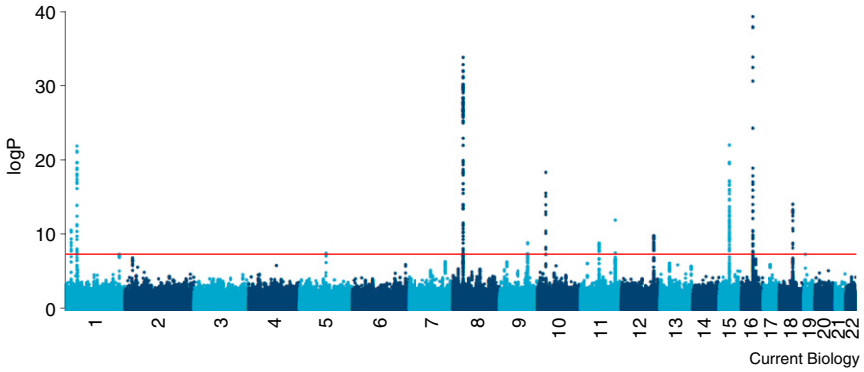

Figure 1. Visualising a GWAS with a Manhattan plot.
The horizontal axis shows the position of every locus that the microarray interrogates. The numbers denote chromosomes. The vertical axis is the negative logarithm (base 10) of the *P*-value (logP) of the association between phenotype and genotype. This plot is based on simulated data, but the experimenters would be pleased, as there are a number of peaks that exceed a genome-wide significance threshold (red line).

population expansion is that most alleles are rare, and are not interrogated by standard commercially available microarrays. The full extent of what is missed became apparent from recent population scale re-sequencing projects: only 13% of variants with a frequency of less than 0.5% had been described previously. If rare variants make a substantial contribution to your disease of interest, beware! GWAS won't find them. You may also have read that GWAS doesn't work because GWAS loci cannot account for much of the known or estimated heritability of a trait ('missing heritability'). For instance, despite finding 180 loci that influence height, these loci account for just 10% of the variation. But, this does not take account of all those SNPs that don't make the significance threshold. They can't simply be ignored, but what to do with them? Peter Visscher has an answer, using an approach routine in plant and animal genetics. Examining the effect of all SNPs, regardless of statistical significance, almost half of height's phenotypic variance can be explained by common SNPs. So is there a 'missing heritability' problem? Well, we still can't explain *all* the variance.

What have we learnt from GWAS?
Two common complaints are that GWAS gives us genetic loci not genes (true!) and that lists of genetic loci don't tell us anything about mechanism (true too!). One of the insights of the ENCODE project is that GWAS hits lie preferentially in regulatory regions of the genome (enhancers, promoters and other less well categorized elements). Tying variation at an enhancer to a particular gene product is admittedly hard, but the nearest neighbouring gene hypothesis works well (ENCODE again helps here, revealing that action on the megabase scale is rare, most elements operate over a few tens of kilobases). Next generation GWAS are now including tests of function, testing gene expression patterns of nearest-neighbour genes in relevant tissues, and (impressively) in a GWAS for human red blood cell phenotypes, haemocyte-specific RNA interference (RNAi) silencing in *Drosophila melanogaster*.

Does this mean GWAS can deliver the holy grail of mechanism? Take note, journal editors, genetics is a hypothesis-free enterprise! How else could mathematicians, statisticians and bioinformaticians partake?

Where can I find out more?

Altshuler, D.M., Gibbs, R.A., Peltonen, L., Altshuler, D. M., Gibbs, R.A., Peltonen, L., Dermitzakis, E., Schaffner, S.F., Yu, F., Peltonen, L., *et al*. (2010). Integrating common and rare genetic variation in diverse human populations. Nature *467*, 52–58.
http://www.nature.com/nrg/series/gwas/index.html
Lander, E.S. (1996). The new genomics: global views of biology. Science *274*, 536–539.
Reich, D.E., Cargill, M., Bolk, S., Ireland, J., Sabeti, P. C., Richter, D.J., Lavery, T., Kouyoumjian, R., Farhadian, S.F., Ward, R., *et al*. (2001). Linkage disequilibrium in the human genome. Nature *411*, 199–204.
Wellcome-Trust-Case-Control-Consortium (2007). Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature *447*, 661–678.
Yang, J., Manolio, T.A., Pasquale, L.R., Boerwinkle, E., Caporaso, N., Cunningham, J.M., de Andrade, M., Feenstra, B., Feingold, E., Hayes, M.G., *et al*. (2011). Genome partitioning of genetic variation for complex traits using common SNPs. Nat. Genet. *43*, 519–525.

Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7BN, UK.
E-mail: jf@well.ox.ac.uk

Correspondences

Children with autism do not overimitate

L. Marsh, A. Pearson, D. Ropar, and A. Hamilton

Copying the behaviour of others is important for forming social bonds with other people and for learning about the world [1]. After seeing an actor demonstrate actions on a novel object, typically developing (TD) children faithfully copy both necessary and visibly unnecessary actions [2]. This 'overimitation' is commonly described in terms of learning about the object, but may also reflect a social process such as the child's motivation to affiliate with the demonstrator [3] or to conform to perceived norms [4]. Previous studies of overimitation do not separate object learning and social imitation because they use novel objects. Even though researchers consider these objects to be causally transparent in their mechanism, young children's causal reasoning about novel objects is unclear [4]. The present study measures the social component of overimitation by using familiar objects, which preclude the learning component of the task. Here we report a significant reduction in overimitation in children with autism spectrum conditions (ASC). This is coherent with reports that these children have profound difficulties with social engagement [5] and do not spontaneously imitate action style [6] (see also [7]).

We tested 31 children with ASC, 30 TD children matched for verbal mental age and 30 TD children matched for chronological age on an overimitation task using familiar objects. All children were assessed for verbal mental age, overimitation and understanding of action rationality (see Supplemental Information). On each of five trials, the child was asked to watch carefully as a demonstrator showed how to retrieve a toy from a box or build a simple object. Critically, each demonstration included two necessary actions (such as unclipping and removing the box lid) and one unnecessary action (such as

tapping the top of the box twice). The apparatus was then reset behind a screen and handed to the child, who was instructed "get/make the toy as fast as you can". These instructions emphasise the goal, and copying was never mentioned. This means any overimitation is spontaneous and socially motivated. All trials were videotaped for analysis, and completion of the unnecessary action was coded as overimitation. After all overimitation trials, children watched the demonstrator complete individual actions from each sequence, and rated each action on a five point scale from 'sensible' to 'silly'. Rationality discrimination was calculated as the difference between a child's rating of the unnecessary action and the necessary action from the same sequence, with high scores indicating good judgement of which action is more rational.

All TD children were able to complete all tasks and retrieve or build the toy on every trial; children with ASC completed the tasks on 97% of trials (see Supplemental Information). However, we found a striking difference between autistic and TD children in both overimitation and rationality discrimination. TD children copied 43–57% of the unnecessary actions but children with autism copied only 22% (Figure 1A). All groups performed significantly above chance in the rationality discrimination task, but children with autism performed worse than the TD children (Figure 1B). These results have several implications.

First, TD children show substantial overimitation of unnecessary actions on familiar objects, despite understanding that these actions are 'silly'. These results lend support for the position that overimitation in typical children is a social phenomenon rather than being driven by the child's causal learning about the objects. This social overimitation may index a child's motivation [5] to affiliate [3] or to conform to perceived norms [4].

Second, children with autism show significantly less overimitation of the demonstrator's actions. This is not driven by weak motor skill because all the unnecessary actions were familiar simple actions (for example, tapping a box) and all children were able to complete the more complex goal-directed

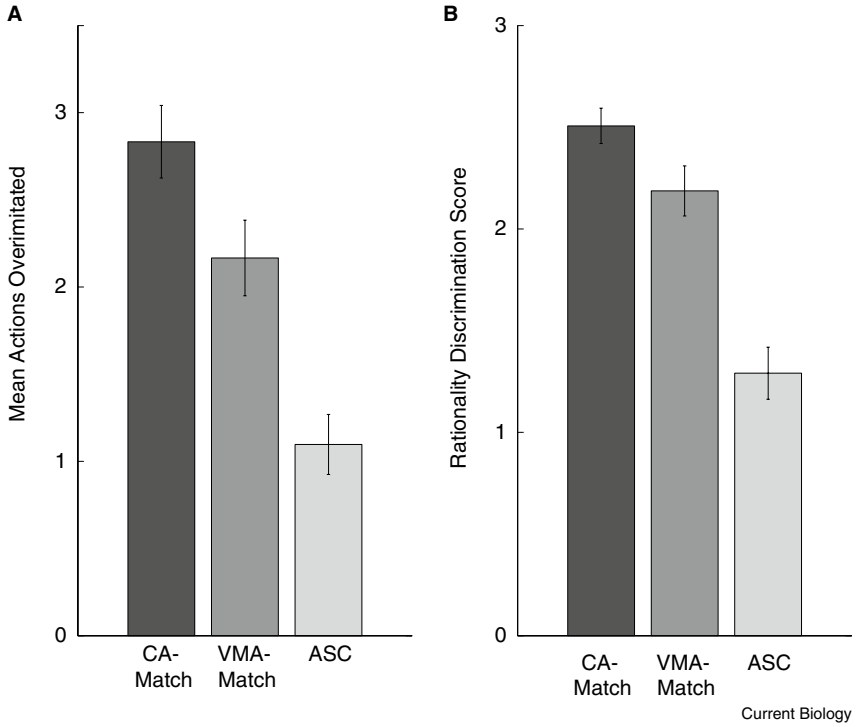

Figure 1. Performance of all children on the overimitation and rationality discrimination tasks. (A) Number of trials where the unnecessary action was copied (maximum 5) in TD and ASC participants. There was a significant reduction in overimitation behaviour in ASC participants compared to CA-match ($F(1,58) = 12.84$, $p < 0.001$) and VMA-match ($F(1,58) = 7.01$, $p = 0.01$) TD controls. Error bars represent ±1 standard error. (B) Mean rationality discrimination score (ranging from –4 to 4) in TD and ASC participants. All three groups performed significantly above chance (zero) (CA-match: $t(29) = 16.1$, $p < 0.001$; VMA-match: $t(29) = 10.2$, $p < 0.001$; ASC: $t(30) = 5.9$, $p < 0.001$). Children with ASC were significantly worse at judging the rationality of actions, when compared to CA-matched ($F(1,58) = 19.62$, $p < 0.001$) and VMA-matched ($F(1,58) = 9.29$, $p = 0.003$) groups. Error bars represent ±1 standard error. (See also Figure S1 in the Supplemental Information.)

actions in the sequence. It is also not driven by superior causal reasoning, because the children with ASC also performed worse on the rationality discrimination task. The data go beyond previous studies which showed reduced imitation of action style [6] and reduced spontaneous imitation [8] where differences in behaviour could be driven by the children with autism failing to adopt the same goal as the demonstrator. In our task, children are instructed that the goal is to make/retrieve the toy, and all are able to do so. The failure of children with autism to spontaneously copy unnecessary actions can best be explained in terms of reduced social motivation in these children, with less desire or ability to affiliate with or conform to the perceived norm.

Previous studies have examined social attention in autism using eye-tracking tasks [9], and have examined social motivation using brain-imaging of high functioning adults with ASC (reviewed in [5]), but simple methods for measuring social motivation in children did not exist. The ease of implementing our task, and the close links between overimitation and social mimicry in adults [3], mean that this approach can provide a powerful and general tool for examining social motivation in child and adult participants. There is an important contrast between our results and a recent study in which children with autism saw unnecessary actions on novel objects and showed the same rate of overimitation as typical children [10]. One possible interpretation of this difference is that the study using novel objects [10] tapped imitation-to-learn which may be intact in autism, while social imitation, as tested with our simple familiar objects, is atypical. Such a distinction is congruent with previous theories that posit normal goal-directed imitation and abnormal

social imitation in autism [7], but further testing of the circumstances that drive children with autism to imitate would be valuable.

Overall, our study leads to two important conclusions. First, studies of social interaction can examine the social component of imitation behaviour independent of the object-learning component, and this can best be done using familiar objects. Second, children with autism do not show overimitation of actions on familiar objects. This specific difference in a behaviour linked to social affiliation and norm conformity is compatible with claims of abnormal social motivation in autism.

Supplemental Information

Supplemental information includes experimental procedures, supplementary results, discussion, references, one figure and two tables and can be found with this article online at http://dx.doi.org/10.1016/j.cub.2013.02.036.

References

1. Carpenter, M. (2006). Instrumental, social and shared goals and intentions in imitation. In S.J. Rogers, and J.H.G. Williams (eds), Imitation and the Social Mind: Autism and Typical Development. (New York: Guildford Press), pp. 48–70.
2. Horner, V., and Whiten, A. (2005). Causal knowledge and imitation/emulation switching in chimpanzees (Pan troglodytes) and children (Homo sapiens). Anim. Cogn. *8*, 164–181.
3. Over, H., and Carpenter, M. (2012). Putting the social into social learning: Explaining both selectivity and fidelity in children's copying behaviour. J. Comp. Psychol. *126*, 182–192.
4. Kenward, B., Karlsson, M., and Persson, J. (2011). Over-imitation is better explained by norm learning than by distorted causal learning. Proc. R. Soc. Lond. B *278*, 1239–1246.
5. Chevallier, C., Kohls, G., Trioani, V., Brodkin, E.S., and Schultz, R.T. (2012). The social motivation theory of autism. Trends Cogn. Sci. *16*, 231–239.
6. Hobson, R.P., and Lee, A. (1999). Imitation and identification in autism. J. Child Psychol. Psychiat. *40*, 649–659.
7. Hamilton, A.F.C. (2008). Emulation and mimicry for social interaction: A theoretical approach to imitation in autism. Q. J. Exp. Psychol. *61*, 101–115.
8. Ingersoll, B. (2008). The effect of context on imitation skills in children with autism. Res. Autism Spect. Dis. *2*, 332–340.
9. Klin, A., Jones, W., Schultz, R., Volkmar, F., and Cohen, D. (2002). Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism. Archiv. Gen. Psych. *59*, 809.
10. Nielsen, M., Slaughter, V., and Dissanayake, C. (2012). Object-directed imitation in children with high-functioning autism: Testing the social motivation hypothesis. Autism Res. Nov 16. doi: 10.1002/aur.1261. [Epub ahead of print].

School of Psychology, University Park, University of Nottingham, Nottingham NG7 2RD, UK.
E-mail: antonia.hamilton@nottingham.ac.uk

Speech-like vocalized lip-smacking in geladas

Thore J. Bergman

Recently, we have seen a surge of interest in identifying possible evolutionary links between primate facial communication and human speech (for example [1]). One suggestion is that primate 'lip-smacking' — a non-vocal, rhythmic movement of lips usually given in conjunction with affiliative behavior — may have been a precursor to speech [1]. This idea arose because lip-smacking shares several production features with human speech that the vocalizations of non-human primates lack, most notably a 3–8 Hz rhythm [1]. Evidence that non-human primates are indeed able to vocalize while simultaneously producing rhythmic facial movements would lend initial, but important, support to the notion that lip-smacking is a plausible evolutionary step towards speech. Here, I report that a wild primate, the gelada (*Theropithecus gelada*), makes a derived vocalization (the vocalization is absent in their close relatives, the *Papio* baboons) that is produced while lip-smacking, called a 'wobble'. The rhythm of wobbles (6–9 Hz) closely matches that of human speech, indicating that a vocalized lip-smack produces sounds that are structurally similar to speech. Geladas are highly gregarious primates with a relatively large vocal repertoire. Their independent evolution of a speech-like vocalization involving complex facial movements provides initial support for the hypothesis that lip-smacking was a precursor to the emergence of human speech.

Research on the evolutionary origins of human speech has often focused on non-human primate (hereafter, primate) vocal communication (for example [2]). But many critical components of human speech are conspicuously absent from the vocalizations of primates, including a diverse repertoire of sounds [3]. Perhaps because of this, researchers have looked to other forms of communication, such as facial communication, for possible evolutionary precursors to human speech [1]. Facial communication may be particularly relevant for understanding the origins of speech, because facial movements are critical for both the production and comprehension of spoken words (for example [4]). One common form of facial movement observed across a wide variety of primate taxa is 'lip-smacking' [5], an action that involves rapid opening and closing of the mouth and lips [1]. More notably, lip-smacking has a periodicity that closely matches the periodicity of the gaps between syllables in many human languages (2–7 Hz [6]). This periodicity may be a fundamental aspect of human speech; and indeed, studies have shown that disruption of this rhythm impairs our ability to comprehend speech [7]. Ghazanfar and colleagues [1] recently demonstrated that the facial movements involved in macaque (*Macaca* sp.) lip-smacking are very speech-like in their synchronization and rhythm (features that contrast with other facial movements such as chewing). These authors suggested that lip-smacking may have been an evolutionary precursor to speech.

Primate vocalizations are, however, typically produced without movement of the lips, jaw, and tongue, resulting in a steady sound that lacks the undulations of human speech [8]. Although some primate vocalizations occasionally include limited facial movements, such movements are neither rhythmic nor do they produce speech-like periodicity (for example, the display call of geladas [3]). One possible example of a call involving complex facial movements is the 'girney' vocalization found in several macaque species. Girneys have been described as being produced in conjunction with lip movements and teeth chattering, though spectrograms of the call do not indicate any periodicity (for example [9]). Published spectrograms may have missed examples of periodic calls that result from simultaneous rhythmic facial movements and vocalizations; however, at present it appears that girneys are simply produced in close temporal proximity to complex facial movements and not simultaneously with them. Even