Cargill M, Altshuler D, Ireland J, Sklar P, Ardlie K, Patil N, et al. in their study on ethnic differences in BDNF Val66Met differing frequencies affect the occurrence of the disorder. Pivac assume it would be of paramount importance to examine how populations, the Val allele is found to be the most common and has allele frequencies dependent on ethnic background. In White Mexican American experimental and control population and found it also to be associated with major depressive disorder.

However, previous studies have found that the polymorphism was found in the amygdala, prefrontal regions of the anterior cingulate cortex and middle frontal and orbitofrontal cortices. The study focused on 79 patients with diagnosed major depressive disorder and 74 control participants, all of White European ancestry. The main effects were of Met carrier status on cortical thinning in the caudal middle frontal cortex in patients with major depressive disorder and controls. The polymorphism in the caudate middle frontal cortex was greater and no significant interaction was found in the amygdala.

One limitation not covered by the authors was the lack of ethnic diversity among the sample population. One previous study investigated the BDNF polymorphism in an exclusively Mexican American experimental and control population and found it also to be associated with major depressive disorder. However, previous studies have found that the polymorphism has allele frequencies dependent on ethnic background. In White populations, the Val allele is found to be the most common and the frequency of the Met allele is 25% to 32%. In Asian populations the Met allele is more frequent, about 40% to 50%. As MacGregor Legge et al found that the Met allele had the greatest effect on major depressive disorder, one would assume it would be of paramount importance to examine how differing frequencies affect the occurrence of the disorder. Pivac et al in their study on ethnic differences in BDNF Val66Met polymorphism in a Croatian and Korean non-clinical sample found that polymorphisms and mood disorders may be dependent on ethnicity.

Searches for studies of the BDNF polymorphism in African–Caribbean and other ethnicities obtained no results. As generalisable conclusions cannot be drawn on the varying effects of the BDNF polymorphism on major depressive disorder or any major psychiatric illness in different ethnic groups, further examination into this topic would be significant.

Authors’ reply: We thank Yeebo for this comment on our paper, raising an important point that the frequency of genetic polymorphisms tends to vary between different ethnic groups. In our study, we had sought to investigate the association of the BDNF Val66Met polymorphism with imaging phenotypes in the context of major depressive disorder, rather than an investigation of an association for the polymorphism with major depressive disorder. As Yeebo states that we had sought ‘to determine whether the same neural effects would be observed in healthy individuals’, we would like to clarify that we had investigated whether the effects of the polymorphism on specific brain regions in healthy individuals would also be observed in the same brain regions in individuals with major depressive disorder.

Yeebo’s general comment on the differing frequency of the genetic polymorphisms between different ethnic groups has long been a source of difficulty in allelic association studies because – unless there is careful ethnic matching of cases and controls – spurious results can arise, including both false-positive and false-negative findings. For this reason, we had restricted our study to individuals of White European origin.

Yeebo draws attention to the possibility that the association between the BDNF Val66Met polymorphism and major depressive disorder is specific to certain ethnic groups, and this raises another but slightly different interesting issue. Disease associations with polymorphisms arise either because the polymorphism itself plays a causal role or because it is in linkage disequilibrium with another variant that has a causal role. The degree of linkage disequilibrium between adjacent polymorphisms is in general approximately proportional to their distance apart but is also dependent on other factors including allelic frequency, so ethnic differences in observed linkage disequilibrium may arise. It has usually been assumed that because the BDNF Val66Met polymorphism is functional, its role in depression is likely to be causal. If the association between this polymorphism and major depressive disorder were found to vary between different ethnic groups, this would be attributable to either different Met allele frequencies between the ethnic groups or the Val66Met polymorphism being in linkage disequilibrium with another variant in BDNF that has a causal role in major depressive disorder.

There are also publicly available data on the Single Nucleotide Polymorphism Database (www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=6265) which indicate that in African and African American populations, the frequency of the Met allele seems to...
be rare (e.g. Yoruba, Met frequency 0.0004 in a group of 226 sampled; African Americans 0.05 in a group of 90) so that a genetic association analysis with depression would require very large samples. Although we would anticipate the functional impact of being a Met carrier to be similar across population groups, we agree with Yeebo that this would warrant further investigation.


Relevance of $^{[123]}$I-FP-CIT SPECT brain scans in routine clinical settings

The findings from Walker et al.'s study do not come as a surprise. The high sensitivity and specificity of $^{[123]}$I-iopropyl injection ($^{[123]}$I-FP-CIT) single photon emission computed tomography (SPECT) in diagnosing dementia with Lewy bodies (DLB) relate to a highly selected group of individuals, where underlying vascular pathology, severe mental and physical illness (including delirium) as well as medication interference were excluded. The working group also based their findings on a large group of patients with DLB, in comparison to rather modest size groups previously reported.

How relevant is this study to those of us working in a routine clinical setting? What is the sensitivity and specificity of the $^{[123]}$I-FP-CIT SPECT brain scan in differentiating DLB from other dementia syndromes and pseudodementia? Our own experience working with older people with mental and medical health problems suggests that patients can be easily misdiagnosed as having DLB based on their $^{[123]}$I-FP-CIT SPECT scans, and it includes individuals with major depression, severe brain trauma accompanied by widespread vascular white matter changes and small vessel disease, HIV encephalopathy, and an older adult with mild intellectual disability with frontal lobe syndrome and severe hypoperfusion as demonstrated on the SPECT brain scan. This is another confirmation of the clinician’s gullibility when faced with $^{[123]}$I-FP-CIT SPECT altered scans, as confirmed by Walker et al.

With the availability of $^{[123]}$I-FP-CIT SPECT scans, it is unclear what we have learned from the use of this imaging technique: do we use them for DLB diagnosis – based on their abnormal findings alone – or do we put them in the wider context of our patients’ clinical symptomatology and medical history? There is a well-documented inverse relationship between vascular lesions and Lewy body pathology: 30% of patients with frontotemporal lobe dementia have abnormal scans and a significant reduction in uptake in the putamen and the caudate (also highlighted by Walker et al.). About 5% of people diagnosed with DLB in fact have vascular dementia and altered suspected $^{[123]}$I-FP-CIT SPECT are also found in Creutzfeld–Jakob disease. It is of note that the influence of antipsychotic and antidepressant medication in older adults has largely been neglected in research studies in the public domain. The evidence from a limited number of animal and human studies clearly indicates that medication (e.g. haloperidol, citalopram, sertraline) reduces $^{[123]}$I-FP-CIT dopamine binding to the dopaminergic transporter. However, there is an overwhelming lack of evidence for the most frequently used drugs in the older population, including a number of dopaminergic antagonists, the influence of polypharmacy, the effect of chronic administration of these drugs and modifying effects of advanced age. Until such data are available, it is not surprising that clinicians would be inclined to diagnose and/or accept the diagnosis of DLB based on the evidence of a dopaminergic abnormality. Even in their strictly controlled study, Walker et al. report 5.4% mismatch between $^{[123]}$I-FP-CIT SPECT scan findings and clinical DLB diagnosis. It is now the responsibility of the DLB research community to provide us with further clarification of clinical situations and exclusion criteria when using $^{[123]}$I-FP-CIT SPECT scans to diagnose DLB in busy clinical settings.


Authors’ reply: The data presented were the culmination of a well-designed European multicentre study which adds a valuable data-set on the clinical usefulness of $^{[123]}$I-FP-CIT SPECT (DaTSCAN). Although it is correct that the participants in the study were a selected group, as is the case in all clinical trials and similar studies, the sample overall was probably not significantly different in terms of general comorbidities and...