Published in final edited form as:

Headache. 2013 April ; 53(4): 628–635. doi:10.1111/head.12076.

Causality and headache triggers

Dana P. Turner, MSPH¹, Todd A. Smitherman, PhD², Vincent T. Martin, MD³, Donald B. Penzien, PhD⁴, and Timothy T. Houle, PhD¹

¹Department of Anesthesiology, Wake Forest School of Medicine, Winston-Salem, NC

²Department of Psychology, University of Mississippi, Oxford, MS

³Division of General Internal Medicine, University of Cincinnati College of Medicine, Cincinnati, OH

⁴Head Pain Center, University of Mississippi Medical Center, Jackson, MS

Abstract

Objective—The objective of this study was to explore the conditions necessary to assign causal status to headache triggers.

Background—The term “headache trigger” is commonly used to label any stimulus that is assumed to cause headaches. However, the assumptions required for determining if a given stimulus in fact has a causal-type relationship in eliciting headaches have not been explicated.

Methods—A synthesis and application of Rubin’s Causal Model is applied to the context of headache causes. From this application the conditions necessary to infer that one event (trigger) causes another (headache) are outlined using basic assumptions and examples from relevant literature.

Results—Although many conditions must be satisfied for a causal attribution, three basic assumptions are identified for determining causality in headache triggers: 1) constancy of the sufferer; 2) constancy of the trigger effect; and 3) constancy of the trigger presentation. A valid evaluation of a potential trigger’s effect can only be undertaken once these three basic assumptions are satisfied during formal or informal studies of headache triggers.

Conclusions—Evaluating these assumptions is extremely difficult or infeasible in clinical practice, and satisfying them during natural experimentation is unlikely. Researchers, practitioners, and headache sufferers are encouraged to avoid natural experimentation to determine the causal effects of headache triggers. Instead, formal experimental designs or retrospective diary studies using advanced statistical modeling techniques provide the best approaches to satisfy the required assumptions and inform causal statements about headache triggers.

Keywords

headache triggers; causality; research design

Corresponding author: Dana P. Turner, Department of Anesthesiology, Wake Forest School of Medicine, Winston-Salem, NC 27157, Phone: +13367168599, daturner@wakehealth.edu.

Conflicts of Interest:

Dana P. Turner: unrestricted grant funding from Merck

Todd A. Smitherman: nothing to disclose

Vincent T. Martin: consultant and speaker with Allergan; consultant with Nautilus and Zogenix; grant funding from GlaxoSmithKline

Donald B. Penzien: unrestricted grant funding from Merck

Timothy T. Houle: unrestricted grant funding from Merck; consultant with Allergan

Introduction

Although ubiquitously used in both lay language and research reports, the term “headache trigger” has rarely been formally or consistently defined. In examinations of the topic, most reports provide examples of stimuli (ie, objects, events, or processes) believed to trigger headache (eg, stress, wine, cheese) instead of formally articulating the properties that would qualify a stimulus as a headache trigger. Martin and Behbehani offered a rare explicit definition in the context of migraine:

A migraine trigger is any factor that on exposure or withdrawal leads to the development of an acute migraine headache (p911).¹

Adding to the potential confusion regarding the intended meaning is the common use of “headache precipitant” interchangeably with “headache trigger.” Examination of accepted dictionary definitions for *trigger* (“anything, as an act or event that serves as a stimulus and initiates or precipitates a reaction or series of reactions”) ·² and *precipitating* (“to hasten the occurrence of; bring about prematurely, hastily, or suddenly”) ·³ reveals that both concepts do involve similar notions as agents of initiation.

Despite these formal definitions, much uncertainty regarding intended meaning remains with a statement such as “X is a trigger (precipitant) of headache.” This confusion in part surrounds whether “trigger” is used to refer to a stimulus that simply precedes a headache (“If X is encountered, a headache will occur”) versus a stimulus that directly causes the headache (“X causes headache”). The first implies a mere temporally precedent association, while the latter ascribes causal power to the triggering stimulus. Research reports, physician advice, and communications with headache patients themselves provide little consistency of usage or clarification regarding what is precisely intended when a given stimulus is identified as a “trigger” for headache.

Do headache triggers *cause* headaches or are they merely *associated* with processes that do? Perhaps neither relationship is accurate and the term *headache trigger* begs the very question of whether headaches can be initiated by any observable phenomenon at all. The methods used for identifying and classifying factors that truly cause headaches are critical because patients and treatment providers often behave as though triggers actually cause headaches. In clinical settings, a common treatment strategy is to have patients first identify and then either avoid⁴ or manage^{5–7} identified headache triggers. Many other patients may avoid perceived triggers without ever being instructed to do so by a physician.⁶ Both sets of behaviors are only logical if made under the assumption that avoiding the trigger, or reducing its effect, will lead to a reduced probability of headache attack. Thus, these behaviors only have therapeutic utility if some form of causal relationship actually exists between identified triggers and headache attacks.

This paper explores the philosophical and statistical underpinnings of the conditions required to assign causal status to headache triggers. The arguments are illustrated using an $n = 1$ natural experiment; such an application is analogous to an individual headache sufferer attempting to identify the potency of a potential headache trigger using only natural variability. Despite a wealth of dedicated thought, no attempt has been made to compare the conditions under which potential headache trigger candidates are studied or observed clinically to what is known about the conditions necessary to assign causal status to these same events. From this work, several areas of thought are explored: First, how the phenomenology of headache triggers comports with the required conditions for causal assumptions; Second, the challenges in assigning causal status to headache triggers in within-person subjective quasi-experiments; Third, a comparison of trigger methodologies from simple natural experiments (ie, a very small number of within-person trials that rely on

natural variability in exposures to discover an effect) to stronger designs using more advanced experimental methods and statistical approaches.

Causality and counterfactual thinking for headache triggers

Causality has a long history within the field of philosophy of science. The types of causes (Aristotle⁸), the nature of cause and effect (Hume⁹), and the validity of assigning causal status to inductive arguments (Berkeley¹⁰) have been of continuing interest to human beings for over two millennia. This sustained interest presumably stems from the great utility of causal understanding of person-environment relationships in controlling our own lives. Although a complete philosophical treatise on causality is well beyond the scope of this manuscript, the underlying conceptual framework hinges on the arguments posited by Holland,¹¹ who relies heavily on Rubin's Causal Model^{12–14} and more indirectly on Lewis' theory of counterfactuals.^{15, 16}

If a headache trigger is said to cause a headache it must be in contrast to some other cause. Simply stated, causes can only be estimated in relation to other causes.¹¹ For headache triggers this is easily observed when a headache sufferer estimates the potency of wine as a trigger for causing her headaches by comparing the chances of experiencing a headache after drinking wine to that of *not* drinking wine. Using a modified version of Holland's notation, our headache sufferer thus estimates the probability of experiencing a headache (H) for a given time (t) during one of two states, that of drinking wine (w) versus *not* drinking wine ($\sim w$). Conceivably, two different conditions are then theoretically possible for this sufferer at this same time (t). In the first, the probability of experiencing a headache after drinking wine may be represented as $H_w(t)$. The second condition, the probability of experiencing a headache when not drinking wine may be represented as $H_{\sim w}(t)$. Then, the causal effect of drinking wine is theoretically quantified as the algebraic difference between the two conditions:

$$H_w(t) - H_{\sim w}(t)$$

As is evident from even this simple notation, trigger effects are not merely specific to the particular trigger itself, but also to a time-trigger pairing. In other words, the causal influence of a potential trigger is only experienced in the context of time for which it is present.

What should be evident is that for any given time, a headache sufferer can only be exposed to one of two possible conditions: for example, the potential trigger or the absence of the potential trigger (eg, drinking wine versus not drinking wine). If wine is actually consumed, then drinking wine is the 'factual' condition for its effects are directly observed. The competing condition is not actually experienced and is thus 'counterfactual' to reality for its effects are only able to be postulated (eg, "what would have happened had I not drank wine?"). For each trigger-time pairing, our headache sufferer must choose one condition (cause) and compare the results to what would have happened had the opposite condition (cause) occurred at the same time. This cognitive process using counterfactual processes has been cleverly described as "comparing reality to its alternatives"¹⁷ or "what-if reasoning".¹⁸

Fundamental Problem of Causal Inference

A major metaphysical problem arises from the fact that only one of these two conditions can be directly experienced for any trigger-time pairing. This limitation gives rise to what Holland (1986) has labeled the Fundamental Problem of Causation,¹¹ which stems from the

fact that the effects of the two competing potential causes (conditions) cannot ever be simultaneously observed. In all areas of science, investigators routinely manage the Fundamental Problem using formal experimental procedures and statistical modeling. However, for an individual headache sufferer attempting to learn about his/her own triggers, a direct implication of this Problem is that making valid causal inferences about headache triggers seems logically impossible, for our sufferer can never directly observe both conditions at the same time or within precisely the same context.

Despite the logical difficulties in making valid causal inferences for headache triggers, sufferers, physicians, and researchers alike ascribe causal status to a large and varied group of these candidate triggers. To do so effectively, we must find methods to overcome the Fundamental Problem of Causation. These methods must be predicated on assumptions about the similarity of different trigger-time pairings. These assumptions, which are all forms of a homogeneity of invariance assumption, will allow us to believe that for an individual headache sufferer, the effect of one trigger-time pairing, $H_w(t_1)$, is equal to the effect of a later trigger-time pairing, $H_w(t_2)$. This belief allows the causal effect of the competing cause, $H_{\sim w}(t_2)$, to be introduced and observed on a second analogous occasion. Using the previous example, if a headache sufferer believes that two potential wine-drinking occasions are equitable, she could drink wine on one occasion and not the other and then compare the effects, $H_w(t_1) - H_{\sim w}(t_2)$.

But what specific assumptions are required to make such a judgment about headache triggers? These rigorous assumptions have not been formally articulated in headache trigger research. The assumptions required to overcome the Fundamental Problem of Causation for an individual headache sufferer are displayed in Figure 1. Although the assumptions could be categorized in several meaningful ways, they are characterized here as individual assumptions about: 1) the constancy of the sufferer; 2) the constancy of the trigger effect; and 3) the constancy of different trigger-time pairings. These categorizations were distilled from Holland's¹¹ individual assumptions about the homogeneity of experimental units and are intended to organize basic assumptions for ease of communication to sufferers, researchers, and clinicians. Each assumption and its implications are outlined below, along with examples of how the assumptions are satisfied or violated within an individual over time.

Required Assumptions for Causal Inferences of Headache Triggers

1. Constancy of the Sufferer

To obtain an estimate of a headache trigger's causal strength, the headache sufferer herself must be the same (or very similar) from one trial to another. Stated somewhat differently, the individual's headache process should be comparable at subsequent trigger-time pairings. In a statistical sense, for the potency of a trigger to be validly assessed, the probability of experiencing a headache conditional on all possible trigger candidates must be equitable during two trigger-time pairings. It is difficult to assess the potency of a single trigger candidate if the probability of experiencing a headache changes due to some non-trigger related cause (e.g., maturation, secondary disease). This assumption also implies that trigger effects are transitory in that they do not permanently alter the headache sufferer. For example, if the effects of two trigger-time pairings are to be compared, and the earlier trigger-time pairing permanently alters the headache sufferer, then no equivalent pairing can ever be found to contrast causal effects. A final implication of this assumption is that the sufferer's *perception* of cause (trigger) and effect (headache attack) does not change over pairings. If a sufferer's definition of a headache attack, a trigger exposure, or the expected temporal association between the two changes from pairing to pairing, isolating the impact of a trigger will be particularly difficult. This could be observed if wine is expected to

induce a same-day headache on one occasion but a next-day headache during another occasion.

This assumption is intuitively valid but may be impossible to verify, as doing so would require that all possible influences on headache be known and measureable. This vast knowledge would allow the calculation of a background headache probability by considering all of the known influences of experiencing a headache. If the background probability of experiencing a headache were the same on two occasions after removing the influences of all triggers (reflecting a constancy in the sufferer), then a novel trigger candidate could be introduced on one occasion with its opposite on the second occasion to evaluate the causal effect. This calculation is infeasible due to our lack of complete knowledge about all influences on an individual's headache and because it would require perfect knowledge of all these influences in real time. In practice, this assumption can be informally assessed through examination of an individual's headache activity over time. Without the assistance of additional information or complex statistical modeling, observing a consistent pattern of headache activity from month to month must at present suffice as evidence that the underlying headache itself is not changing significantly and that the sufferer herself is relatively constant over time.

Despite the difficulty in definitively evaluating the constancy of a headache sufferer, this assumption may be satisfied in a wide array of situations. Even a cursory examination of the literature reveals that most popular trigger candidates have proposed mechanisms of action that are transitory and thus are unlikely to permanently alter the sufferer. For example, the most commonly-reported food triggers (e.g., caffeine, alcohol, chocolate, and monosodium glutamate) have stimulant properties with transitory effects.¹ The same is true of triggers such as weather, acute stress, noise, blood-glucose fluctuations, disturbed sleep, and hormonal influences. Certainly, potential triggers could be conceived that permanently alter the sufferer (eg, oxaliplatin), but these are not typically considered frequently-encountered or naturally-occurring triggers of headache. A greater threat to the satisfaction of this assumption is the well-known changes in headache state that occur during maturation (eg, puberty, menopause).^{19–21} Additionally, many sufferers experience attacks that can last 72 hours or longer, making the days after an attack has begun difficult to compare to other trigger-time pairings because a headache process has already been initiated. Finally, the observation that certain individuals experience an escalation of headache frequency (eg, chronification, transformed migraine) over time is also a strong threat to this assumption given that the probability of headache for these individuals appears to increase absent other known headache triggers (excluding medication overuse and other personal characteristics).²² The limitations imposed by the constancy of the sufferer assumption make precarious the examination of trigger-time pairings that are either too close to the initiation of a headache or too temporally distant from each other, as the sufferers themselves may differ substantially between these delayed pairings.

2. Constancy of Trigger Effect

To obtain an estimate of a headache trigger's causal strength, the candidate trigger must be the same (or very similar) and have a similar effect on subsequent trials. This is akin to an assumption of trigger temporal stability and implies constancy in trigger effect over time. If true, the order of pairings of two potential triggers is irrelevant, as the same effect would be observed regardless of presentation order. This assumption can be expanded to both sets of trigger-time conditions indicating that for example, $H_w(t_1) = H_w(t_2)$, as well as $H_{\sim w}(t_1) = H_{\sim w}(t_2)$, are both true. The implications of this assumption are that a trigger's effect does not accumulate or diminish with repeated exposures and that a trigger's effect is not modified by another trigger, such that a constant effect is produced on every encounter with a candidate trigger.

This assumption is impossible to verify for a single trigger-time pairing, as it cannot be known how representative an effect that is observed from a single trigger-time pairing is of all possible trigger-time pairings. If a trigger exhibits an inconsistent effect on headache activity, a single trigger-time pairing may or may not be a representative indication of effects on future pairings. Further, the very assumption possesses a temporal component that precludes its assessment in a single pairing. Valid assessment of the consistency of a trigger candidate's effect must be evaluated using repeated pairings to estimate variability in the effect and/or any dynamic changes that occur over repeated exposures. These repeated trials sample the causal strength of the trigger and provide information about the likely effect of future pairings. The validity of expected effects in future pairings is what this assumption truly protects.

The constancy in trigger effect assumption is frequently violated in common practice. Assessing trigger effects using instances where an uncontrolled carry-over influence is present from one time to another precludes valid inferences. This problem complicates meaningful inferences from trigger-time pairings where the effect of the first pairing is still active on a second pairing. Slow moving weather patterns, viral insults, or ovarian hormone changes that occur over the course of several days are all examples where a causal effect might linger between pairings spaced too close together. Further, the causal effect gleaned from a single exposure does not provide information concerning future exposures if the first exposure serves to sensitize the sufferer to future exposures of the same trigger. An example of this can be gleaned from anaphylaxis, wherein a first exposure primes the individual for a radically enhanced effect on a second exposure.²³ Alternatively, repeated exposures to a triggering agent might result in a diminished effect. Martin and colleagues have shown that exposure to some triggers (eg, noise, visual disturbance) actually reduces their potency over time, so long as the exposure is not of a very short duration.^{24–26} Finally, a candidate trigger may exhibit a differential effect when experienced in the presence of another trigger. For example, Holm and colleagues have demonstrated that stress has an increased association with headache when experienced at perimenstrual time periods.²⁷ In this way, ovarian hormones moderate the effect of stress on triggering headaches. In each of these examples, trigger candidates exhibit an inconsistent effect over repeated trials, highlighting the limitations imposed by violating the constancy in trigger effect assumption. So long as trigger effects vary from pairing to pairing, making valid inferences about the causal strength of candidate triggers is extremely difficult.

3. Constancy of Trigger Presentation

To obtain an estimate of a headache trigger's causal strength, the pattern of other potential triggers must be the same (or similar) on subsequent trials. This is related to an assumption of independence of observations in that the effect of a novel trigger must be independent of the population of other triggers also present during that trigger-time pairing. For example, if the causal effect of wine is being examined to that of not drinking wine and drinking wine was also accompanied by eating cheese, then the causal effect of drinking wine cannot be isolated from eating cheese if cheese was eaten on one pairing but not the other. This assumption requires that other triggers that might obscure the proposed causal relationship are held consistent between trigger-time pairings (ie, the other triggers are either both absent or both present to the same degree).

This assumption is intuitively valid but is likely the most difficult of the three to satisfy. In the companion study of this manuscript,²⁸ this assumption is examined in great detail using a host of common triggers (e.g., weather, stress, ovarian hormones). The methods from this companion study are those that would be required to truly evaluate this third assumption. Briefly, headache sufferers would require knowledge about the levels of all of their relevant triggers to identify two days that have a high degree of similarity in terms of the levels of

these triggers. With this knowledge, two similar days could be selected, and a candidate trigger cause could be compared to a competing cause in these two trigger-time pairings. To conduct this natural experiment prospectively, this knowledge of other relevant triggers would be required ahead of the trigger-time pairings, which in many cases is infeasible for more unpredictable triggers such as weather, stress, and hormonal fluctuations.

The constancy of trigger presentation assumption is violated in most circumstances. The companion study demonstrates that because of the sheer number of potential headache triggers and the natural variability in these triggers, finding even two similar days that are well-balanced in regards to 10 or more other triggers is incredibly difficult.²⁸ Considering weather triggers alone, a given headache sufferer will experience only 2.3 days each year that are 90% similar on factors such as wind speed, visibility, temperature, dew point, and precipitation.²⁸ Thus, it is likely that a natural experiment that is conducted on two trigger-time pairings is conducted with a non-trivial imbalance in one or more other potential triggers that are high/low on one pairing but not the other. As with the other assumptions, the limitations imposed by violating the constancy of trigger presentation assumption complicate valid inferences about the causal strength of candidate triggers.

Summary and Recommendations

Multiple assumptions are required to allow the assignment of causal-type status to a headache trigger. This work grouped these assumptions in three intuitive categories that are easily communicated to a sufferer attempting a natural experiment (i.e., to someone examining his or her own triggers using natural variability) or to researchers attempting to study particular triggers among groups. The proposed individual assumptions could be grouped in any number of meaningful ways, and this three-category grouping is not presented with the intention of an exclusive order but instead as a framework to communicate the assumptions to sufferers, researchers, and clinicians. Indeed these groupings overlap/interact with one another, and each has implications for the others. As but one example, the constancy of trigger presentation assumption overlaps substantially with constancy of trigger effect assumption whenever a differing pattern of triggers presents on subsequent pairings that alone or in combination modify any of the other trigger effects. Thus, in practice, these assumptions are even more difficult to verify than in the clear divisions presented here.

For the sake of simplicity, the assumptions were illustrated using one simple trigger-time pairing. In this formulation, the necessary assumptions that would be required to assess the causal effect of one trigger in comparison to another trigger were presented as though this single pairing would be sufficient (eg, one wine versus non-wine occasion). Although it is unknown how many actual pairings individual headache sufferers use to make estimations about their own triggers, or even how sufferers identify which candidate triggers to consider, a single pairing is unlikely to provide definitive information regarding causal effects. Instead, a sufferer would be well-advised to attempt repeated trigger-time pairings to sample the causal effects under a range of conditions and in the context of their headache process (ie, how many headaches are experienced when the trigger is *not* present?). However, what should be clear is that each of the three assumptions required to validly assign causal status to headache triggers is likely to be violated, even when using repeated pairings, and as a result the use of natural experimentation used by many headache sufferers may have limited value (see companion manuscript for more discussion).

For these reasons, researchers, practitioners, and headache sufferers are strongly encouraged to avoid relying on natural experimentation to “learn” about the causal effects of headache triggers. Instead, one of two approaches can be used to satisfy the required assumptions.

First and foremost, the use of randomization methods is used throughout scientific inquiry as an elegant approach to assess causal relationships. In this approach, a headache sufferer would prospectively and randomly assign triggers to occasions and assess the impact of the trigger candidate versus some competing cause. Using the previous example, a headache sufferer could design an experiment where he or she drank a glass of wine on some number of randomly selected days during a month. The number of headaches encountered on these days could then be compared to the competing cause (eg, not drinking wine) using a number of methods including randomization tests.²⁹ By randomly assigning trigger encounters to calendar days, randomization methods minimize threats to causal interpretations because, over the long run, confounding influences are expected to be identically distributed amongst the collection of trigger-time pairings. With some forethought, the random assignments can also be adjusted to allow sufficient time between pairings to better ensure that the constancy in sufferer assumption also is not violated (i.e., that a previous pairing is not influencing a later pairing). This randomization strategy also lends itself well to both within- and between-subjects research designs using larger samples.

The second approach to meet the required assumptions is to use retrospective daily diaries and advanced statistical techniques. This combination of approaches would involve collecting data on a number of potential triggers and then to account for those factors that violate any of the three assumptions by incorporating them into a statistical model. For example, a modeling approach could be used to estimate the probability of headache after drinking wine while controlling for the influences of a host of other trigger patterns (ie, satisfying the constancy of trigger presentation). Interactions between triggers could be assessed in the model (ie, one form of constancy of trigger effect) while adjusting for gross increases or decreases in headache frequency that might occur during the observation period (ie, constancy of the sufferer). Although statistical approaches of this type do not provide the same support for a causal relationship as the randomization approach, they are far better than a natural experiment wherein many of the assumptions are probably violated.

Acknowledgments

Financial support: Research reported in this publication was supported by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health under award number 1R01NS06525701.

References

1. Martin VT, Behbehani MM. Toward a Rational Understanding of Migraine Trigger Factors. *Medical Clinics of North America*. 2001; 85:911–941. [PubMed: 11480265]
2. Dictionary.com [Internet]. Available from: <http://dictionary.reference.com/browse/trigger>
3. Dictionary.com [Internet]. Available from: <http://dictionary.reference.com/browse/precipitating>
4. santé Omdl. Neurological Disorders: Public Health Challenges. World Health Organization; 2006.
5. Martin PR, MacLeod C. Behavioral Management of Headache Triggers: Avoidance of Triggers is an Inadequate Strategy. *Clinical Psychology Review*. 2009; 29:483–495. [PubMed: 19556046]
6. Martin PR. Behavioral Management of Migraine Headache Triggers: Learning to Cope with Triggers. *Current Pain and Headache Reports*. 2010; 14:221–227. [PubMed: 20425190]
7. Martin PR. Managing Headache Triggers: Think ‘Coping’ not ‘Avoidance’. *Cephalalgia*. 2010; 30:634–637. [PubMed: 19673895]
8. Aristotle, BCE, IV. *Complete Works of Aristotle*. Barnes, J., editor. Princeton, NJ; 1995.
9. Hume, D. *A Treatise of Human Nature: Being an Attempt to Introduce the Experimental Method of Reasoning Into Moral Subjects; And, Dialogues Concerning Natural Religion*. Longmans, Green, and Company; 1890.
10. Berkeley, G. *The Works of George Berkeley*. Clarendon press; 1901.

11. Holland PW. Statistics and Causal Inference. *Journal of the American Statistical Association*. 1986; 81:945–960.
12. Rubin DB. Estimating Causal Effects of Treatments in Randomized and Nonrandomized Studies. *Journal of Educational Psychology*. 1974; 66:688. *Journal of Educational Psychology*.
13. Rubin DB. Assignment to Treatment Group on the Basis of a Covariate. *Journal of Educational and Behavioral Statistics*. 1977; 2:1–26.
14. Rubin DB. Bayesian Inference for Causal Effects: The Role of Randomization. *The Annals of Statistics*. 1978:34–58.
15. Lewis D. Causation. *The Journal of Philosophy*. 1973:556–567.
16. Lewis D. Counterfactuals and Comparative Possibility. *Journal of Philosophical Logic*. 1973; 2:418–446.
17. Kahneman D, Miller DT. Norm Theory: Comparing Reality to Its Alternatives. *Psychological Review*. 1986; 93:136.
18. Trickett SB, Trafton JG. “What If...”: The Use of Conceptual Simulations in Scientific Reasoning. *Cognitive Science*. 2007; 31:843–875. [PubMed: 21635319]
19. Lipton RB, Silberstein SD, Stewart WF. An Update on the Epidemiology of Migraine. *Headache: The Journal of Head and Face Pain*. 2005; 34:319–328.
20. Scher AI, Stewart WF, Liberman J, Lipton RB. Prevalence of Frequent Headache in a Population Sample. *Headache: The Journal of Head and Face Pain*. 2003; 38:497–506.
21. Schwartz BS, Stewart WF, Simon D, Lipton RB. Epidemiology of Tension-type Headache. *JAMA: the Journal of the American Medical Association*. 1998; 279:381–383. [PubMed: 9459472]
22. Scher AI, Stewart WF, Ricci JA, Lipton RB. Factors Associated with the Onset and Remission of Chronic Daily Headache in a Population-Based Study. *Pain*. 2003; 106:81–89. [PubMed: 14581114]
23. Kemp SF, Lockey RF. Anaphylaxis: a Review of Causes and Mechanisms. *Journal of Allergy and Clinical Immunology*. 2002; 110:341–348. [PubMed: 12209078]
24. Martin PR. How do Trigger Factors Acquire the Capacity to Precipitate Headaches? *Behaviour Research and Therapy*. 2001; 39:545–554. [PubMed: 11341251]
25. Martin PR, Reece J, Forsyth M. Noise as a Trigger for Headaches: Relationship Between Exposure and Sensitivity. *Headache: The Journal of Head and Face Pain*. 2006; 46:962–972.
26. Martin PPR, Lae L, Reece J. Stress as a Trigger for Headaches: Relationship Between Exposure and Sensitivity. *Anxiety, Stress, and Coping*. 2007; 20:393–407.
27. Holm JE, Bury L, Suda KT. The Relationship Between Stress, Headache, and the Menstrual Cycle in Young Female Migraineurs. *Headache: The Journal of Head and Face Pain*. 2002; 36:531–537.
28. Houle TT, Turner DP. Natural Experimentation is a Challenging Method for Identifying Headache Triggers. *Headache: The Journal of Head and Face Pain*. 2013; 53:636–643.
29. Edgington, E.; Onghena, P. *Randomization Tests*. Chapman & Hall/CRC; 2007.

Figure 1.

Three assumptions for causal inferences of headache triggers. To infer that a headache trigger causes a headache (or causes the processes that do), several assumptions must be satisfied during pairings (Time 1 versus Time 2) of a trigger (e.g., drinking wine) and its opposite (e.g., not drinking wine). A headache sufferer must be the same across pairings such that they are equally as likely to have a headache absent the trigger. The trigger and its effect must be the same across pairings such that future encounters are likely to have the same influence. The pattern of background triggers (black and white circles) must be equivalent across pairings such that other trigger effects are not mistaken for the candidate trigger (wine).