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Early prediction and psycho-immunologic mediation of minor illness in adulthood

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ORIGINAL ARTICLE

Abstract

BACKGROUND: The Barker Hypothesis suggests that an unfavourable uterine environment can have the effect of programming the body for disease later in life. Research indicates a bidirectional relationship between thought and biochemical reactions, that may be influenced by early programming. Reports suggest that 25% of variance in birthweight is a result of foetal environment and that the health and cognitive deficits do not just affect those with an officially low birthweight.

OBJECTIVE: This study investigates the influence of birthweight on cognition and minor illness in adults.

METHODS: This is a retrospective, cross sectional design with an opportunity sample of 75 adults. Participants whose birthweight ranged from 2.5 kg to 4.88 kg, completed a symptom check list and general self-efficacy scale, reporting on the previous month.

RESULTS: Analysis of variance indicates that those with higher birthweight have fewer minor illness symptom days and higher general self-efficacy. Regression analysis indicates that birthweight is significantly predictive of levels of minor illness and general self-efficacy.

CONCLUSION: From the findings of this and previous studies, it is possible to infer vertical coactions between foetal environment and immuno competence. It is suggested that birthweight is an early predictor of levels of a cognitive mediator and minor illness. Data were applied to an equilibrium model to represent the relationship in terms of Gottlieb's concept of horizontal and vertical coactions.

Introduction

Psychoneuroimmunology

Psychoneuroimmunology (PNI) investigates interactions between neural and neuroendocrine systems, psychological function and immunity [1]. The immune system works in two ways. Humoural immunity is most effective in dealing with pathogens that are still outside the body's cells. Here antibodies are secreted that bind to pathogens rendering them inactive. With cell-mediated immunity, immune cells destroy the pathogen along with the host cell it has invaded. This is most effective in dealing with pathogens that have entered the body, such as virus and bacterial infections [2].

The immune system can fail in one of two ways. First, it may not be vigilant and allow pathogens to enter the body, or it could be over vigilant, so that the immune system itself is causing illness as in autoimmune disease. Secondly, it can become unbalanced; when one branch of immune function is operating, cytokines are produced that inhibits the alternative branch. When operating normally, a person will fluctuate between the functions over a 24 hour period. However, stress and other psychological attributes such as cognition and emotion can influence the balance.

Stress for example can cause an increase in T-helper2 cells [3]. The presence of T-helper2 cells indicates an increase in humoural immunity and associated decline in cell-mediated immunity [1]. Short term stressors have the effect of promoting antibody production in saliva (SIgA) whilst long term stressors depress it [4].

Likewise, a small increase in stress in normal circumstances results in increases in catecholamines and enhanced performance, whereas in already stressful conditions, increased catecholamine production results in deterioration of mental function and dysfunctional behaviour. One of the functions of catecholamine secretion in the "fight-or-flight" response to stress is to increase heart rate, reduce blood flow to major organs and make blood more prone to clotting thus reducing danger of heavy bleeding in case of injury. At the same time however, this increases the risk of arterial obstruction, hypertension and myocardial infarction. In response to physical threat, catecholamines provide an efficient mechanism for survival should the organism need to fight or flee. However, in modern society, threat is more likely to be of a social or mental nature rather than physical [5].

Secretion of catecholamines is regulated by the influence of the cortex on the hypothalamus in the central nervous system. Research indicates that certain variables predict responses to stimuli and have a buffering effect on cardiovascular, endocrine and immune function. These variables include coping, optimism [6] and self-efficacy [7], which have been experimentally linked to a number of biochemical changes in stress situations. Interactions influencing levels of health and minor illness are many and complex, and it is possible that predictors are a result of early life coactions.

The association between birthweight and major disease such as coronary heart disease in later life has been confirmed by epidemiological studies [8]. Size at birth is determined by interactions between the intrauterine environment and the foetal genome, with 25% of the variance arising from environment [9]. Birthweight has also been associated with minor illness in adulthood [10], where it was argued, that foetal programming may have resulted in compromised immunocompetence.

Minor illnesses such as common cold, upper respiratory tract infection (URT) and 'flu have frequently been investigated in PNI research, as they are relatively common in the population, are influenced by psychological factors [1] and are known to be associated with changes in immune function such as increased levels of T-helper2 cells [3]. The purpose of this report is to extend a previous study [10] by investigating an additional cognitive variable and applying data to a model representing psycho-immunologic coactions. The assumptions are that according to Barker's Hypothesis, in unfavourable conditions, blood may be diverted from one part of the developing foetus, e.g. the pancreas, in order to protect the growth of another part e.g. the brain. This diversion or foetal compensation can leave the body programmed for future illness and reduced cognitive function.

The Baby In The Womb, *In Utero* Coactions And Adult Minor Illness

Gottlieb's [11,12,13] theory of experiential canalization defends that epigenesis is probabilistic and views the individual as an "emergent, coactional, hierarchical system". The consequence of horizontal (e.g. cell to cell) and vertical (e.g. cell to environment) coactions is the emergence of new structural and functional properties [14].

Examples of these new structural and functional properties are reported by Gupta [15] who presents evidence from human and animal studies. He suggests that an imbalance of foetal neurotransmitter production can influence later life e.g. possible gender identity influences, sterility in male rats, anxious and depressed behaviour in animals. Also, low secretions of hormones and neurotransmitters produced by the central nervous system and pineal gland can affect the immune system and leave person susceptible to many infections.

The link between birthweight and major disease is well established [8]. Bellingham-Young & Adamson-Macedo [10] reviewed a number of studies which suggested that through a process of foetal compensation, (the diversion of nutrients to protect development), environment may affect immune function. Evidence was presented that lower birthweight was predictive of some types of minor illness in adulthood. The population in that study were above 2.5kg low birthweight, and as far as we are aware, this was the first indication that health deficits (i.e. minor illnesses) of foetal programming continued into the range of normal birthweight.

Psychological Links To Early Environment

Low IQ, and cognitive deficits have been found in children with low birthweights both in performance and verbal IQ [16]. Studies suggest a linear relationship between birthweight and intelligence that continues into the normal birthweight range [17,18,19,20,21]. These findings hold when controlling for external factors such as social class and family environment. Matte et al. [22] reported a linear relationship between neuropsychological assessments at age 7. A 1000g increase in birthweight relates to a 4.6 point increase in IQ for boys and a 2.8 point increase for girls. Analysis with same sex sibling pairs suggests a causal relationship between birthweight and IQ.

A further study demonstrated a linear relationship between birthweight and cognitive function up to the age of 43 years, although the effect was less marked at age 43 than 26 [23]. This relationship was found not only in those with low birthweight, but also those with a birthweight of 2.5 kg and above.

Literature thus suggests a relationship between birthweight and cognitive function, even where weight at birth is normal; a lower birthweight is associated with lower IQ. This relationship remains when confounding variables are controlled for and the deficit remains in adulthood.

One of the most popular constructs investigated in the health psychology arena is that of the cognitive mediator self-efficacy. A large body of research is dedicated to various aspects of self-efficacy theory and the influence on health and health behaviours [24], and as mentioned briefly in the previous section, is associated with a number of biochemical effects which will be discussed in the next section.

General Self-efficacy

Self-efficacy is a cognitive behavioural construct which makes the difference on how people think, feel and act. Proposed initially by Bandura [25], self-efficacy influences health by buffering against stress and negative emotions [7]. Exposure to stressors with a perceived inefficacy to control them, activates autonomic, catecholamine and opioid systems, impairing immune function [7]. In experiments, the range of perceived coping self-efficacy was predictive of catecholamine levels when exposed to a phobic threat. Levels of epinephrine, norepinephrine and dopac were low when phobics coped with tasks, but increased substantially when efficacy to cope was low [26]. Increased coping self-efficacy has also been shown to have an immunoenhancing effect; plotting increased levels of Lymphocytes, total T-cells and Helper T-cells over time as coping self-efficacy increased [26].

The experiments described above measured domain specific self-efficacy, Schwarzer [28] however argues that self-efficacy can also be a general construct, concerned with a broad and stable sense of personal competence, involving optimistic resource beliefs and optimistic action beliefs. This differs from optimistic personality trait and Seligman's [29] explanatory style and learned optimism which requires a person to imagine an event has already happened before deciding on actions. Schwarzer's concept of optimistic beliefs posits that future actions and outcome beliefs are based on previous experience.

The relationship between thoughts and beliefs and biochemical responses is bi-directional. For example, cytokines have a direct effect on the central nervous system and on behaviour by affecting the hypothalamus; indirect influence on behaviour is through the neuroendocrine network [6]. Increased levels of cytokines have also been associated with major depression. Another chemical associated with depression is serotonin. It is known from animal and human studies that foetal compensation reduces production of serotonin, [15]. Once serotonin was depleted in young monkeys it remained low for a long time [30].

Studies cited in the previous sections suggest that birthweight is associated with reduced cognitive ability and disrupted neurotransmitter secretion. As there is a bi-directional relationship between cognition, biochemical and immunologic responses, it is plausible to consider that birthweight may be linked to a cognition involving optimistic beliefs. The stability of general self-efficacy over time and age have been well documented [31,32,33], so even though optimistic beliefs are based on experience, levels of those beliefs may be set at an early age.

An Equilibrium Model For Minor Illness

In studying psychological and physiological relationships in pre-term neonates, Adamson-Macedo [34,35] proposed The Equilibrium Model (ThEM) to represent a state of balance between behavioural, immunological and endocrinological functions. That model is based on Gottlieb's [12,13,14] theory of experiential canalization which posits the concept of horizontal and vertical coactions. Using three dimensional space, and hypothetical values, the model demonstrated that change on one or more axes influenced movement along the other axes, see [35] for a full description.

A secondary purpose of this report is to present an Equilibrium Model for Minor Illness Mediators (EMMIM), which develops Adamson-Macedo's original model by applying actual data to the three axes, and computing the value of compound angle ∂ as a way of demonstrating individual differences in minor illness and other variables.

This study tests the hypothesis that birthweight is an early predictor of minor illness in adulthood which is psycho-immunologically mediated. It is anticipated that as the immune system is compromised by foetal compensation, lower birthweight will be associated with higher rates of minor illness. Based on the idea that levels of optimistic self-beliefs may be influenced by serotonin secretion, which is known to be disrupted by foetal compensation, it is expected that lower birthweights will be associated with lower levels of general self-efficacy. A related construct, perceived coping self-efficacy has been linked experimentally to changes in biochemical and immune function, so it is expected that low general self-efficacy will be linked with increased levels of minor illness.

Methods

Design. Data were collected as part of a larger study. In the demographic details, participants were asked to state their birthweight, with an option of "don't know". This is a retrospective design, with participants reporting symptoms for the previous month.

Participants. An opportunity sample of 78 students (63 female, 15 male) with a mean age 25.33 standard deviation 8.96 took part in study. Birthweight ranged from 1.93 kg to 4.88 kg., as this study is interested in participants who are not officially low birthweight, those under 2.5 kg were excluded. The remaining 75 had a mean birthweight of 3.4 kg., median of 3.31 kg., and mode 3.18 kg.

Measurements. Minor illness symptom check list developed by Bellingham-Young & Adamson-Macedo [10] was used. This measures minor illness in 8 categories: Common cold or upper respiratory tract infection (URT), digestive illness, skeletal problems, cough and sore throat, sinus problems, allergic reactions, sleep problems and miscellaneous illness.

General self-efficacy was measured using a scale developed by Jerusalem and Schwarzer [36]. This is a 10 item Likert-type scale with responses ranging from "Not at all true" to "Very true". Items include statements such as "*I can always manage to solve difficult problems if I try hard enough"* and *Thanks to my resourcefulness , I know how to handle unforeseen situations"*.

Data analyses. Since the median is a measure of central value it was used as a cut off point to identify 2 groups. Group 1 with a birthweight below the median of 3.31 kg had 36 participants; group 2 with a birthweight above the median had 39 participants. Factorial one way (1 x 2) analysis of variance (ANOVA) was used to establish whether membership of birthweight group can account for the variance in reports of minor illness and general self-efficacy. A series of linear regressions were carried out to identify minor illnesses that could be predicted by membership of birthweight group.

Results

Figure 1 shows the mean scores for the high and low birthweight groups. Results of a one way Factorial ANOVA (1x2) indicate that those in the lower birthweight group reported more upper respiratory tract infection [F (1,71) = 7.10; p = .009] cough and sore throat [F (1,71) = 4.22; p = .005] sinus problems [F (1,71) = 5.43; p = .023] and lower general self-efficacy [F (1,71) = 8.56; p = .005].

Results of linear regression confirm that the variances revealed by the ANOVA can be predicted by membership of birthweight group. Membership of the lower birthweight group is significantly predictive of higher incidence of URT illness ($b = -.29$, $r^2 = .08$, p = .009) cough and sore throat ($b = -.23$, $r^2 = .05$, p = .043) and sinus problems ($b = -.26$, $r^2 = .07$, p = .023). Mem-

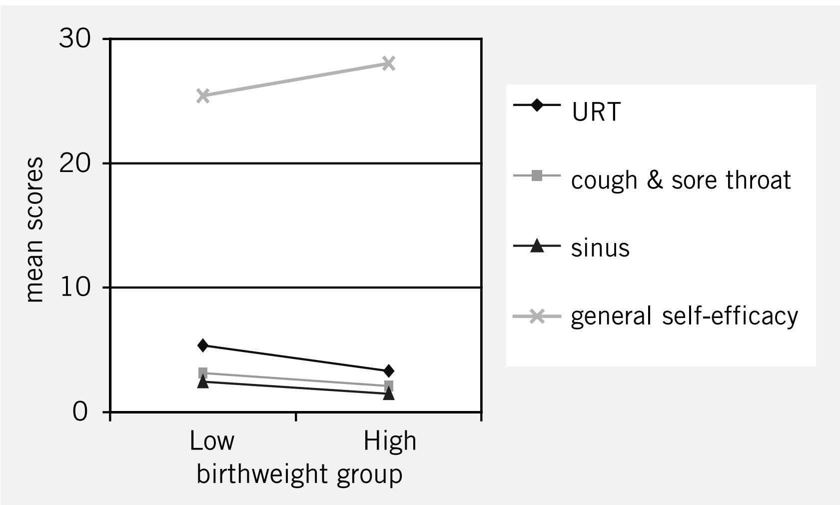

Figure 1. Mean number of symptom days and general self-efficacy for high and low birthweight groups.

bership of this group is also predictive of lower general self-efficacy ($b = .32$, $r^2 = .10$, p = .005).

Unexpectedly, there was no relationship between general self-efficacy and minor illness symptom days. This may be a result of measuring the general form of self-efficacy, a point that will be explored in the discussion. These data will be applied to the new model (EMMIM) to demonstrate the coactions between variables and immunologic mediators.

Table 1. Values for ***Y, X*** and ***Z*** axes of Equilibrium model for minor illness mediators.

	Participant 1 (MI1)	Participant 2 (MI2)
Y = minor illness symptom days	42	9
X = general self-efficacy	21	32
Z = birthweight kg	2.72	3.63

Applying Data To A New Equilibrium Model. In order to demonstrate individual differences, data from 2 participants were applied to a new Equilibrium Model for Minor Illness Mediators (EMMIM). The *Y* axis represents the number of minor illness symptom days, *X* the general self-efficacy score, *Z* the birthweight, as can be seen in Table 1 above.

Figure 2 below shows EMMIM utilising the co-ordinates from Table 1. Adamson-Macedo's original model has been enhanced by depicting the parallelepipeds which appear in three dimensional displays. Horizontal and vertical coactions are demonstrated by movement along one or more axes, the position of co-ordinates along the axes, determining the shape and size of the parallelepipeds. The number of minor illness symptom days causes the dotted line parallelepiped of MI_1 to be taller than the solid line parallelepiped of MI_2; lower values for birthweight and general self-efficacy makes MI_1 narrower and thinner than MI_2.

Utilisation of parallelepipeds allows a further development. Since all parallelepipeds have a common origin "0", the length of the diagonal of any one parallelepiped and the compound angle ∂ which it makes with the X–Y plane defines that parallelepiped. ∂, thus becomes an efficient way of defining a particular parallelepiped and particular MI.

∂ can be calculated as follows:–

$$\tan \partial = \frac{y}{P}$$

$$\text{but } P = \sqrt{x^2 + z^2}$$

$$\tan \partial = \frac{y}{\sqrt{x^2 + z^2}}$$

$$\text{and } \partial = \tan^{-1} \frac{y}{\sqrt{x^2 + z^2}} \quad \ldots\ldots\ldots\ldots\ldots \quad (1)$$

Figure 3 indicates the origin of the co-ordinates in the above equation. Lower case x, y, z represent the length (x) height (y) and width (z) of the parallelepiped. Values assigned to these co-ordinates are the value from table 1 for the X (cognition) Y (minor illness) and Z (birthweight) axes.

Using the formulas presented above, ∂ for participant 1, $MI_1 = 26°$, for participant 2 $MI_2 = 15.6°$. A lower value of ∂ represents a lower number of minor illness symptom days. It also represents higher general self-efficacy and higher birthweight. Application of EMMIM and computation of ∂ in this way can therefore be seen as an efficient way of demonstrating horizontal and vertical coactions between variables.

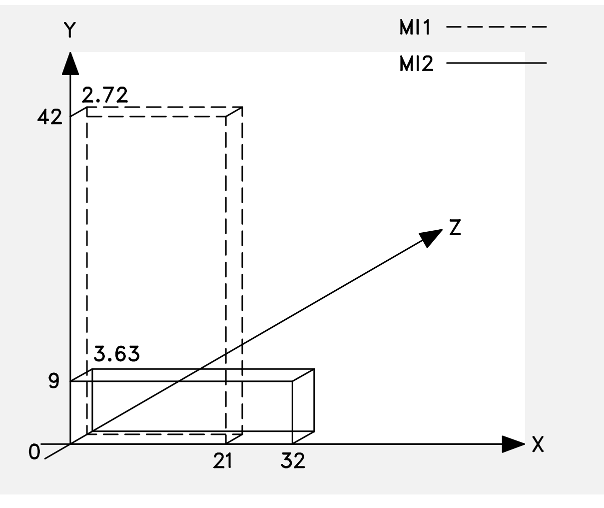

Figure 2. An Equilibrium Model utilising minor illness, birthweight and general self-efficacy data.

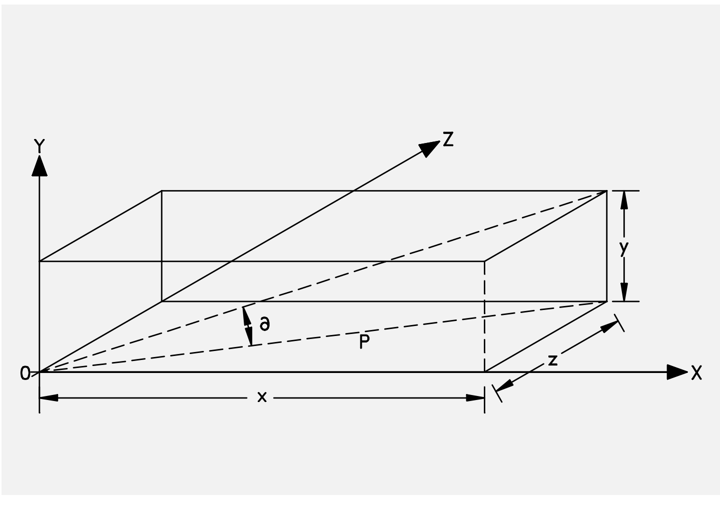

Figure 3. Co-ordinates for the calculation of the compound angle ∂.

Discussion

Results were mainly as expected, participants with lower birthweight report more incidence of upper respiratory tract infection, cough and sore throat and sinus problems than those in the higher birthweight group, indicating a compromised immune system. The lower birthweight group also reported lower general self-efficacy. The predictive nature of these relationships is demonstrated by the regression results where membership of a higher or lower birthweight group is predictive of levels of minor illness symptoms, and general self-efficacy. These results indicate that general self-efficacy is also associated with birthweight as well as minor illness and major disease, and thus adds a new dimension to Barker's hypothesis [8] and concept of early programming.

A large body of evidence has shown the relationship between low birthweight and IQ, with recent studies extending that relationship to performance and verbal neuropsychological measures in those with normal birthweight, where the effects continued into adulthood. The relationship between general self-efficacy and birthweight suggests that not only functional cognitions, but also thought based behavioural cognitions may also be influenced by early programming. The mechanism by which this occurred requires investigation, although it is possible to postulate it is linked to the hormone serotonin. As Gupta's work shows secretion of a number of chemicals, including serotonin, can be disrupted by an adverse uterine environment [15], and these disruptions can have long lasting effects. As the construct of general self-efficacy pertains to optimistic self-beliefs, a mild disruption of serotonin secretion may lead to a reduced propensity to acquire and maintain optimistic beliefs.

Given previously documented links between self-efficacy and immunoncompetence, a link with general self-efficacy and minor illness was expected, but not found. One reason could be, that the experiments cited from previous research involved phobics subjected to stressful phobic threat. When the threat was removed (either at the end of the experiment, or because self-efficacy to cope was so low participants rejected the task) biochemical levels returned to baseline levels.

The experiments measured specific phobic related self-efficacy, whereas because our participants were not in a specific task related situation, our study measured general self-efficacy. Differences in self-efficacy constructs may be responsible for not finding a link with minor illness; it should be noted that low general self-efficacy has been associated with high levels of illness in previous studies, although they have also been in chronic circumstances e.g. a population of unemployed economic migrants. It is therefore likely that self-efficacy, general or otherwise, influences immunocompetence only under chronic conditions.

Barker's hypothesis, suggests that foetal compensation may result in physiolgocial deficits leading to increased susceptibility to chronic heart disease (CHD). Based on the findings in this report, it is possible to speculatively suggest an additional way in which interuterine coactions influence risk of CHD in later life. If lower birthweight individuals are programmed to have a lower general self-efficacy as these findings suggest, then they may be less able to deal with stressful situations. This in turn may lead to increased levels of catecholamines and increased risk of heart disease. Despite not being linked with minor illness in this study, because the mediating effect of specific and general self-efficacy on illness and biochemical changes has been well documented, these findings offer birthweight as an early predictor of psycho-immunologic mediation.

These findings also indicate that health deficits are not confined to those with officially low birthweights, and that the deficits of "mid zone" babies are carried forward to adulthood. Although PNI methods have not been used, this research has implications in that field, especially as those minor illnesses that are linked to birthweight are of similar nature and affect the same physiological system.

For example, a number of minor illnesses were investigated; interestingly only URT, cough, sore throat and sinus problems are linked to birthweight. Other minor illnesses such as digestive problems, allergic reactions, headaches or skeletal problems were not significantly linked. This suggests that birthweight impacts on a particular physiological system and affects cell-mediated immunity, responsible for dealing with infections. The effect could be due to reduced efficiency of cell mediated immunity or disruption of the balance between cell-mediated and humoural systems, with the humoural system reducing activity of the other system. Further research is required, however, it is suggested that the effect is a result of reduced efficiency of cell-mediated immunity, as over activity of the humoural can be associated increased allergic reactions which were not found.

Following Bellingham-Young and Adamson-Macedo [10], relationships reported are explained in terms of horizontal and vertical coactions as described by Gottlieb [13]. From findings in this report and previous studies, it is possible to speculatively infer two sets of vertical coactions; first between interuterine environment, serotonin production and general self-efficacy. Secondly, coactions between interuterine environment, immune function and minor illness outcomes.

Presentation of an Equilibrium Model for Minor Illness Mediators (EMMIM) demonstrates these horizontal and vertical coations. Use of parallelepipeds within the model provides a visual representation. Movement along one axis (horizontal coaction) has an effect upon the other axes (vertical coactions). Computation of ∂ demonstrates change in outcomes. For example, a change on the birthweight axis will change the shape and (potentially) the size of the parallelepiped, which in turn changes the value of the compound angle ∂, demonstrating a change in minor illness and general self-efficacy outcomes.

Social factors have not been controlled for in this study, although as Matte [22] reports, the relationship between birthweight and cognition holds when such controls are in place, as have epidemiological studies into the link between size at birth and major disease. Notwithstanding this limitation, these findings are adding to a body of research which suggests that deficits in health and cognition are associated with lower birthweight which continues into adulthood. Further work to develop EMMIM as a tool for demonstrating relationships between variables and estimating outcomes is suggested.

In conclusion, this study identifies links between birthweight minor illness and general self-efficacy in adults. It is suggested that links with minor illness and general self-efficacy may only be evident in chronic stress situations. Notwithstanding this, it is argued that these findings present evidence of psycho-immunologic mediation. It is also suggested that a series of vertical coactions can explain results. Application of data to a model provides a visual demonstration of the concept of horizontal and vertical coactions.

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