to my later obsession with the theory that there is a weak drive for meaning in autism, known as the theory of weak central coherence. The next most influential papers for me were '*Does the chimpanzee have a theory of mind?*' by David Premack and Guy Woodruff and '*Beliefs about Beliefs*' by Heinz Wimmer and Josef Perner. These papers were key to the development of the hypothesis that autistic children lack the ability to attribute mental states to others and themselves, sometimes referred to as a mentalising deficit or mindblindness.

Why autism? I came across autistic children for the first time at the Institute of Psychiatry. This was just as dramatically mind-changing for me as the presentations of patients with different kinds of mental disorders had been earlier. I was instantly captivated by these strange children, and my fascination has never diminished. They gave me riddles that just demanded to be confronted — though never to be solved. I still feel the sense of wonder and amazement at the paradoxical combination of strengths and weaknesses in the autistic mind. Nobody has explained the savant phenomenon yet, but the paper by Hermelin and O'Connor that made such a big difference to me is probably still as near as you can get to the processes underlying this phenomenon.

What advice would you offer someone wondering whether to start a career in biology? I would like to speak to women in particular, because there are still too few women in science. I would say: it is fine to start a career in biology even if you come with an arts background, because you can catch up if you really want to. Universities should recognise that it is a good idea to give a second chance to motivated students. I still believe that it is easier to find a fulfilling career in science than in the humanities. Also, I would like to stick up for psychology as a way into science. Even if you choose psychology, because you didn't have the qualifications in maths and biology that now you wished you had, go on and learn what you need in these subjects. For science-phobics psychology is the perfect medium to get introduced to scientific methods.

Here are some other things I would say to a woman starting a career in science: Show courage and resilience and aim high. Don't play on femininity, but don't get taken in by typical male power struggles; why waste the emotional energy when you can network with other women and go shopping instead? Be kind, generous and collaborate, but take the credit.

Do you have a scientific hero? My heroes come from fiction, like Mary Shelley's Frankenstein (not the monster — the scientist!), or Conan Doyle's Sherlock Holmes. Frankenstein is so incredibly courageous and ambitious as to want to find the secret of life. He works very hard and with great imagination, and he tragically fails. This is the intensely passionate and romantic side of science. It is often ignored and worse, derided. But perhaps without a dash of the romantic passion you can only be a good but not a brilliant scientist. Sherlock Holmes is the opposite of romantic, and he never fails. He shows the dash of autism that may be as vital for the genius detective as for the genius scientist. The hallmark of this style is keenly perceptive attention to what others consider minor details. Conan Doyle speaks of the 'significance of trifles', and made Holmes the author of a "little monograph on the ashes of 140 different varieties of pipe, cigar and cigarette tobacco". The deeply romantic and the obsessively pedantic are both part of my image of a scientific hero.

What do you think are the big questions to be answered next in your field? Developmental cognitive neuroscience could and should have an impact on education. The science of the mind/brain has huge potential for improving our mental capacities in all sorts of ways. Learning changes the brain for sure, but teaching enhances learning and is capable of changing the brain even more. Learning through others is what really sets humans apart from other species. Once improved education has made us cleverer and less ignorant, we might get wiser too. But this is another very big question — this is for the long term.

Institute of Cognitive Neuroscience, University College London, 12 Queen Square, London WC1N 3BG, UK; and Center for Functionally Integrative Neuroscience, Aarhus University, Denmark.
E-mail: u.frith@ucl.ac.uk

Quick guides

Gaze following

Klaus Zuberbühler

What is gaze following? Gaze following occurs if an individual perceives another's gaze and, as a result, comes into contact with the object or event the other is attending to.

Why is this interesting? Trying to understand how other minds work, particularly those of non-human, non-linguistic animals, is not a trivial task. Researchers are limited to a small set of behaviours from which to interpret mental states, and 'gaze following' is one of particular interest. Gaze usually indicates attention, and one important question is how and why an individual is motivated to find the object of that attention. Is this due to a simple automated response, or is it the result of a mental calculation about the underlying cause?

How widespread is gaze following? Gaze following probably occurs in most primates, from prosimians to humans, but it is not a uniquely primate behaviour. The behaviour has been documented in some domesticated animals, for example dogs and goats, and has recently also been demonstrated in ravens. One hypothesis, therefore, is that gaze following is a general behavioural feature of social species, although empirical data are still lacking for most animal groups.

Why follow gaze? Monitoring another individual's gaze is adaptive for various reasons, particularly during foraging or for detecting predators. Individuals capable of gaze following enjoy a selective advantage over non-gaze-followers because they can benefit from discoveries made by others. For example, in chimpanzees and marmosets, gaze can signal possession, and animals avoid food that others are looking at, presumably to avoid competition. Gaze following also increases the probability of witnessing rare but important social interactions, such as rank reversals, thus helping animals

Figure 1. Diana monkeys have evolved a highly contrasting pelage colouration in the neck region, which facilitates gaze following in their natural visually dense rainforest habitat (picture Florian Moellers).

to keep track of other group members and their relationships. As mentioned, chimpanzees can discriminate what others can and cannot see in competition over food, but it remains to be seen if this ability extends to social interactions. Gaze following may be particularly important during cooperation. For instance, dogs prefer objects that are socially marked by a gaze cue, a useful predisposition for social carnivores that must decide on one particular prey individual prior to group hunting.

What is the neurobiological basis of gaze following? Primate brains contain groups of cells in the parietal and temporal cortex that respond specifically to changes in gaze direction. In humans, gaze following is impaired in individuals suffering from autism and similar effects can occur after certain brain lesions, suggesting that gaze following in primates is governed by shared neural circuitry.

What cognitive mechanisms are involved? Should we conclude from the neurobiological studies that gaze following is a cognitively low-level automatic process? Not necessarily. Although animals generally follow gaze because they are biologically endowed to do so, some species display additional cognitive processes during gaze following: they facilitate their own gaze following, they 'check-back', and they can project sight past distracters. To facilitate gaze following, great apes sometimes reposition themselves to follow an experimenter's gaze around a barrier. When 'checking-back', chimpanzees that fail to encounter anything interesting when tracking someone's gaze tend to look back at the gazer's face in order to track the gaze for a second time. Lastly, many primates are able geometrically to project an imaginary line of sight to search for the gazer's focus of attention, even if irrelevant objects interrupt this line. Similar results have also been obtained from ravens, which do not just orient to a target following another's gaze, but appear to take visual perspectives into account. In humans, finally, gaze following provides much of the foundations for a variety of higher cognitive achievements, including 'theory of mind' and language.

Why is gaze following relevant for language? During language acquisition, one productive strategy is to acquire novel word-reference links by following a speaker's gaze after hearing a novel utterance. In these instances gaze following cannot be automatic, but is guided by a selective process that picks out utterances of unknown referential significance. Similarly, infants only follow gaze if the speaker has an intention to inform, rather than being engaged in other sorts of communication. From the start of their second year of life, infants begin to converge with others on interesting phenomena for the purpose of sharing attention. Such 'joint attention' goes beyond automated co-orienting to an external object. Instead, a triadic relationship is formed between the gazer and the gaze follower, allowing them to interact with each other through the external phenomenon. This is a developmental landmark that psychologists grant special status, and it is clear why: many of the higher cognitive abilities unique to humans, such as theory of mind and language, develop during such joint attentional episodes. Gaze following, and joint attention that derives from it, is truly a socio-cognitive hotspot.

How does gaze following develop? Newborn humans already show rudimentary forms of gaze following. The behaviour undergoes elaboration between 6 and 18 months during which infants learn to track gaze in response to eye movements alone, and beyond their immediate visual fields. From about 12 months, infants begin to engage in joint attention. In macaques, gaze following is already seen in juveniles, and performance improves into adulthood. For apes, a 13-month old chimpanzee already shows reliable gaze following to an object indicated by a gaze. Complex geometrical gaze following emerges in chimpanzees before adulthood, although it is difficult to make firm statements about the social insights that young chimpanzees experience during these events, a topic of ongoing research.

What other directional cues are there? Interestingly, although primates are good at following gaze, they experience difficulties with following pointing, much in contrast to some domesticated animals. Primates have forward facing eyes and strongly developed facial musculature, making the eye region particularly useful for providing gaze cues. Non-primates with a more lateralised visual apparatus may be more disposed to attend to other body parts, such as head or torso, to locate the source of another's

attentive behaviour. Nevertheless, relying on head and body orientation is also important for primates, particularly in visually difficult habitats, such as dense rainforests. It is interesting that many forest primates have evolved conspicuous visual markers that facilitate gaze following (Figure 1).

What about gaze as a communicative signal? In contrast to other primates, humans have evolved a large white sclera and marked eyebrows, making the eye region highly conspicuous and ideally suited for gaze following, and it has been argued that this is an evolutionary byproduct of the cooperative nature of humans. Not only can humans follow gaze, but they can also use gaze to actively direct each other's attention, or, by eye squinting and lowering eyebrows, to make it more difficult for others to follow gaze (something that is perceived as unfriendly and uncooperative). Non-human primates are clearly sensitive to the directed gaze of others, and therefore they already possess a fundamental prerequisite for using gaze as a communicative signal. Whether or not they are also able to influence the attention of receivers by manipulating gaze cues is currently being investigated.

Where can I find out more?

Brooks, R., and Meltzoff, A.N. (2005). The development of gaze following and its relation to language. Dev. Sci. *8*, 535–543.

Bugnyar, T., Stowe, M., and Heinrich, B. (2004). Ravens, Corvus corax, follow gaze direction of humans around obstacles. Proc. R. Soc. Lond. B *271*, 1331–1336.

Emery, N.J. (2000). The eyes have it: the neuroethology, function and evolution of social gaze. Neurosci. Biobehavioral Rev. *24*, 581–604.

Gomez, J.C. (2005). Species comparative studies and cognitive development. Trends Cogn. Sci. *9*, 118–125.

Okamoto-Barth, S., Call, J., and Tomasello, M. (2007). Great apes' understanding of other individuals' line of sight. Psychol. Sci. *18*, 462–468.

Povinelli, D.J., and Eddy, T.J. (1996). Chimpanzees: Joint visual attention. Psychol. Sci. *7*, 129–135.

Scaife, M., and Bruner, J.S. (1975). The capacity for joint visual attention in the infant. Nature *253*, 265–266.

Tomasello, M., and Carpenter, M. (2007). Shared intentionality. Dev. Sci. *10*, 121–125.

Tomasello, M., Hare, B., Lehmann, H., and Call, J. (2007). Reliance on head versus eyes in the gaze following of great apes and human infants: the cooperative eye hypothesis. J. Hum. Evol. *52*, 314–320.

School of Psychology, University of St Andrews, Scotland, UK.
E-mail: kz3@st-andrews.ac.uk

The MRN complex

Agnieszka Rupnik, Muriel Grenon and Noel Lowndes*

Also known as... The Mre11 complex or MRX in yeast.

What is MRN? A complex of three proteins — Mre11, Rad50 and Nbs1 (also known as Nibrin or p95). It is essential for the viability of vertebrate, but not yeast, cells. The MRN complex is engaged in DNA metabolic events involving DNA double-strand ends. Orthologues of human Rad50 and Mre11 have been identified in all taxonomic kingdoms whereas Nbs1 seems to be unique to eukaryotic cells as no orthologues have been identified in prokaryotes or archaebacteria. The well-characterized yeast homologue of MRN, MRX, contains the Mre11, Rad50 and Xrs2 proteins, the later showing weak homology to human Nbs1.

Why is it essential for vertebrate cell viability? The genetic material of all eukaryotic cells is constantly exposed to both endogenous and exogenous DNA-damaging agents. Even a single double-stand break (DSB) can be lethal. Left unrepaired, DSBs can lead to chromosome instability, rearrangements, gene mutations and cancer. It is therefore extremely important for the cell to be able to sense the break, signal this damage and effect the appropriate biological responses as soon as possible. The MRN complex functions in both sensing and signaling of DSBs. It also has roles in both major DSB repair pathways — homologous recombination (HR) and non-homologous end joining (NHEJ). The MRN complex is also required for cell-cycle checkpoint signaling after DSB in all phases of the cell cycle. Additionally, it plays an important role in processing DNA structures that arise during normal S phase, is involved in preventing DNA re-replication and is essential for telomere maintenance.

How do Mre11, Rad50 and Nbs1 contribute to MRN function? The three members of the complex have distinct roles within the intact MRN complex. Mre11 interacts with both Rad50 and Nbs1, which do not directly contact each other (Figure 1). Rad50 has two globular domains linked by a long coiled-coil region forming extended arms. At the end of each arm a hook domain allows Rad50 molecules to dimerise and tether DNA ends together (Figure 1). Mre11 is responsible for DNA binding and also has both exo- and endonuclease activities, which have been characterized *in vitro,* and an ability to unwind DNA locally. Finally, Nbs1, which has no known enzymatic activities, is responsible for the rapid re-localization of the complex into large focal structures, as well as for most of the interactions with other DSB-signaling and DNA-repair proteins. Its binding partners include ATM, γH2AX and MDC1. The carboxy-terminal region of Nbs1 has also been reported to regulate irradiation-induced apoptosis (Figure 1).

Is there a connection between MRN and cancer? Yes. Mre11, Rad50 and Nbs1 are known tumor suppressors. Loss of function of any of these proteins results in genome instability, the principal feature of cancer cells.

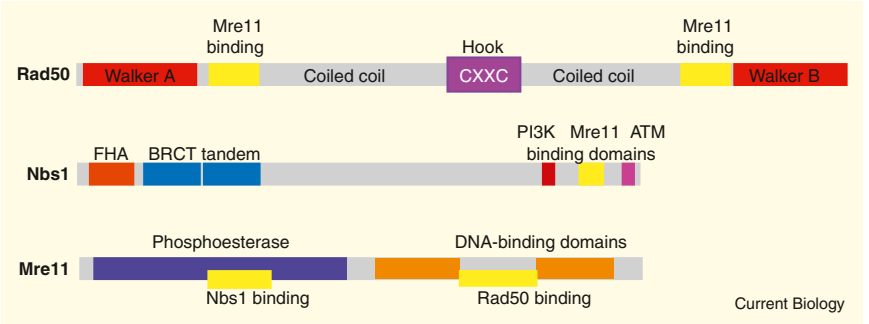

Figure 1. Domain structure of the MRN components.

Domains responsible for interactions within the complex are shown in yellow. CXXC hook, zinc hook; FHA, Forkhead associated domain; BRCT, BRCA1 carboxyl terminus domain. Note that the PAR domain of Mre11 localized between the two DNA binding motifs is not shown.