Biological Psychiatry

Citation Distortions in the Literature on the Serotonin-Transporter-Linked Polymorphic Region and Amygdala Activation

To the Editor:

A seminal finding in imaging genetics is that carriers of the short (S) allele of the serotonin-transporter-linked polymorphic region (5-HTTLPR) exhibit an increased amygdala response to negative emotional stimuli. The original article by Hariri *et al.* (1) has been cited >1000 times since its publication in 2002. Although meta-analyses have shown a statistically significant (but small) effect across published studies, the validity of these findings is undermined by the presence of publication bias (2,3). In addition, the strength of evidence has declined over time (3,4). However, the strength of belief does not seem to have decreased comparably. For instance, a more recent review (5) maintained that up to 5% of differences in amygdala activation can be explained by variation in the 5-HTTLPR.

One factor that may contribute to the persistence of belief in an effect is preferential citation of positive studies (6). For the network of studies reported in the most recent meta-analysis on the 5-HTTLPR and amygdala activation by Murphy *et al.* (3), citation differences between positive (n = 10) and negative studies (n = 15), although present, are not very pronounced. Although 40% of studies are positive, they receive 55% of within-network citations and 67% of citations via Web of Science (49% excluding Hariri *et al.* (1)). A positive study is cited, on average, by 39% (SD = 32%) of subsequent studies in the network, and negative studies are cited by 25% (SD = 24%). In Web of Science, average yearly citation rates for negative and positive studies are 11 (SD = 11) and 24 (SD = 32) times, respectively, with the latter declining to 15 (SD = 17) times when Hariri *et al.* (1) is excluded.

However, citation rates of negative studies can be confounded by studies with inflated claims or "spin" in their abstracts—spin being the (intentional or unintentional) use of reporting strategies to emphasize the presence of an effect,

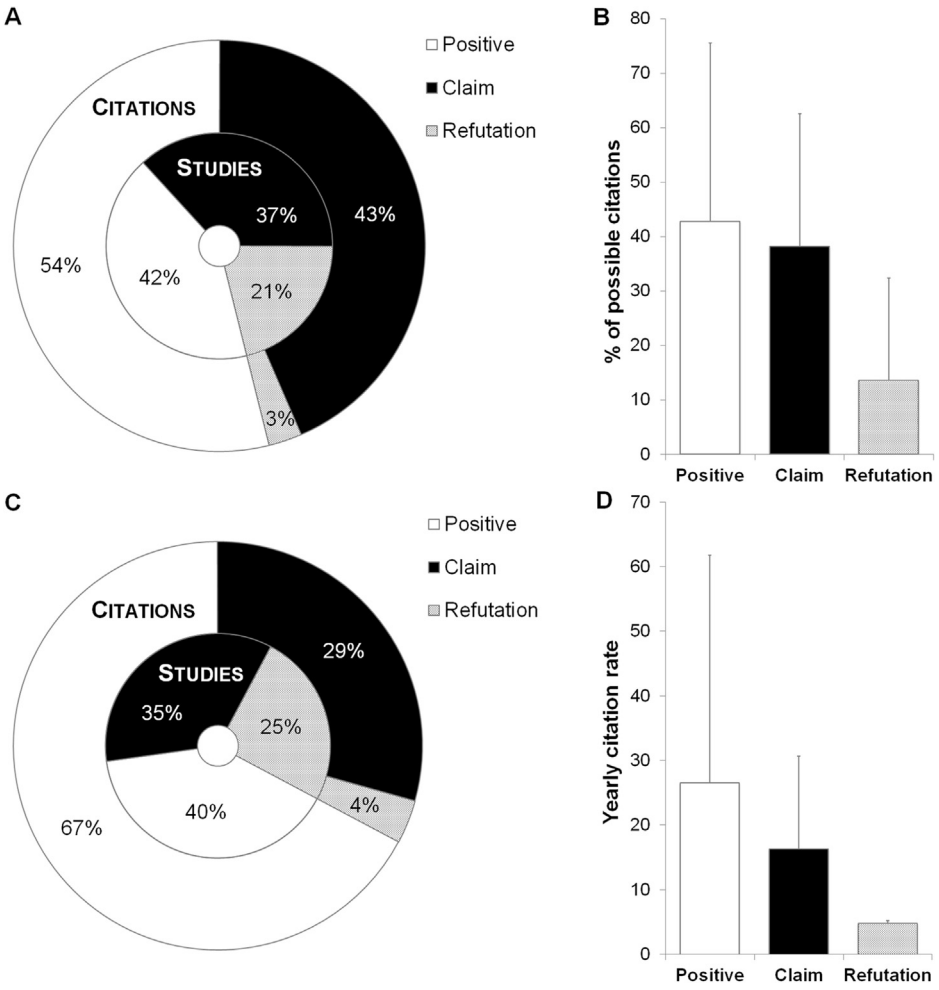

Figure 1. Distribution of within-network citations **(A, B)** and Web of Science citations **(C, D)** for positive, claim, and refutation studies (n = 20; 2 positive and 3 negative studies did not make a clear claim about the main effect in the abstract (8) and were excluded). **(A)** Pie chart showing the proportion of within-network citations to each study type (outer ring) compared with the proportion of studies of each type (inner ring). **(B)** Bar graph depicting the average percentage of subsequent studies in the network that cite a study of each type (with SD). Exclusion of Hariri *et al.* (1) decreases the percentage of subsequent studies citing a positive study to 36% (not shown). The last study within the network was excluded for measures shown in **(A)** and **(B)** because it could not have been cited by the other studies (n = 19). **(C)** Pie chart showing the proportion of Web of Science citations to each study type (outer ring) compared with the proportion of studies of each type (inner ring). **(D)** Bar graph depicting the yearly citation rate by study type. For positive studies, the yearly citation rate decreased to 16 after exclusion of Hariri *et al.* (1) (not shown).

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for instance, by focusing on statistically significant findings from subgroup analyses or secondary outcomes (7). It was previously shown (8) that many of the studies in the meta-analysis by Murphy *et al.* (3) make stronger claims in their abstracts than is warranted by the reported data when a standardized analytic approach is employed. Figure 1 illustrates that "claim" studies—that is, negative studies that claim to have found an effect, but for which a standardized analysis does not indicate statistically significant evidence—are cited comparably to positive studies. In contrast, studies that neither report nor claim the existence of an effect (i.e., "refutation" studies) are overlooked. For instance, refutation studies are cited by only 14% of subsequent studies within the network (Figure 1B), and they receive only 4% of citations in Web of Science (Figure 1C). Refutation studies appear to face a double difficulty in contributing to and changing the common perspective: not only is it hard to publish them, but also, once published, they are cited infrequently. Studies are rewarded for making positive claims by higher citation rates, resulting in a literature that presents a distorted impression of the strength of evidence.

Effect estimates by meta-analyses are not affected by spin and often swiftly become the new standard in the field. Although meta-analyses can potentially override the effects of citation distortion, they can also lead to further distortion when important issues they raise are neglected. Two independent raters coded whether the 37 peer-reviewed English-language articles citing Murphy *et al.* (3) (source: Google Scholar, November 2014) referred to these authors' concerns about issues of statistical power and publication bias or mentioned only the presence of a statistically significant effect. Three methodological articles did not address the outcome of the meta-analysis, and one did not provide enough information for coding. Of the remaining 33 articles, only 7 reported the concerns discussed by Murphy *et al.* (3), and 1 article discussed similar issues more broadly. In other words, 76% of more recent studies cite the meta-analysis as evidence for the association without expressing concern regarding the validity of this conclusion.

Who and what are cited color the common perception of an evidence base. For the association of 5-HTTLPR variation with amygdala activation, we have shown that refutation studies are typically ignored, and methodological concerns reported by a meta-analysis are often overlooked. Researchers should focus on the nuance and caveats associated with any result (including results derived from a meta-analysis) in their articles and should be encouraged to publish and cite refutation studies. A recent study (4) published individual (null) results together with an updated meta-analysis. This approach may help increase the visibility of refutation studies. Citation analysis of other topics could help clarify why certain beliefs remain deeply rooted in the field and support researchers in distinguishing fad from fact.

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Article Information

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