeneous disorder.[3] Different epilepsy types may be associated with varying profiles of co-occurring conditions. Many of these conditions may be risk factors which, when present in sufficient quantity or importance, lead to epilepsy.[3] The social determinants of health (SDH) may follow this pattern.

We argue for the need to refocus on epilepsy as a "symptom" rather than as an index disease to a set of comorbidities. This could deepen our understanding and improve the management of epilepsy, its associated conditions, and the SDH.

Comorbidities: what are they, and how do they occur?

Comorbidity's original definition, albeit broad, is still used, perhaps due to its simplicity and versatility.[1] Comorbidities are not required to have a temporal or pathophysiological link with an index disease. Conditions arising before, during, or after an index disease and seemingly unrelated to an index disease can all be considered comorbidities.[1] The "index disease" notion is vague, and there is no consensus on the criteria to identify it.

Once an association between conditions is established, the putative associative mechanisms must be explored. We have previously presented a classification scheme for these association mechanisms, which we update in **Supplementary Figure 1**[2]. It is tempting to presume that epilepsy is causally upstream to its comorbidities, but this is not always the case. The association mechanisms at play can be much more intricate, with comorbidities playing a causal role in epilepsy.[2]

Epileptogenesis

Epileptogenesis is a dynamic, progressive process of brain structural, functional, and/or network changes leading to spontaneous seizures. Epileptogenesis pertains to structural (acquired) and

genetic epilepsies, although it has classically been assessed in the context of structural epilepsies, such as post-traumatic epilepsies.[4]

The two-hit hypothesis, popularised in oncology over 50 years ago, has resurfaced in discussions around epileptogenesis.[5] This hypothesis stipulates that both alleles of most tumour suppressor genes must be inactivated for the phenotype to change. The first allele could be turned off due to a germline mutation, and the second due to a somatic mutation or epigenetic silencing.[5] There is evidence that this two-hit model generates focal cortical dysplasia (FCD), a common cause of focal epilepsy.[6] The question then becomes whether this two-hit model can extend beyond genetic/epigenetic "hits" and can apply to other epilepsy forms.

A combination of a first germline mutation with a second somatic mutation may cause FCD, but not everyone with FCD has epilepsy. The prevalence of asymptomatic FCD is unknown but may be higher than anticipated. There is some evidence that up to a third of children with FCD might not have epilepsy.[7] FCD may be inactive in some people without additional "hits", such as traumatic brain injury (TBI).[8] One can presume that other comorbid conditions may also operate as additional "hits" and that multiple "hits" may act in tandem to generate epilepsy. As such, the two-hit model oversimplifies epileptogenesis, and a more nuanced model for causality would be helpful.

The sufficient-component cause model

The sufficient-component cause (SCC) model is a popular epidemiological causation model.[9] This model, depicted in **Figure 1a**, stipulates that different determinants can act together to produce a disease. A "sufficient cause" consists of a minimum set of "component causes", which, when all present, inevitably generate a disease. One component cause may be all that is needed to cause a disease, as is the case in several monogenic epilepsies. Alternatively, one disease may have many sufficient causes, such as how different pathogenic genetic variants may lead to FCD. When a component cause is present in all these sufficient causes, it is deemed a "necessary cause." In neurocysticercosis, ingesting *Taenia solium* eggs would be a necessary cause.

The SCC model suits epilepsy. Epileptogenesis relies on a complex interplay of component causes. A structural brain lesion alone may be a sufficient cause for epilepsy in some people, but others may require some precipitating factors to generate epilepsy. Similarly, although two people may have the same cause for their epilepsy, one may have drug-resistant epilepsy, whereas the other does not. Several comorbidities have been suggested to cause, precipitate, or worsen epilepsy. The association mechanisms behind many of these comorbidities remain unknown.[2]

Epilepsy as a symptom: a paradigm shift

There are challenges with conceptualising epilepsy as an index disease to a set of comorbidities. Firstly, this model often conjures up the mental image of a web, with epilepsy at the centre and

comorbidities in the periphery. Some may erroneously conclude that epilepsy is more important than or causally upstream to its comorbidities. Epilepsy specialists might be at risk of such misperceptions, demoting the importance of the comorbidities. Secondly, the mechanisms of association between epilepsy and other disorders can be intricate, with many such disorders possibly contributing to epileptogenesis. A model focusing on comorbidities as potential component causes of epilepsy would be harmonious with our understanding of epileptogenesis. Thirdly, epilepsy is heterogeneous, and comorbidities may relate differently to different epilepsy types. Several comorbidities may even be specific to certain epilepsy syndromes. A conceptualisation which directly integrates this phenotypic variability would be ideal.

Some consider epilepsy a disease, a term usually understood to represent a disorder with recognisable signs and symptoms. A disease is a biological process leading to noticeable manifestations: the symptoms. Epilepsy, in its most elementary form, is a predisposition for unprovoked seizures. We argue that this predisposition is not a disease alone but should be understood as a symptom (i.e., a manifestation of underlying biological processes).

The case against defining epilepsy as a disease is strong. Misdiagnosis is common, and epilepsy definitions and classification schemes change over time.[3] Epilepsy is a manifestation of numerous causal mechanisms and may present itself differently depending on risk factors or aetiology.[2] Defining epilepsy as a disease implies its symptoms are solely due to epilepsy, which may be incorrect. These symptoms may instead be due to the underlying epileptogenic process, a process which includes comorbidities.

Focusing on epilepsy as a symptom of biological processes, each with its causes (see **Figure 2b**), solves the challenges of viewing epilepsy as an index disease to a set of comorbidities. Epilepsy is no longer at the model's centre but is the byproduct of many component causes, consistent with the SCC model.[9] Epilepsy can easily be regarded as a comorbidity itself, which may push us to investigate conditions co-occurring with epilepsy as index diseases in their own right. A focus is put on co-occurring disorders contributing to the causal pathways leading to epilepsy, but other association mechanisms still have their place.[2] Conceptualising epilepsy as a symptom recognises the heterogeneity of diseases and other component causes which lead up to it. There is also recognition that unprovoked seizures may be one of the many manifestations of a joint, underlying biological process.

The social determinants of health

A strength of the “epilepsy as a symptom” model is its fluid integration of the SDH as component causes. Epilepsy remains a condition more often seen among people of lower socioeconomic status, with an almost double incidence in low- and middle-income countries (LMIC) versus high-income countries (HIC).[10] In HIC, socially disadvantaged individuals are more likely to develop seizures than their wealthier counterparts.[11] Surprisingly, little is known about the nature, causes, and consequences of health inequities in epilepsy.[12] Income disparities

are the most reported inequity, but the SDH encompass many lesser explored inequities, such as those due to race/ethnicity and biological sex.[12]

Considering epilepsy as possibly resulting from the SDH stresses the importance of these determinants in epileptogenesis, urging further research on more equitable epilepsy care. Investigating the SDH may also be a path forward to determining more preventable causes of epilepsy and predictors of outcome. There has been, for instance, a recent surge of interest in the role of air pollution in epilepsy.[13] If an association is proven, the global public health implications could be substantial, as pollution is more prevalent in poorer regions. In 2021, 80% of people exposed to unsafe air pollution levels lived in LMIC.[14] Air pollution is a common risk factor for other health conditions such as stroke and heart disease, which only further prompts research on its role in epilepsy.[13]

In 2022, the WHO, recognising the disparities in epilepsy knowledge, care, and research, issued the Intersectoral Global Action Plan on epilepsy and other neurological disorders (IGAP).[15] This document has set 10-year targets to bridge knowledge and treatment gaps worldwide. With a 90-80-70 target, the IGAP aims for 90% understanding of the treatable nature of epilepsy, 80% access to safe antiseizure medications, and 70% seizure control. For this, efforts to understand the social structures underlying inequities in epilepsy care at the global and local levels are necessary. Viewing epilepsy as a symptom partially resulting from the SDH can empower the epilepsy community to advocate for more equitable care and destigmatisation efforts with policymakers.

It is time to move beyond a simplistic view of epilepsy comorbidities. Epilepsy should be considered a symptom rather than an index disease. We believe this conceptualisation may breathe new life into research on the association between epilepsy and other conditions. The use of the word “symptom” to describe epilepsy is purely conceptual. Some experts may prefer another term. Ultimately, this framework should compel the scientific community to think of epilepsy as the comorbidity of other disorders rather than the opposite, driving a focused investigation into the role of the SDH in epilepsy.

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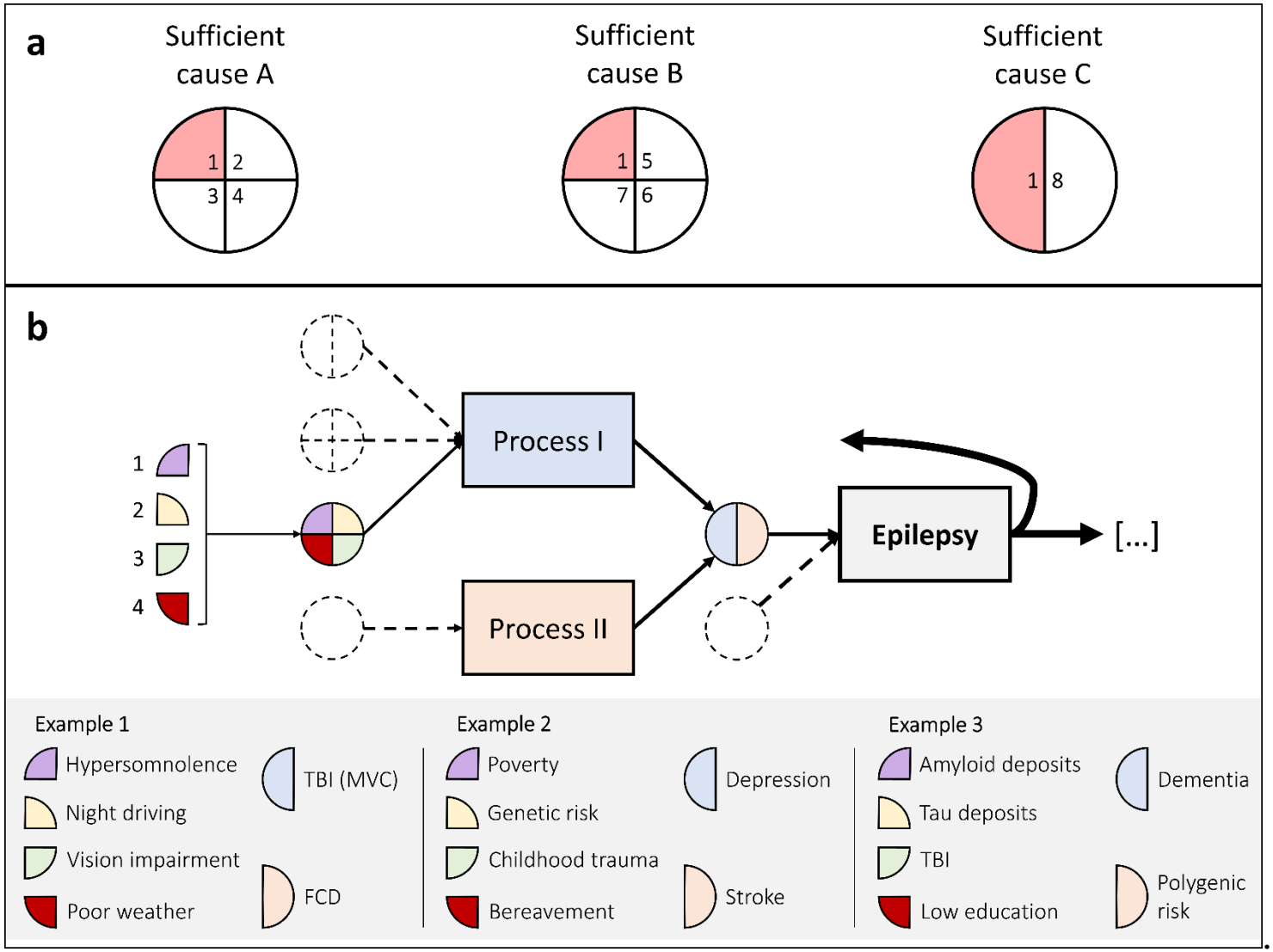
Figure 1: (a) The sufficient-component cause (SCC) model. (b) Framework for epilepsy as a symptom, inspired by the SCC model



(a) Introduced by Rothman in 1976, the SCC (also known as the causal pie model) is a general epidemiological causation model. Each complete pie represents a “sufficient cause” leading inevitably to the development of a particular disease. Each slice of a pie is a “component cause”, which, when merged with other such slices, can form a sufficient cause. When a component cause is present in every sufficient cause for a disease, it is deemed a “necessary cause.” In this figure, three sufficient causes (A, B, C) are presented along with eight component causes (1-8) and one necessary cause (in red). Each sufficient cause showcases a different combination of component causes.

(b) Epilepsy is depicted as a manifestation of one or more pathogenic processes. Some of these processes, such as brain infections/infestations, can be considered diseases, whereas others, such as polygenic risk or poverty, may be more challenging to define. Borrowing ideas from the SCC model, these processes represent component causes which may form alone or in combination with other component causes a sufficient cause to produce epilepsy. Each pathogenic process may result from one or more sufficient causes, each with one or more component causes. This exercise of identifying the causes of causes can continue until an entire, hierarchical “causal tree” is completed. In this figure, component causes are identified as pie slices, and sufficient causes are identified as complete pies. Epilepsy has consequences (thick arrows on the right) which may or may not involve its underlying pathogenic processes. For simplicity’s sake, only two processes (I and II) and one sufficient cause of process I (component causes 1-4) are detailed here. Using this simplified structure, three hypothetical scenarios where different causes act together to generate epilepsy are depicted. Elements in dashed lines represent additional hypothetical causes of epilepsy omitted from the Figure. FCD = focal cortical dysplasia; MVC = motor vehicle collision; TBI = traumatic brain injury.