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Dear participants and parents

During 2003 or 2004 you participated in our magnetic resonance imaging experiments at the Autism Research Centre and Addenbrooke's Hospital, Cambridge. It can be a long road from doing a scientific experiment to deriving the experiment's conclusions, but we're happy to say that the third and final report based on the work that you did with us has now been completed and published – and we've not forgot our promise to update you with the end results! To reduce the bulk of this mailing we're enclosing only the front pages of each of these three reports; we'll summarise our findings in this letter, but if you'd like to read the complete reports you can download them from http://www.mit.edu/~belmonte/Publications/ .

Our results focus on two general parts of the brain, prefrontal cortex and inferior parietal cortex. Prefrontal cortex is rather like the conductor of an orchestra; it signals and coordinates many other parts of the brain and cues them as to just when to come into the symphony, as it were, so that they can all cooperate to solve complex problems and tasks. Parietal cortex is a bit like a lead violin; it coordinates all the other violins (parts of the brain responsible for sensory perception) but it takes its cues from the conductor (prefrontal cortex). You may recall that we asked you (or your child) to do three tasks: first, you listened to sounds without having to pay any especial attention to them – some of these sounds were frequent, others were less common, and some were strange, new sounds; second, you listened to these sounds again but had to press a button whenever you heard a weird sound; third, you glimpsed pictures of lines and had to decide whether one set of lines had a particular orientation at the same time as another had a particular colour. All of these tasks evoked brain activity in prefrontal and parietal cortices that differed between those children with autism spectrum conditions and those without – and the combination of differences in all three experiments was very informative!

Before we get into the results, it's crucial to note that the differences that we found appear at the level of groups and not, in general, at the level of individual people. That is, when we say that people with autism spectrum conditions (or their siblings) had more or less of a particular trait than people without autism spectrum conditions, we don't mean to imply that every individual person with an autism-spectrum condition had more or less of that trait than every individual person without. Instead, what we mean is that the *average* level of this trait, calculated over every person with an autism-spectrum condition, differed significantly from the average over every person without an autism-spectrum condition. We do in most instances find a great deal of overlap between these groups: there are people with autism-spectrum conditions who are in the non-autistic range, and there are people without autism-spectrum conditions who are in the autistic range. So when we say that there are differences, we don't mean to make any sort of pronouncement about individuals. Everyone is different.

In the hearing task in which you just listened and didn't have to pay particular attention to the sounds, we found that both prefrontal and parietal cortices were less active in the autism-spectrum children than in the non-autistic children. These results are reported in a scientific paper published in January 2006. In particular, activations in one particular prefrontal region, the "dorsal anterior cingulum" had very little overlap between these two groups of children: most of the non-autistic children activated it more in response to the rare sounds, whereas autism-spectrum children had the inverse pattern, activating dorsal anterior cingulum more in response to common sounds and letting the rare ones go by, seemingly unremarked on by the brain. Most of us involuntarily notice the rare, once-in-a-while occurrences in the environment, but people with autism spectrum conditions tend more to notice repeating events.

This is not to say, however, that people with autism spectrum conditions aren't *capable* of noting rare events. In a follow-up paper published in September 2008, we reported on how these autism-spectrum brain activations change when people are instructed to listen for the rare sounds and to note these by pressing a button: in this scenario, in which participants are explicitly asked to pay attention to the rare sounds, we find that children with autism-spectrum conditions activate prefrontal and inferior parietal cortices *more* than children without autism-spectrum conditions do, and the amount of this activation correlates with their scores on the Autism Spectrum Quotient (the checklist of autism symptoms that you filled in). So when they aren't asked to do anything in particular, children with autism spectrum conditions focus on the repeatable aspects of their environments, but when they're asked explicitly to focus on the rare aspects, they do so very intensely, to an extent that exceeds the level of focus of non-autistic children – and the more autistic they are, the more they focus. As in so many other aspects of brain function and behaviour in autism spectrum conditions, the issue in this case seems not one of incapacity but rather one of flexibility – at a biological level, the capacity to respond to new information is intact and even superior, but it's simply not engaged in the absence of any specific instruction to do so. This verification that children with autism spectrum conditions are quite capable, biologically, of paying attention to new, informative events rather than to repetitive events raises the question of how we might prompt them to do so as a matter of course during everyday experiences, and how such prompting might help them extract information from novel events such as social cues.

Interestingly, we found that this relationship between the level of autistic traits as measured by the Autism Spectrum Quotient and the level of frontal lobe activity as measured by the MRI scanner held not just within the children with autism-spectrum conditions but also within the children without autism-spectrum conditions. Each of us, autistic or not, has some level of "autistic" cognitive and personality traits, and it turns out that these correlate with frontal lobe activation. This result suggests that autism may be an extreme of normal variation in personality traits within the general population: the stronger one's frontal lobe activity, the more autistically one thinks and behaves.

Our final result, published just this month, puts a capstone on this relation between frontal and parietal lobe activities and autistic behaviour, by showing that what distinguishes children with and without autism spectrum conditions isn't so much the absolute presence or absence of brain activity but rather the *timing* of this activity. As you know, we studied three groups of children: those with autism spectrum conditions, those without, and also the siblings of people with an autism spectrum condition who did not themselves have an autism spectrum condition. You may recall that in our third experiment we compared your responses to some difficult pictures where you had to ignore distracting lines of various colours and orientations, and less difficult pictures where most of the lines were the same colour and the same orientation and there was therefore less distraction. Although this experiment was very difficult for everyone who tried it – that's the way it was designed to be! – we found that the children with autism spectrum conditions had a bit more trouble with it than those without autism spectrum conditions. We also found that the siblings of people with autism spectrum conditions were smack in the middle, doing a bit better than the autism-spectrum children but a bit less well than the non-autistic children who did not have any autism-spectrum siblings. In this case again, it seems, autism is revealed as an extreme of normal cognitive variation. All of us have more or some amount of the genes for such variation, and those of us who have autism-spectrum siblings have more of these genes.

It was when we compared *brain* activations, though, that a very interesting pattern appeared. First of all, we found that autism-spectrum children had less of a *difference* in frontal and parietal activity between the difficult and easy conditions – probably because they were activating these parts of their brains *more* overall, so that when we subtracted a very large activation for the easy condition from a similarly large activation for the hard condition, we found only a very small difference between the two. In contrast, non-autistic children had a large difference, probably because they activated only slightly for the easy condition. It's rather like pressing the accelerator pedal in a car: when one wants to climb a steep hill, one stamps the pedal all the way down so that the engine has the necessary power, but when one wants to ascend only a gradual incline, one gently taps the pedal. What we've found is that people with autism spectrum conditions tend not to differentiate: when they add power to their mental 'engine,' they gun it all the way.

This very intensity of brain activation may perhaps be reflected in the intensity with which people with autism spectrum conditions approach so many of their interests and activities: when they're committed to a goal, they pursue it narrowly, relentlessly and single-mindedly – and in the right contexts, this intensity is quite a beneficial trait! Supporting this idea, we found that *greater* levels of autistic traits as measured by the Autism Spectrum Quotient, and also as measured by our detailed diagnostic interviews with the parents of children with autism spectrum conditions, correlated with *lesser* differences in levels of brain activation between the difficult and easy conditions – and, just as in our previous experiment, this correlation held not only in children with autism spectrum conditions but also in children without autism spectrum conditions.

Most interestingly, both in children with autism-spectrum conditions and in their non-autistic siblings, this difference in brain activations between the difficult and easy conditions (a small one in the autism-spectrum group, a large one in the non-autistic siblings) began to appear only after about three seconds *after* the appearance of the lines – and because participants were given only three seconds to make a decision about the lines, this timing was just too late to influence that decision! This result seems a biological corroboration of what many people with autism spectrum conditions report about their interactions with the world, and in particular with the *social* world: events move so quickly that there isn't time to "jump in."

Although children with and without autism spectrum conditions within these families had the same delayed pattern of frontal lobe response, it was only those with autism spectrum conditions who showed a great deal of parietal-lobe activity that was independent of frontal-lobe activity: in people without autism, the parietal lobe tended to become active only once it had received a signal from the frontal lobe, whereas in people with autism spectrum conditions, parietal lobe activated without having to be told to do so. We say that this parietal activity in non-autistic children is "top-down" in that it depends on signalling from a sort of control centre in the frontal lobe – like the lead violinist receiving a cue from the conductor. In the autism-spectrum children, the parietal activity is "bottom-up" in that it's driven directly by sensory experience, without mediation by the frontal lobe – like the violinist responding directly to the music and knowing when to come in without the conductor's cue. This bottom-up strategy confers some unique cognitive skills and also some unique drawbacks: it's more efficient because it doesn't depend on such elaborate processing, but the trade-off is that it produces a symphony that is less directed and coordinated. And in fact we see this uncoordinated pattern throughout the brain in children with autism spectrum conditions, but not in their non-autistic siblings: it's only in the people with autism spectrum conditions that every player in the orchestra, as it were, is doing their own thing without a lot of control from the conductor. What may be going on, we suspect, is that this slow conductor (that is, a delayed timing of frontal activation) is what runs in families. Within those families, the individuals who develop autism spectrum conditions may be particularly susceptible to the influence of this slow conductor: some orchestras can get on quite well without a conductor but some very much need one in order to coordinate the music that they make.

Our question now is how might this developmental process unfold: what are the factors that make an individual especially susceptible (or on the other side of the issue what are those that make an individual especially resilient), and how does a familial liability to autism translate, as development of the brain and the mind proceeds, into autism itself? If we can answer this question, then perhaps we can find a way to block this process, preserving all the special cognitive skills that come along with autism conditions (for example intense focus and strong attention to detail), but preventing the problems that people with autism spectrum conditions face (for instance difficulty sending and receiving social cues). You can find further details on this current work at http://www.mit.edu/~belmonte/

None of this work would have been possible without you, and for that we thank you very much. You were willing to be part of this research, even knowing that there would be no direct benefit to you other than a generally increased knowledge about the neurobiology of autism. Your altruism has allowed us to take one more step – one of many – towards an understanding of autism.

Best regards

Matthew Belmonte

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