PANDORA'S BOX

Pandora searches the world literature for evidence, news and other sources on matters of interest (doesn't shy away from controversy) to bring to the reader. She welcomes comments and suggestions (via ip@rcpsych.ac.uk)

Musical trivia?

Did you know that 3–5% of us do not get any pleasure out of listening to any type of music? Before you dismiss this minority as ignoramuses, read on. There is a condition known as 'musical anhedonia' and it has a neurobiological basis. Researchers from the Bellvitge Biomedical Research Institute and the University of Barcelona, Spain, in collaboration with the McGill University in Montreal, Canada, have worked out the brain mechanisms associated with insensitivity to music.

It is already known that the pathway responsible for musically induced pleasure connects the auditory cortical networks with the mesolimbic reward networks. Using functional magnetic resonance imaging (fMRI) in three groups of 15 participants, each with different sensitivity to music reward, the researchers demonstrated that the music anhedonic participants had selective reduction of activity for music in the nucleus accumbens, while retaining normal activation levels for a monetary gambling task. They also showed decreased functional connectivity between the right auditory cortex and ventral striatum (including the nucleus accumbens). In contrast, individuals with greater than average response to music showed enhanced connectivity between these structures.

Martínez-Molina, N., Mas-Herrero, E., Rodríguez-Fornells, A., *et al* (2016) Neural correlates of specific musical anhedonia. *PNAS*. Published online 31 October 2016 (https://doi.org/10.1073/pnas.1611211113).

How good are you at multitasking?

If you get frustrated at your difficulty in keeping several bits of information in your head at the same time, don't get annoyed with yourself: blame the GABA content of your dorsolateral prefrontal cortex (DLPFC)!

Working memory is a key function of the DLPFC but its neural correlates are still to be unravelled. This study examined the role of the inhibitory neurotransmitter GABA (gamma-aminobutyric acid) in 23 healthy young adults, who were asked to complete a task that measured the contribution of memory load, maintenance and distraction resistance, all three functions being the major components of working memory in humans. The research participants had their DLPFC GABA content measured by single-voxel proton magnetic spectroscopy.

Those with higher GABA content in the DLPFC performed better on load capacity (the ability to juggle several bits of information simultaneously). The relationship between GABA and working memory was specific to component, neurochemical and brain region. That is, DLPFC GABA content did not predict performance sensitivity to other components tested (maintenance or distraction resistance); furthermore, DLPFC glutamate + glutamine and visual cortical GABA content did not predict load sensitivity.

Given the importance of working memory in many cognitive and behavioural capabilities in humans, this finding could have a significant impact on our understanding of the neural basis of complex human behaviour. Preserving or increasing brain GABA levels could ameliorate deficits in working memory in neuropsychiatric conditions such as schizophrenia.

Yoon, J. H., Grandelis, A. & Maddock, R. J. (2016) Dorsolateral prefrontal cortex GABA concentration in humans predicts working memory load processing capacity. *Journal of Neuroscience*. Published online 16 November 2016 (https://doi.org/10.1523/JNEUROSCI.1970-16.2016).

Phantom limb pain – the wonders of neurofeedback

Limb amputations are more common than you might think. About 5000 amputations are carried out in the UK every year. Most of the people affected continue to feel the existence of the amputated limb and as many as 50–80% experience pain in the phantom limb. The cause of this is believed to be a maladaptive reorganisation of the sensorimotor cortex.

A research group from Osaka University in Japan and the University of Cambridge in the UK used a brain–machine interface (BMI) based on real-time magneto-encephalographic signals to reconstruct affected hand movements with a robotic hand; they trained ten individuals to control the robotic arm using their brains. The BMI training induced significant plasticity in the sensorimotor cortex, which improved the ability to discriminate movement information and also gave better prosthetic control.

Unexpectedly, the functional restoration achieved with BMI training intensified rather than reduced pain. In contrast, BMI training that dissociated the prosthetic and phantom hand did actually decrease the pain. In simpler terms, when the individuals tried to control the prosthesis by associating the movement with their missing hand, they experienced more pain, but when they associated the movement of the prosthetic hand with the unaffected hand their pain decreased!

These results showing a functional relevance between sensorimotor cortical plasticity and pain may provide a novel treatment with BMI neurofeedback.

Yanagisawa, T., Fukuma, R., Seymour, B., *et al* (2016) Induced sensorimotor brain plasticity controls pain in phantom limb patients. *Nature Communications*. Published online 27 October 2016 (https://doi.org/10.1038/ncomms13209).

Effective placebo pain-killing

Nobody disputes the effectiveness of placebo in various conditions, including pain. In the era of personalised medicine, can we do better? Scientists from the Northwestern Medicine and the Rehabilitation Institute of Chicago, USA, claim that fMRI technology, specially developed for the study, has the potential to enable targeted pain medication based on how an individual's brain responds to a drug. Using fMRI they identified a unique brain region within the mid-frontal gyrus that identifies placebo pill responders with 95% accuracy. They hope that their findings could lead the way to personalised medicine for people with

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chronic pain and to more accurate clinical trials for effective analgesics by eliminating people with a high placebo response before the trials.

Tétreault, P., Mansour, A., Vachon-Presseau, E., *et al* (2016) Brain connectivity predicts placebo response across chronic pain clinical trials. *PLOS Biology*. Published online 27 October 2016 (https://doi.org/10.1371/journal.pbio.1002570).

Early diagnosis of Alzheimer's disease – is the retina a window to brain pathology?

As dementia is catching up with cardiovascular disorders as the leading cause of disability, the pressure for early diagnosis and early intervention is increasing. Researchers from the University of Texas, USA, had previously shown that a toxic form of tau protein might underlie the early stages of Alzheimer's disease. Tau protein is needed by brain cells to receive nutrients and get rid of waste. In Alzheimer's disease it changes into a toxic form called tau oligomers that clump together to form neurofibrillary tangles. These prevent the movement of molecular nutrients and so result in neuronal toxicity and brain cell death.

They also found that the tau oligomers may induce inflammation in Alzheimer's disease, and spreading between connected brain regions may initiate inflammation in these regions, creating a vicious cycle of toxic tau, inflammation and cell death throughout the brain over time. Inflammation and loss of connections between nerves within the brain happen before the formation of the tangles that are characteristic of this disease and it is possible that the tau oligomers may be responsible for this inflammation.

The researchers now have also found that tau oligomers are present in the retina and are associated with inflammatory cells, which suggests that the retina may be a valid and non-invasive biomarker for brain pathology in Alzheimer's disease.

So brush up on your ophthalmoscopy skills and get started!

Nilson, A. N., English, K. C., Gerson, J. E., *et al* (2016) Tau oligomers associate with inflammation in the brain and retina of tauopathy mice and in neurodegenerative diseases. *Journal of Alzheimer's Disease*. Published online 12 September 2016 (https://doi.org/10.3233/JAD-160912).

'Birdbrain' an insult? Not any more!

Small brains don't always mean less cognitive ability! Many birds' cognitive abilities match or surpass those of mammals. Corvids and parrots rival great apes in many psychological domains. They manufacture and use tools, solve problems, make inferences about causal mechanisms, recognise themselves in a mirror, plan for future needs and use their own experience to anticipate the behaviour of conspecifics or even humans; these are only a few of their abilities!

Researchers from Charles University of Prague, the University of Vienna and University of Rio de Janeiro used the 'isotropic fractionator' to determine the numbers of neurons in specific brain regions. They found that parrots and corvids have forebrain neuron counts equal to or greater than primates with much larger brains and they suggest that this high neuron count substantially contributes to the neural basis of avian intelligence.

Olkowicza, S., Kocoureka, M., Radek, K., *et al* (2016) Birds have primate-like numbers of neurons in the forebrain. *PNAS*, **113 (26)**, 7255–7260.

The gene for good sleep and happiness

As psychiatrists we are well aware of the close relationship between sleep and mood. Now we know there is a molecular genetic basis to this, at least as far as seasonality is concerned.

In a study of the genetics of a family with both seasonal affective disorder (SAD) and familial advanced sleep-phase syndrome (FASP) researchers identified two rare variants of the circadian clock gene PERIOD3 (PER3). These variants destabilised PER3 and failed to stabilise PERIOD1/2 proteins, which are of critical importance to circadian timing. Mice lacking PER3 showed consistent depression-like behaviour, particularly when studied under a short photo-period. The authors suggest PER3 may be the connection between sleep and mood regulation and their fine-tuning to enable them to adapt to seasonal changes.

Zhang, L., Hirano, A., Hsu, P.-K., *et al* (2016) A PERIOD3 variant causes a circadian phenotype and is associated with a seasonal mood trait. *PNAS*, **113**, E1536–E1544 (https://doi.org/10.1073/pnas.1600039113).

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