Computational methods determine effectiveness of pain relievers

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More than 90% of central nervous system drugs fail when they're tried in large human trials. The team at the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) hope that combining information from many brain imaging studies with their computational methods will provide a cheaper way of filtering out drugs that are not likely to work, without the need for expensive human clinical trials.

Many drugs, such as those for pain relief, work on the central nervous system: they cross into the brain and directly affect its function. But drug

effects are often subtle, and the same drug can have varying effects on different people.

As a result, it is difficult to work out whether a new drug is likely to be effective enough to justify further development: testing it in many people takes time and is expensive. 'There is a great need for markers that can help to prioritize and direct drug research prior to full-scale clinical trials, which currently have high failure rates,' says Dr Eugene Duff, the lead author of the study.

The study included more than 130 people, and is published in *Science Translational Medicine*.

The researchers wondered if imaging brain responses to drugs can potentially provide a better way of identifying promising drugs. Previous work has used functional brain imaging to track drugs in action, but individual studies have usually tested only at one drug at a time, using a small number of people.

'We wanted to see if brain imaging could be used as a general method in drug discovery,' says Dr Duff.

To get around the problem of limited numbers of people in a single study, the researchers put together brain imaging data from eight previous studies. While these studies differed in exactly what the participants did, all of them included a condition where the participants had a drug known to relieve pain before they were exposed to something painful, such as a sharp point pressed onto hypersensitive skin. As a comparison, the database also included brain activity recorded from the same participants receiving a placebo before being exposed to pain.

The researchers then used a technique called machine learning to discriminate brain activity in participants when they had received a drug

from when who had received a placebo. They 'trained' a computer algorithm with several examples of data acquired from people who had received the drug. In the same way, they trained the algorithm with data from people who had received the placebo.

From this 'training', the algorithm was able to build up a picture of what the brain looks like when exposed to a working drug versus a placebo, all by itself. 'This was a fully automated process – we didn't specify anything further,' according to Dr Duff.

The crucial test was whether the algorithm would then be able correctly classify an unknown dataset as coming from a placebo or a drug condition, based on the knowledge it had acquired in the training phase.

Since all of the results are from drugs already known to relieve pain, the researchers knew which condition each dataset belonged to. They used this information to track how well the algorithm did.

They found that the algorithm was able to classify data as coming from a drug versus a placebo condition with an average accuracy of around 70%.

The research team hopes that the same method can be used to winnow out new candidate drugs which are most likely to be most effective from those that are not likely to work.

'We've shown a 'proof of principle' with analgesic drugs. But in theory, this method would also work for other drugs that cross the barrier into the brain. So it could also be used to test drugs for conditions such as schizophrenia,' says Dr Duff.

More information: "Learning to identify CNS drug action and efficacy using multistudy fMRI data." Sci Transl Med 11 February 2015:

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