EDITORIAL

Incidental neuroimaging findings: lessons from brain research in volunteers

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Over the last few years, brain research in volunteers that are considered healthy has increasingly used neuroimaging methods. The actual imaging techniques are tailored to the scientific issue under investigation but such imaging sessions often include high-resolution structural brain imaging. Accordingly, these brain scans are not ideal but nonetheless sensitive for detecting the presence of brain pathologies. Analyses of large cohorts of brain scans obtained for nondiagnostic reasons in volunteers who were deemed healthy have revealed incidental findings in up to almost every fifth individual [1]. Only a minority of these findings, however, are clinically significant and only about 1% showed findings that required rapid medical attention. These levels of prevalence are largely in accordance with those reported for disease-unrelated observations in clinical populations and for populations screened for fitness such as air pilots [2,3]. Not surprisingly, there is an age-related increase in incidentally detected findings but asymptomatic anomalies may be found as early as in paediatric populations [4,5].

Even though most incidental neuroimaging findings have little if any clinical relevance, the discovery of unattended findings may cause psychological problems in the affected individual and the rare research 'accident' of a significant pathology can have a considerable medical and socioeconomic impact. This impact can be a blessing thanks to prophylactic interventions but also a curse [6,7]. The related concerns are not novel but the domains in which such observations are made have expanded [8]. In keeping with the trend towards a 'predictive medicine', the impact from biological data sampling in asymptomatic individuals is gaining in momentum, most notably in the neurosciences and genetics [9]. Due to the lack of a full consensus in the neuroimaging research community, differences between individual institutions persist, but many research centres have developed formal guidelines on how to deal with incidental neuroimaging findings and these apply as soon as informed consent is obtained [10–12].

In absolute terms, incidental neuroimaging findings in patients – individuals who have consulted doctors for a medical problem – largely outnumber those in research volunteers. After all, many more brain scans are performed in a medical than in a research context. Despite less coverage in the biomedical literature, the issue of incidental brain scan findings is far more relevant for neurological practice than for brain research. Moreover, patients are probably even more susceptible to misinterpretation and overinterpretion of incidental findings and, at least in this author's experience, clinicians are less aware of this inherent risk of any neuroimaging study. One reason for this lesser awareness may be that in patients the problems associated with incidental findings are clouded by the fact that any brain imaging study is motivated by a clinical indication. Hence, in principle, the probability of obtaining nonincidental – that is, symptom-related – findings is above average and serves to justify not only the cost but also the risks of imaging, including those from unexpected findings. This editorial argues that developing standards and procedures for dealing with incidental neuroimaging findings in patients could be informed by the debates and considerations that have revolved around incidental findings in individuals volunteering for research.

Before extrapolating from results in research volunteers, however, I pose the question of whether the rate of incidental neuroimaging findings in persons who volunteer for brain scans is representative of the clinically latent prevalence of brain scan anomalies in the general population. A concern may be that research volunteers are exercising a form of self-referral. Advertisements for study participants sometimes highlight the opportunity of 'looking into your head', 'seeing your mind work' or 'getting your brain scanned for free'. Such promises may be more appealing to some volunteers than the generally modest remuneration involved [6]. Indeed, questionnaires have revealed that the majority of volunteers expect to be informed if any abnormality is detected [13]. Moreover, the rate of incidental findings in these volunteers is roughly comparable to that in Japanese volunteers who went through a self-referral procedure called 'brain docking' at their own expense [14]. A more likely interpretation, however, is that self-referral for screening purposes is simply inefficient and does not yield a higher rate of findings than those to be expected in the overall population.

A different situation arises when a patient consults a neurologist who in turn refers him for brain imaging. Since clinical symptoms motivated the physician to request a brain scan, the patient will be inclined to consider any pathological result on this scan as related to the symptoms, and this tendency may aggravate or unveil somatoform disorders. The clinician, therefore, should warn the patient prior to the brain scan that results may emerge that bear no relation to the patient's symptoms but that nonetheless may have important consequences. The patient should also be informed before any neuroimaging study that the existing data show that the vast majority of incidental findings are meaningless from a clinical perspective. Finally, it is important to convey to the patient that only the clinical expert can label neuroimaging findings as 'symptom related', 'incidental but without consequences' or 'incidental with consequences', which helps the neuroradiologist who is under an obligation to report any anomaly but is not in a position to assess its clinical significance. In addition, this may help to prevent the patient from indulging in discouraging haphazard speculations.

Recommendations have evolved for neuroimaging research whereby many institutions, including the author's, have all scans reviewed by a trained neuroradiologist, thus alleviating the responsibility (and liability) from brain researchers who are not necessarily medically trained. Subsequently, volunteers with scan anomalies are referred to clinicians to decide whether the findings are medically relevant. Many research centres include an interview and examination by a physician in the inclusion criteria for volunteer selection, but once brain scans have revealed an anomaly, neurological history taking and physical examination are much more sensitive than screening procedures and may thus lead to a revision of the status of a volunteer as 'healthy' and 'asymptomatic'. A point of heated debate in the research community is whether asymptomatic volunteers should have the option to 'opt out', that is, to declare prior to the neuroimaging study that they do not wish to be informed of potentially discovered pathologies [15].

For patients returning after a neuroimaging study, neurologists must not only confirm whether the finding is incidental but they are also required to determine its clinical significance and propose a course of action. This is also the case for research volunteers in whom a brain scan anomaly is incidental by definition. The related recommendations, however, are subject to several uncertainties. One major uncertainty arises because, as opposed to symptomatic brain disease, few if any evidence-based recommendations can be made for asymptomatic processes, especially in populations that are not established with a clinical selection bias. It is probably fair to say that any brain pathology is less threatening when the patient is asymptomatic than when this pathology has a clinical manifestation. Yet, the natural history of asymptomatic pathologies is still poorly characterized. The clinician's task is hence compromised by the fact that the individual outcome is unpredictable and, in many instances, not even the probability distribution of outcomes for the pathology detected has been adequately determined. If the individual is truly asymptomatic any treatment strategy qualifies as prophylaxis, and overall, prophylactic treatments struggle to show that they yield a net risk reduction. This concern is aggravated and complicated by the fact that the medical risk from the natural history of a currently asymptomatic pathology is cumulative over time whereas risk from prophylactic intervention is immediate.

Brain scanning with MRI is noninvasive from a technical perspective. It has a tremendous clinical impact and has revolutionized neurological practice in many domains. Yet, the two-millennium-old tenet of 'primum nil nocere' must be borne in mind when referring any patient to a neuroimaging study, and the associated risk must be weighed against the expected benefit for the patient. Although greater awareness of these issues – together with cost-efficiency considerations – may lead clinicians and patients alike to refrain from neuroimaging studies, the detection of incidental findings will inadvertently continue and thus advance our understanding of their significance and permit more solid, empirically founded recommendations on how to handle them. White matter lesions in the elderly are an example in the current issue of the journal that reminds neurologists how careful we need to be in evaluating the clinical significance of even incidental neuroimaging results.

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