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the Starkstein Apathy Scale. The participants had not engaged in vocational rehabilitation prior to assessment.

Table 1 compares participants who did and did not return to work. Lower education, aggression, apathy, and a diagnosis of personality change were associated with non-return to work. These behavioral variables were significant predictors of non-return to work in separate multiple logistic regressions, including education as a covariate (personality change: adjusted odds ratio [AOR] = 4.4,  $p = 0.047$ , Nagelkerke  $R^2$  [NR<sup>2</sup>] = 0.25; aggression: AOR = 5.0,  $p = 0.037$ , NR<sup>2</sup> = 0.24; apathy according to Robert criteria: AOR = 7.9,  $p = 0.021$ , NR<sup>2</sup> = 0.31; Starkstein Apathy Scale score: AOR = 1.1,  $p = 0.024$ , NR<sup>2</sup> = 0.31).

Study limitations include the relatively small sample and the fact that work was not characterized (e.g., according to complexity level). We also did not perform a neuropsychological assessment of the participants, although it has been proposed that personality changes and cognitive impairment represent two aspects of the same phenomenon.<sup>4</sup>

Our results add to the literature by linking aggression and apathy to work disability in severe TBI. Given the importance of reproducibility in psychological research, it is also noteworthy that our previous findings were replicated. Apathy and aggression could serve as timely markers of attention for vocational rehabilitation after severe TBI, since they emerge early in the course of the disease and are easily observed by relatives and clinicians.<sup>2,5</sup> Larger longitudinal studies that comprehensively evaluate vocational and cognitive functioning and characterize distinct presentations of personality change may help identify accurate predictors of work disability, in addition to potential targets for interventions.

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## Disclosure

The authors report no conflicts of interest.

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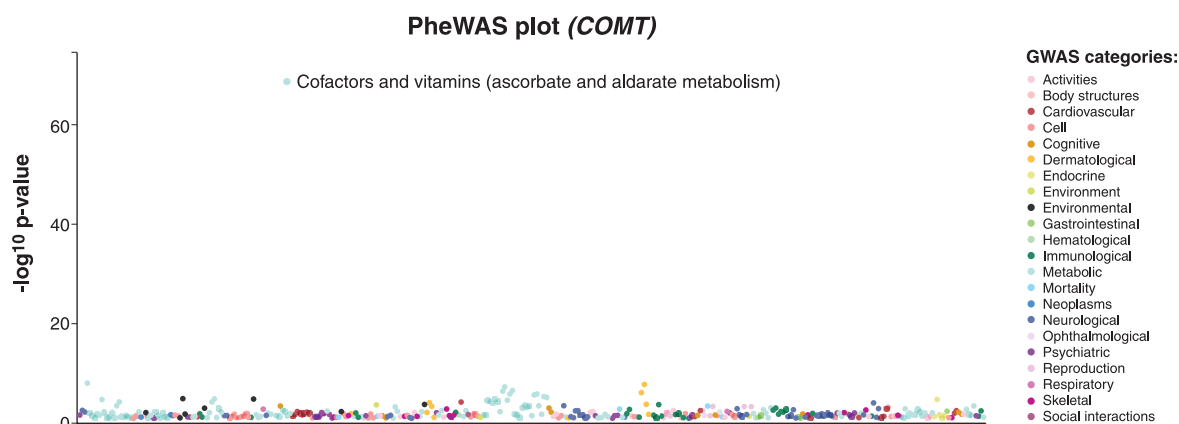
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# Ditching candidate gene association studies: lessons from psychiatric genetics

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For decades, candidate association studies represented a cost-effective approach to investigate the genetic factors underlying heritable human traits, including psychiatric disorders. This methodology entailed testing variants in genes hypothetically related to phenotypes of interest, based on gene function and historical relevance. However, the genes selected for candidate association studies were typically gleaned from rare, familial instances of disease that do not necessarily translate to the wider population, or were based on weak empirical data that yielded false associations, often due to the presence of hidden confounders in the small samples analyzed. Another issue was that we currently do not know the full repertoire of functional variants regulating human gene expression and, therefore, candidate studies were unlikely to have selected the correct regulatory variants to test for association in the first place. Ultimately, this approach contributed to a publication bias in the literature and hindered the identification of the true biological risk mechanisms underlying psychiatric disorders. A lack of consistency and trust in the results arising from these studies led to replication studies and meta-analyses that altogether discredited most candidate gene associations in psychiatry.<sup>1-3</sup>



**Figure 1** The phenome-wide association plot of *COMT*, based on an analysis of 4,756 GWAS results, separated into 22 categories, shows that no psychiatric, behavioral or neurological traits are strongly associated with this gene. The Bonferroni p-value threshold is  $1.05 \times 10^{-5}$ . Retrieved from the GWAS Atlas.<sup>6</sup>

Following the cost reduction in whole-genome genotyping and the establishment of collaborative international initiatives, candidate studies were superseded by large-scale genome-wide association studies (GWAS). In this approach, virtually all independent common variants in the genome are tested for association, for example, with case-control status, personality traits, or drug response, often in cohorts of hundreds of thousands of individuals. These studies have implicated specific cell types like pyramidal neurons and interneurons in the etiology of schizophrenia,<sup>4</sup> and frontal brain regions in depression.<sup>5</sup>

Psychiatric genetics has largely moved away from historical candidate association studies, as most candidate genes failed to show associations in GWAS. In fact, a study that analyzed results from a schizophrenia GWAS showed that common variants in 25 historical candidate genes, including *COMT*, *BDNF* and *DISC1*, were no more associated with schizophrenia than control sets of non-candidate genes.<sup>1</sup> Even for candidates that turned out to be associated with schizophrenia (e.g., *DRD2* and *GRM3*), their biological relevance remains unclear considering there are many other genes with a stronger association. Another study depicted a similar scenario for depression.<sup>2</sup> However, despite the lack of success in candidate studies, a PubMed search for *COMT* revealed 269 research outputs published in 2020 alone (checked on January 20th, 2021). Many of these tested this gene for association with complex traits like pain, cognitive performance, behaviors, etc., even though the evidence of association between *COMT* and behavioral, psychiatric or neurological outcomes is weak, according to a phenome-wide association study (PheWAS) from the GWAS Atlas,<sup>6</sup> which analyzed 4,756 GWAS results (Figure 1).

Due to their reduced costs and analytical ease, the candidate approach still has a place in studies investigating panels of single nucleotide polymorphisms derived from large-scale GWAS in populations that are currently under-represented in those studies (e.g., Latino and African populations), or in studies investigating related phenotypes. However, considering the polygenic nature underlying complex human traits and the limitations of the candidate

approach, we should be ditching association studies, especially if these are based solely on historical gene relevance. Psychiatrists, geneticists and neuroscientists must reconsider the cost-benefits of candidate studies when there is no prior robust evidence of trait association, particularly now that there are hundreds of genes unbiasedly associated with many psychiatric traits. Ultimately, only the analysis of large cohorts using genome-wide methods and replication studies using panels of putatively-causal (i.e., fine-mapped) single nucleotide polymorphisms, selected through robust evidence, will provide the means to expand our understanding of the genetic architecture of complex human traits.

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