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BEHAVIOURAL NEUROSCIENCE

# Genes and the anxious brain

Andreas Meyer-Lindenberg

**Some people are naturally more anxious than others. A brain-imaging study in monkeys provides surprising insights into which brain regions are under the influence of genes in this phenomenon and which are not.**

How anxiously we react to threat or adversity is part of our personality. This stable characteristic is called trait anxiety, and those with high trait anxiety are more prone to mental disorders such as depression, substance abuse and psychosis[1]. Trait anxiety is heritable, with genes explaining much of the variability between individuals[2]. In this issue, Oler *et al.*[3] investigate genetic effects on the activity of brain regions that mediate trait anxiety (page 864).

The subjects of this study were rhesus monkeys — 238 from several generations of a single-family pedigree — at an average age corresponding to that of humans just before puberty. The authors exposed the animals to a human intruder, a validated social-threat procedure that reveals an anxiety trait. They found, by examining both blood levels of the stress hormone cortisol and behaviours such as 'freezing', that some monkeys reacted with high anxiety, and others with less.

Concurrently, Oler *et al.* measured metabolic activity in the brain by injecting the monkeys with $^{18}$FDG, a radioactive analogue of glucose that is taken up and trapped in nerve cells according to their activity at the time of exposure to the social threat. The authors then anaesthetized the monkeys in order to image, using positron emission tomography, a 'snapshot' of regional brain metabolism during the preceding stress procedure.

The results indicate that, in anxious monkeys, brain activity is higher in a variety of areas, but most prominently in two key signalling structures for negative emotion, the amygdala and the anterior hippocampus. Activity in these two structures explained a sizeable proportion of the variance in anxiety behaviour from monkey to monkey (Fig. 1).

Much research in anxiety has focused on the amygdala[4], which signals environmental danger and triggers 'fight-or-flight' responses. But extensive evidence also links the anterior hippocampus — an essential structure for 'declarative' memory — to anxious behaviour and trait anxiety[4]. Furthermore, there are strong interactions between the amygdala and hippocampus, which mediate emotional memory.

What proportion of anxiety-related activity in the brain of monkeys is genetic? In their well-characterized pedigree, Oler *et al.* could precisely estimate genetic similarity between any two monkeys. They thus mapped heritability (the proportion of variability that can be attributed to genes) across the brain. Surprisingly, they found that activity in the anterior hippocampus was under strong genetic influence, but observed no significant heritability in the amygdala (Fig. 1). Given the importance of these two structures for trait anxiety, and their close functional connection, this pronounced difference is unexpected.

Do these findings mean that the amygdala is no longer to be considered part of the neurogenetic pathway for trait anxiety? Not necessarily. The amygdala is a structure that shows bursts of activity and can be fickle where imaging is concerned. Furthermore, Oler *et al.* investigated the brain of each animal only once — during the stress condition. They may, therefore, not have been able to fully characterize the proportion of neural activity that was truly due to stress. For this, a control condition during which animals are not stressed is needed.

Previous studies in monkeys[5] and humans[6] that involved a control condition have, in fact, revealed effects of gene variants on the amygdala. Moreover, genetic mechanisms do not just play out in regional brain activity, but also shape the neural networks in which these regions participate. In particular, interactions between the amygdala and another brain region, the prefrontal cortex, may be highly relevant to the effect of genetic variation on trait anxiety[7], because the resulting circuit regulates the activity of the amygdala during the processing of negative emotion. In addition, interactions between the hippocampus and the amygdala have been linked to aspects of personality[8]. To characterize these circuits, other techniques such as functional magnetic resonance imaging must be used, because measuring interactions between different regions requires repeatedly imaging them over time.

If Oler and colleagues' data can be confirmed in humans, research on the neurogenetic basis of anxiety and psychiatric disorders should focus more on the hippocampus than it has so far. Changes in hippocampal size and function have been reported[9] in depression and anxiety disorders, but have often been considered a consequence of stress-related hormonal changes. This paper[3] suggests that hippocampal processing of threat and stress signals could also be on the causal pathway that links genetic risk to disease manifestation: genes affect personality through their effect on hippocampal threat processing, which therefore becomes an intermediate, or 'endo', phenotype.

Indeed, genetic variants that have been identified through genome-wide association studies of mental illnesses such as bipolar disorder or schizophrenia modulate hippocampal activity[10]. With the knowledge that hippocampal activity is a heritable component of the neural network mediating trait anxiety, this activity can itself be used in genome-wide association studies to discover gene variants affecting the hippocampus. This approach deserves particular attention because drugs that target the products of these genes, and the hippocampus, could be a new entry point into the treatment of mental disorders. Oler and co-workers' paper[3] could, therefore, not only change thinking about

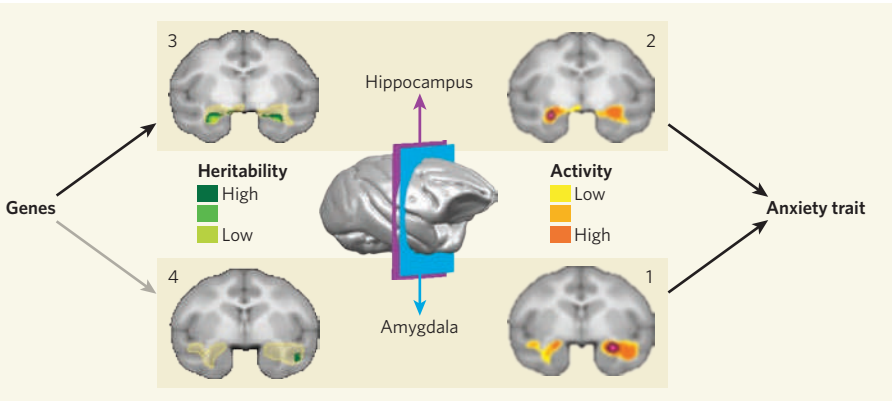


**Figure 1 | When anxiety runs in a family of primates.** Oler *et al.*[3] exposed monkeys to a social threat and then measured $^{18}$FDG distribution in their brains as an indicator of metabolic activity there. They show that both the amygdala (scanned brain slice 1) and the hippocampus (2) mediate variations in trait anxiety. However, the authors find that only hippocampal activity (3), and not amygdalar activity (4), is explained by genetic relatedness. (Brain images from ref. 3.)



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how genes act in the brain to affect our habitual reactions to stress and adversity, but also benefit patients with mental conditions such as depression, anxiety disorders and psychosis. ■

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PALAEOANTHROPOLOGY

# Australopithecine butchers

David R. Braun

**How far back in the human lineage does tool use extend? Fossil bones that bear evidence of butchery marks made by stone implements increase the known range of that behaviour to at least 3.2 million years ago.**

Palaeoanthropologists have long associated tool use with the later part of human ancestors' evolutionary history. One of the key features of 'handy man' (*Homo habilis*), first discovered at Olduvai Gorge in Tanzania, was the use of stone tools. More recently, the discovery[1] of sharp-edged stone tools in the Gona region of Ethiopia, dating to about 2.5 million years ago, modified this definition, extending the time over which tools were known to be used. But the implements found at these sites seemed too well made to have been early humans' first attempt at making such sharp-edged tools.

Evidence from the Dikika area of Ethiopia now indicates that human ancestors may have been practising for almost 800,000 years before the first appearance of chipped stone tools. On page 857 of this issue, McPherron *et al.*[2] report that the fossilized bones of two animals show clear evidence of early humans using stones to remove scraps of flesh from the carcasses of large mammals. These bones were found in a region where the sediments are at least 3.2 million years old.

The Dikika specimens were found in the Andedo drainage system, and a systematic survey of the area recovered several well-preserved fossils of animals that lived on this ancient landscape, possibly near a large lake. McPherron *et al.* realized that some of the bone surfaces had marks indicative of butchery, presumably of carrion. Detailed analyses confirmed that the marks were made by the cutting and scraping of flesh from animal bones and therefore are evidence of butchery practices by early humans. Other marks that represent pounding on the bone surfaces suggest that these hominins (members of the human lineage) also took an interest in the nutrient-rich bone marrow.

Until now, there has been no direct evidence that meat and marrow formed part of the diet of hominins at this early age. Furthermore, it is notable that these early humans departed from the typical primate pattern of disregarding relatively large animals as food. The meat and marrow of large animals must have been a valued resource, because McPherron *et al.* conclude that the tool users incurred the cost of transporting stones 6 kilometres from where they occurred naturally to the site where the butchery took place. Further costs that were associated with the consumption of carrion, and were apparently worth the risk, include exposure to parasites and competition with large carnivores. This kind of behaviour may have set the stage for a greater reliance on animal tissues and more sophisticated stone-tool production by other hominin species, including our own immediate ancestors in the genus *Homo*.

Although palaeoanthropologists have been studying butchery marks on bones for 30 years[3], their studies have largely been restricted to evidence from the past 2 million years. Recent discoveries show that as soon as stone tools appear in the archaeological record, hominins were using them to cut and scrape flesh from bones[4]. However, many processes can make marks on bone surfaces. McPherron *et al.*[2] used various types of scanning electron microscopy to confirm that the marks on the fossil bones they studied were made by sharp-edged stones, and chemical analyses of the bone surfaces confirmed that the marks were made in the deep past.

This is not the first surprise from the Dikika region. The well-preserved skeleton of a juvenile *Australopithecus afarensis* was recovered[5] less than 300 metres from the DIK-55 site where the butchered bones were found. McPherron *et al.* relied on extensive geological mapping of the region to show that the youngest deposits in the Andedo drainage system date to more than 3.2 million years ago. This therefore is the minimum age for the specimens, but they may be up to 3.39 million years old.

McPherron *et al.* attribute the butchered bones to the use of sharp-edged stones by *A. afarensis*, the species that the famous specimen 'Lucy' belongs to. Although no hominin bones were found at DIK-55, the only early human known to be present in the Dikika region at that time is *A. afarensis*. This provides exciting evidence of how *A. afarensis* behaved. At one time, the species was considered to be a relatively primitive hominin, but this perception is being redefined. For example, it now seems that Lucy's kin had body proportions that were more similar to those of humans than of apes[6]. Analyses of the hand of *A. afarensis* show that it had relatively short fingers that would allow the kind of fine-scale manipulation necessary for tool use[7]. A recently discovered skeleton from the Woranso–Mille area of Ethiopia suggests that *A. afarensis* did not have the ape-like, 'funnel-shaped' thorax usually associated with a large digestive tract and low-quality diet[8]. Perhaps the findings that these hominins used tools and had a carnivorous component to their diet should not have been so unexpected.

Nonetheless, many scientists will be surprised that hominins were using tools more than 3 million years ago, because of the scant evidence of this behaviour until now. McPherron *et al.* note that early tool use was probably infrequent and did not result in the large accumulations of artefacts and bones that usually catch the eye of archaeologists and palaeontologists. The authors can confirm only the use of sharp-edged stones, which may have been picked up from the ground rather than made by actively chipping rocks. If tool use has such a deep ancestry in the human lineage, the value of using sharp-edged stones may have been independently discovered by hominins at several points during our evolutionary history[9]. This makes identifying the tenuous link between stone-tool forms and hominin species later on in time even more difficult.

There is the potential for discovering more evidence of this behaviour not only at Dikika but also elsewhere. Fossils of *A. afarensis* have been found in various places in Kenya, Tanzania and Ethiopia, and determining whether this species was a habitual tool user will require the identification of several sites where butchered bones occur in sediments of similar antiquity. More surprises surely await us in the fossil-rich sedimentary basins of East Africa. ■

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