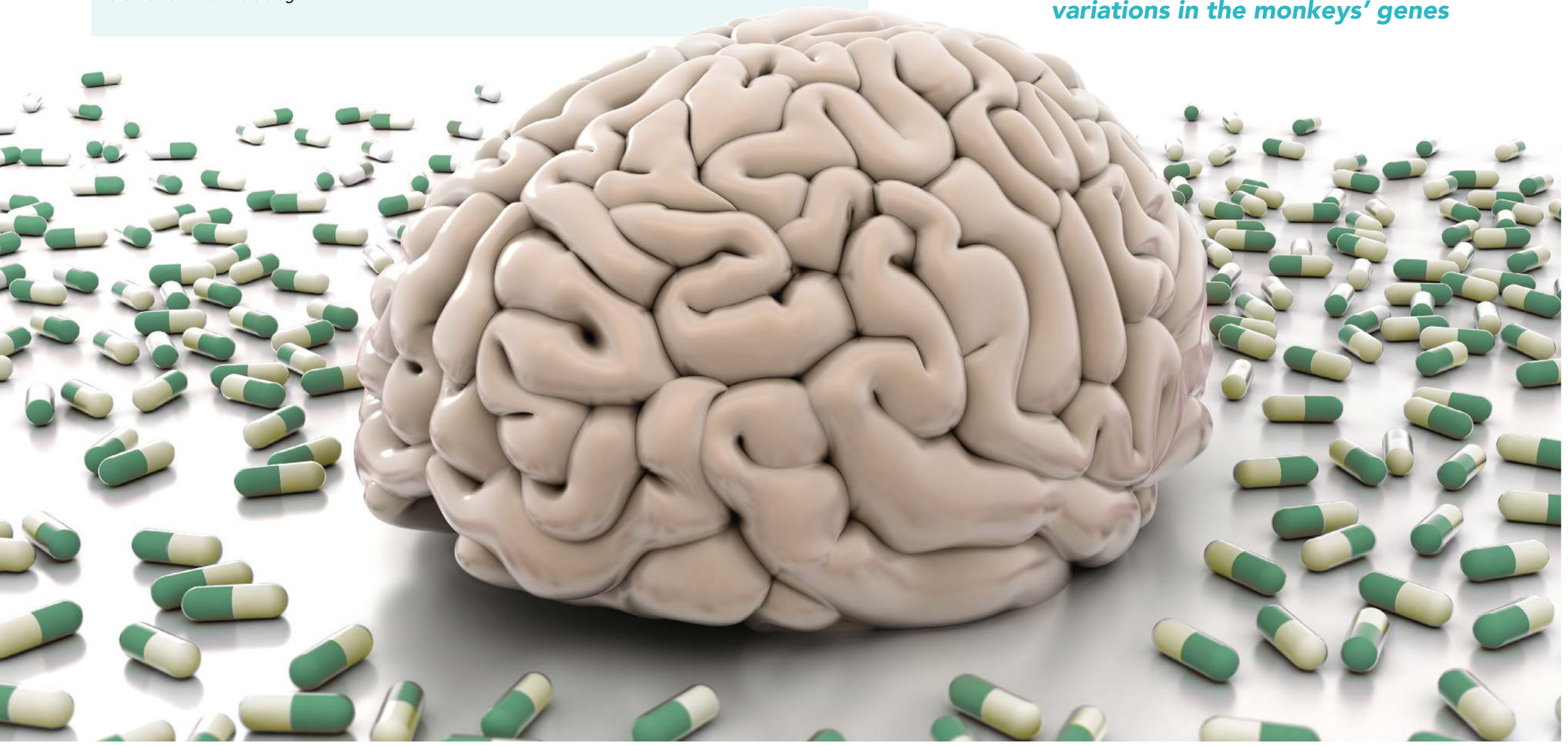
Fluoxetine (Prozac) use in children:

working towards a customised approach

***Dr Mari Golub** from the Environmental Toxicology Department at the University of California at Davis, has recently completed a five-year research project looking at the behavioural effects of fluoxetine (Prozac) on brain development. Her findings, which have so far been published in eight academic papers, supplement information on the safety of fluoxetine use in children, and show for the first time that an individual's genetic make-up can influence their reactiveness to the drug.*



Fluoxetine therapy has been used to treat children with Major Depressive Disorder (MDD) and Obsessive Compulsive Disorder (OCD) for over 14 years in the USA, and its use has recently been expanded to other behaviour disorders, including Attention Deficit Hyperactivity Disorder (ADHD), anxiety and autism. The drug, which has been used in adults since 1987, was approved for use in children by the US Food & Drug Administration (FDA) in 2003, following a 19-week clinical trial in children. Apart from the findings of this trial, and those from a later toxicology study in rats, experiments evaluating the safety of fluoxetine use in children are limited. Dr Golub's work has focused on the potential adverse effects of fluoxetine on brain development, using the juvenile rhesus monkey as a model.

More startling, and entirely new, was the observation that behavioural responses to fluoxetine were influenced by variations in the monkeys' genes

Monkeys were given a dose of fluoxetine each day for two years before the onset of puberty. The dose used was selected because it produced comparable levels of fluoxetine and its metabolites in the monkeys' blood serum as found in the blood serum of children successfully treated with the recommended dose of 20 mg per day. The monkeys were assessed for growth, impulsivity, activity, sleep, social interaction, attention and emotional response, after one and two years of dosing.

RESPONSES: BEHAVIOURAL AND BIOLOGICAL

The results showed that monkeys treated with fluoxetine had poor sustained attention, were more impulsive, had more disrupted sleep and displayed more social interaction compared to vehicle-treated controls (counterparts who received a sham preparation with no active ingredient). These results confirmed some previously described effects of fluoxetine in adults and children. More startling, and entirely new, was the observation that behavioural responses to fluoxetine were influenced by variations in the monkeys' genes, and the identification of several metabolic biomarkers of response to fluoxetine.

DRUG-GENE INTERACTIONS

Fluoxetine belongs to a group of drugs known as selective serotonin uptake inhibitors (SSRIs). SSRIs are believed to work by blocking reabsorption of the neurotransmitter serotonin into the pre-synaptic cell, thus increasing the level of extracellular serotonin available to bind to the post-synaptic receptor. Regulating the level of extracellular serotonin helps neurons to transmit messages, resulting in a more stable mood.

Under normal circumstances, serotonin levels are intrinsically regulated. Monoamine oxidase A (MAOA) is a protein that catalyses the degradation of amines, such as serotonin. The amount of MAOA produced by an individual can vary depending on their genetic make-up.

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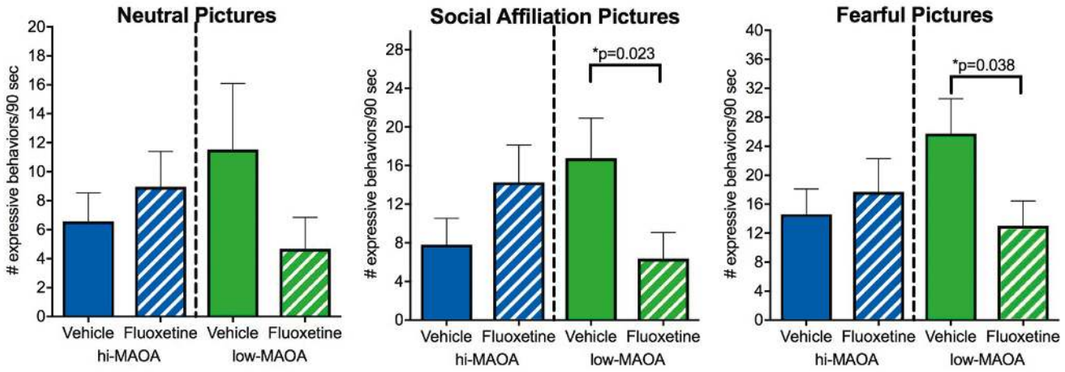

When shown pictures with different affective content, the monkeys with low-MAOA genotypes had fewer emotional responses when they were treated with fluoxetine. Reprinted from Golub MS et al. Regulation of emotional response in juvenile monkeys treated with fluoxetine: MAOA interactions. Eur Neuropsychopharmacol. 2016 Dec;26(12):1920-1929.

In Dr Golub's study, the monkeys' genetic make-up was characterised to establish for each individual whether they had versions of the gene that produced higher or lower levels of MAOA. Using this information, Dr Golub has shown, for the first time, that genetic variation between individual monkeys can influence their responsiveness to fluoxetine. This was most significant when looking at emotional responsiveness. Monkeys treated with fluoxetine who produced low levels of MAOA were less emotionally reactive than their vehicle-treated counterparts. Genes also affected aspects of other behaviours. For example, social invitations and initiations were greater in treated monkeys with the high MAOA version of the gene, whilst grooming was enhanced in treated pairs with the low MAOA version.

The biomarkers were correlated with impulsivity – a behavioural test affected by fluoxetine after one year of treatment

CORRELATING BIOMARKERS WITH BEHAVIOURS

The outcome of fluoxetine treatment can be uncertain for patients. In a recent clinical trial, around 57% of children with MDD or OCD were found to respond to fluoxetine (compared to 33% who were treated with a placebo). Prolonged dosing is often the only way to determine whether the treatment will work. Clearly, it would be more advantageous if clinicians could predict how their patients might respond to fluoxetine before recommending it as a course of treatment, and the results of Dr Golub's study could be a first step towards the development of such precision medicine.

Precision medicine seeks to use biomarkers to optimise the use of drugs such as fluoxetine in individual patients. With this in mind, Dr Golub looked for metabolites that appeared in the blood serum, cerebrospinal fluid and fibroblasts (skin cells) of monkeys after one year of treatment with fluoxetine. To understand whether these biomarkers of fluoxetine response predicted behavioural effects, the biomarkers were correlated with impulsivity – a behavioural test affected by fluoxetine after one year of treatment. The MAOA genotype of the subjects was also included in the analysis to define individual response.

Several metabolic pathways that were influenced by fluoxetine treatment were identified through the course of the study, including some which were also influenced by MAOA genotype and associated with the impulsivity measure. Continued research in this area could yield potentially useful biomarkers for predicting response to fluoxetine in young patients.

At its completion, this five-year study has advanced our understanding of the effects of fluoxetine treatment on juvenile brain development, helping to maintain safe and effective use of this therapy, and provided a glimpse of future treatment options that may be available to children with mood and behavioural disorders.

Behind the Bench

Dr Mari S. Golub

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Research Objectives

Dr Golub's research has focused on the effects of drugs, toxicants and poor nutrition on brain development using the rhesus monkey model. Her most recent project assessed the effects of fluoxetine (Prozac) on brain development.

Funding

- HD065862 – this grant supported research to supplement information on the safety of fluoxetine for children by using a juvenile non-human primate model
- OD011107 – this grant supports the facility and staffing of the California National Primate Research Center
- OD010962 – this grant supported the genotyping of infants, to study genetic sensitivity to the drug

Collaborators

- Christoph Turck, Max Planck Institute of Psychiatry
- Csaba Leranth, Yale University
- Richard Sherwood, University of Missouri
- Casey Hogrefe, University of California at Davis
- Alicia Bulleri, University of California at Davis

Bio

Mari Golub received graduate degrees in psychology, pharmacology and toxicology from University of Michigan and the University of California. Over a 40-year career at the University of California at Davis she has conducted studies of adverse effects on brain development in animal models including poor nutrition, drugs and toxicants.

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Q&A

Why were juvenile rhesus monkeys chosen as a model to study human brain development?

Non-human primates, like humans, have a prolonged period of development between infancy and puberty. During this time, which we call childhood, the brain continues to develop higher cognitive abilities and acquire experiences that will guide the individual in the future. For this reason, the effects of psychoactive drugs on children are most appropriately studied in non-human primates.

Dr Golub with her great-nephew Alex, who has been a source of inspiration for her research

What motivated you to research the possible adverse effects of fluoxetine treatment in children?

After fluoxetine was approved for children, an increase in suicidal thinking was reported in young people. This alarmed the medical community and activated biomedical researchers like myself to investigate the side effects of this drug in children versus adults. Also, our family has a young member with autism who had been prescribed psychoactive drugs. When I spoke to his mother, she described her concern about using the drugs and the value of more information on their safety.

What other genetic variations could interact with fluoxetine treatment?

Researchers are studying several genes for interaction with fluoxetine in adults, and also in transgenic mice. Prominent among these is the gene for the serotonin transporter (SERT). Monkeys will continue to be valuable for this research as they share many polymorphisms with humans, including SERT polymorphisms.

When will we see the use of precision medicine in prescribing drugs such as fluoxetine?

Our monkey subjects were not selected for any of the behavioural disorders that occur in children, like depression, anxiety, ADHD or autism. We hope that our study will encourage physicians to look into a possible role of MAOA polymorphisms in response to treatment in children. Only at that point will we have contributed to the use of precision medicine in childhood fluoxetine therapy.

As you near retirement, what have been the highlights of your career in developmental neurotoxicology research?

When I began studying psychopharmacology in the 1960's, this class of drugs was just being developed and coming into widespread use. Our fluoxetine study in non-human primates was a fitting conclusion of my research in this area.

This study has advanced our understanding of the effects of fluoxetine treatment on juvenile brain development