RESEARCH SUMMARIES

Serotonin transporter gene (SLC6A4) polymorphism and susceptibility to a home visiting maternal-infant attachment intervention delivered by community health workers in South Africa: Reanalysis of a randomized controlled trial

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Many recent studies have suggested that targeting those who care for infants and young children with help, to improve their quality of care and nutrition they offer, and their own mental wellbeing, can improve outcomes for the children involved later in childhood and beyond. These interventions are cost-effective and can be particularly helpful for children who are raised in poverty. However, rigorous statistical analysis of such studies has often found the size of the effect to be small. This analysis typically involves taking a simple average of the outcomes over each child in a study, which can be misleading if some children are, for whatever reason, significantly more susceptible to that intervention than others.

And there is plenty of evidence for differences between individual children in their response to psychosocial intervention. Furthermore, since 2003 – about the time when the first human genome sequence was completed – it has been known that genetics can play a part in this. In particular, variations in a gene known as the serotonin transporter are linked to differences in susceptibility to depression linked to early childhood trauma. This gene carries the code to form a protein that 'recycles' the so-called 'mood chemical' serotonin from the space between neurons (nerve cells) back into the neuron from which it was released. It can take two forms that vary only in the length of a small piece of its DNA and that are therefore referred to as 'short' and 'long'. Each individual inherits one copy of this gene from each parent and may thus carry two short genes, two long ones or one of each; carriers of the short form are thought to benefit more from early childhood interventions.

In psychology and medicine, the most powerful way of proving a definite link between an intervention and an outcome is through a randomised controlled trial (RCT), in which participants are randomly allocated to receive the intervention tested or not. So far, few RCTs testing a genetic component to susceptibility to early childhood intervention have been published, but a combined analysis of those few did suggest a link between intervention benefits and the short form of the serotonin transporter gene. However, these studies all have some limitations: the sample size may be small, or there may be little diversity between participants. And crucially, given the link between poverty and poor early childhood development, all these studies took place in the US or Europe, with most subjects being white and middle-class.

An international group of scientists led by Barak Morgan of the University of Cape Town in South Africa has now performed the first randomised trial of the effect of serotonin transporter gene variants on susceptibility to early childhood intervention in

a low-income country. They did this by re-analysing the results of a South African trial to take account of this genetic variation. In the original trial, a total of 452 low-income black women in Khayelitsha, South Africa who became pregnant between 1999 and 2003 received either an intensive intervention programme involving home visits by community health workers or standard ante- and post-natal care. The intervention concerned, known as 'Thula Sana' ('hush baby' in the local language, Xhosa) promoted secure attachment between infants and their mothers by helping the mothers understand and communicate with their infants and manage their distress. Each mother in the intervention group was visited 16 times from the third trimester of pregnancy until her infant was six months old. Infants were tested for attachment at 18 months using a standard procedure known as the 'strange situation' in which the toddlers were observed in an unfamiliar playroom, with their mothers present during only some of the test. Those who had been in the intervention group in babyhood were found to be more likely to be securely attached to their mothers, although the effect was quite small.

Morgan and his co-workers re-analysed the results of this trial to include genotype information by contacting as many as possible of the families involved when the children who had taken part in the study reached 13 years of age. A total of 279 adolescent children were contacted in this way and agreed to provide a sample of DNA for genotyping; attachment data at 18 months was also available for 220 of these children, exactly half (110) of whom had been in each of the original groups.

In analysing the effect of genotype on the results of the intervention study, the researchers grouped together into one category those individuals with two copies of the 'short' form of the gene and those with one copy. The 'short' form is the less common, and 40% of the adolescents with both a genotype and historical attachment data had the short/long or short/short genotype and therefore fell into this 'likely susceptible' category. When the attachment results were separated according to genotype, the results became dramatic. The only real difference was found in those individuals with at least one 'short' form of this gene. Taking these separately, the proportion of toddlers found to be securely attached to their mothers was only 48% in the control group but about 84% in those who received the intervention (see graph). In contrast, the intervention made almost no difference to those babies who were later found to have two long forms of the gene. Most of these infants did well, with 79% of the intervention group and 80% of the control group being securely attached at 18 months.

This study illustrates a case in which an intervention that confers a small benefit on average over a large population is shown to have a much larger benefit for genetically susceptible individuals. The findings raise questions about whether, when resources are limited, it would be ethical to confine a programme such as 'Thula Sana' to those individuals who are genetically most likely to benefit. The authors also comment that the original trial included mothers and babies from a socially and ethnically homogenous group. Also, although the study participants were poor, the infants were not maltreated or deprived in any other specific way. More similar studies, particularly in other middle and low-income countries, will be useful for discovering how replicable these findings are and, perhaps more importantly, if treatments can be devised to

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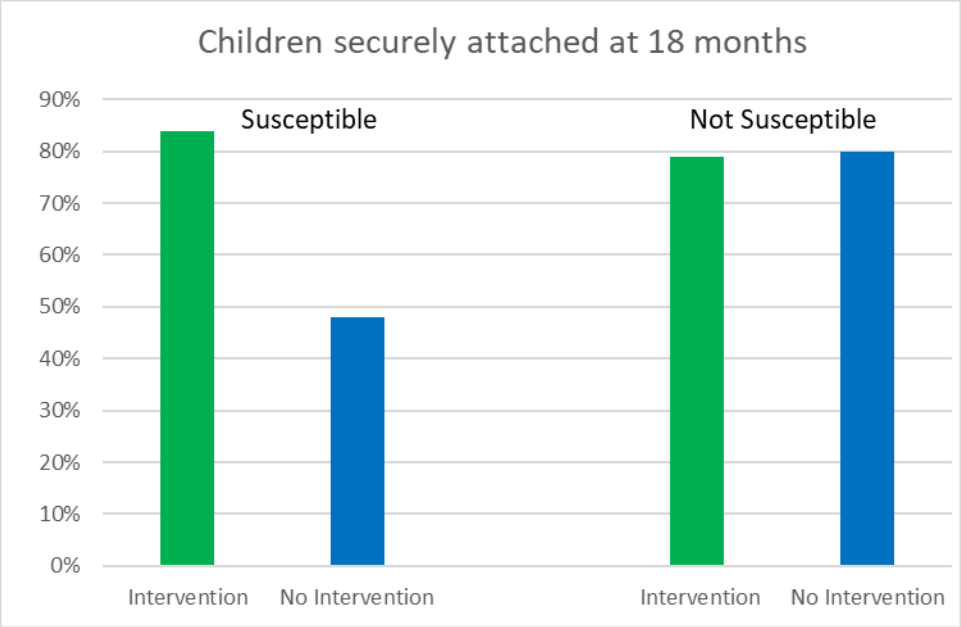
benefit that majority of infants who are genetically unsusceptible to this type of intervention.



Children with at least one short form of the serotonin transporter gene (susceptible children) are much more likely to benefit from the 'Thula Sana' intervention than those with two long forms of the gene.

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