serine-9 or inactivation via other signaling pathways. In contrast, growth-inhibitory signals act in the opposite direction to dephosphorylate the serine-9 residue.

All of these results suggest a potential strategy for promoting axonal regeneration after neural injury using pharmacological inhibitors of GSK-3β. Indeed, we have recently demonstrated that inactivation of GSK-3β is necessary for axon regeneration from mature neurons of the peripheral nervous system after nerve transection (*20*). However, it must be emphasized that efficient axon extension probably requires localized inactivation of GSK-3β at the distal end of the growing axon, as well as activity of GSK-3 toward "unprimed" substrates. Although low concentrations of GSK-3β inhibitors lead to elaboration of multiple axons by hippocampal neurons, more complete global inhibition of GSK-3β almost certainly impedes axon growth (*5*, *14*). Thus, manipulation of GSK-3β may be a promising therapeutic strategy to promote functional recovery after injury to the central nervous system. But an important challenge remains how to achieve appropriate local regulation of GSK-3β using pharmacological inhibitors or gene therapeutic constructs.

GSK-3β may be a "master" kinase that mediates convergent signals from multiple extracellular cues affecting axon morphogenesis. It achieves this by coordinating regulation of all three aspects of microtubule assembly: polymerization, stabilization, and dynamics (see the figure). However, regarding the functions of GSK-3β in regulating neuronal morphology, its control of microtubule assembly may only be the "tip of the iceberg." GSK-3β almost certainly regulates actin filaments, the other important component of the axonal cytoskeleton (*17*). Furthermore, GSK-3β presumably regulates metabolism required for axon growth both locally in the axon and at the level of gene transcription by controlling the NFAT (nuclear factor of activated T cells) family of transcription factors and possibly other transcriptional regulators. Surprisingly, in view of its importance, the nervous system of mice that lack GSK-3β has not been extensively analyzed, and no animals lacking the related isoform, GSK-3α, have yet been reported.

Developing inhibitors of GSK-3β is a major target of the pharmaceutical industry because of the potential of such drugs for treating type 2 diabetes and Alzheimer's disease. The success of lithium in treating mood disorders may reflect its ability to inhibit GSK-3β, among other effects (*6*). Given the evidence that GSK-3β is important for regulating nervous system development, the use of GSK-3β inhibitors during pregnancy will need to be very carefully evaluated.

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PSYCHOLOGY

Infants' Insight into the Mind: How Deep?

Josef Perner and Ted Ruffman

Although primates and other animals seem to have some understanding of mind (that is, the behavior of others), the concept of belief seems to be a specifically human ability. Comprehending false belief is the clearest sign of understanding a critical aspect of the mind: its subjectivity and its susceptibility to manipulation by information. It is thought that children develop an understanding of false belief around 4 years of age. However, on page 255 of this issue, Onishi and Baillargeon (*1*) report that infants as young as 15 months have insight into whether a person acts on the basis of a mistaken view (false belief) about the world. This discrepancy touches on important issues. An understanding of false belief at 4 years of age suggests that this ability may be constructed in a cultural process tied to language acquisition. In contrast, competence at 15 months suggests that this ability is part of our purely biological inheritance. What could account for the discrepant findings?

Children's understanding of false belief has hitherto been assessed using a verbal false-belief task in which the experimenter enacts stories. An example of such a story is as follows: A protagonist (let's call him Max) puts a toy or doll (object) in one location and then doesn't see it moved to a second location (*2*). When asked by the experimenter, most 3-year-olds wrongly claim that Max will look for the object in the second location (where they know it is). This finding with 3-year-olds has been confirmed despite many attempts to improve the potential shortcomings of the verbal false-belief task [see meta-analysis by Wellman *et al*. (*3*)]. These results contrast with those from Onishi and Baillargeon's study in which 15-month-old infants were tested with a nonverbal false-belief test. In this test, infants were familiarized with an adult actor hiding and then retrieving a toy (a plastic slice of water melon) in either a yellow or a green box (see the figure). The looking times of the infant subjects were then computed in a series of trials that tested whether the actor held a true or false belief about the location of the toy. Onishi and Baillargeon found that the infants "expected" the actor to search for the toy based on the actor's belief about its location, regardless of whether the location was actually correct. So, why would 3-year-olds fail to provide the correct answer in a verbal false-belief test, when 15-month-old infants can correctly anticipate erroneous actions in the nonverbal false-belief test?

Part of the explanation might come from previous studies that used eye gaze as a measure of understanding in 3-year-olds. Three-year-olds look to the correct (initial) location when anticipating Max's return there, even when they explicitly make the incorrect claim that Max will go to the second location. This early indication of understanding Max's mistake has been dubbed implicit, because many of these children show no awareness of the knowledge implicitly conveyed in their correct eye gaze (*4*). Nonetheless, children at the age of $2\frac{1}{2}$ years show absolutely no sign of this earlier, implicit understanding (*5*).

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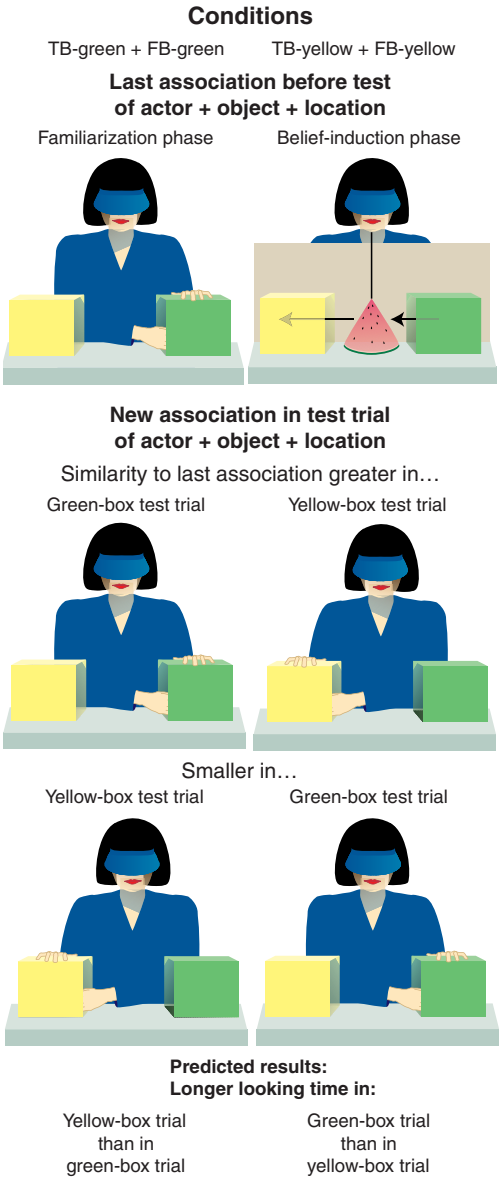

CREDIT: PRESTON HUEY/*SCIENCE*, ADAPTED FROM (*1*)

Now you see it...now you don't. Reanalysis of Onishi and Baillargeon's experimental conditions in a nonverbal false-belief task (*1*). The left column shows the critical events for test trial conditions in which infants looked longer in the yellow-box than in the green-box test trials. These two conditions have in common that the last appearance of the adult actor was during the familiarization phase, where the actor was grasping the object in the green box ("actor-object-green box" association). This makes it possible that the looking time by the infant subjects was shorter in the green-box test trials—as reported (*1*)—because the actor-object-location combination in this test trial is more similar to the last seen association of these three elements than in the yellow-box test trial. The right column shows the same results for the other two conditions, in which looking time for test trials was reversed. This can be explained by the fact that the last appearance of the adult actor was during the belief-induction phase, where the actor observed the object disappear into the yellow box ("actor-object-yellow box" association). Hence, under these conditions, infants found the yellow-box test trials more similar to the last actor-object-location combination than the green box trials, which explains the reversal in looking times. (TB, true belief; FB; false belief)

Converging evidence comes from children's word learning, which also shows sensitivity to false belief around 3 years and not before (*6*). In sum, the evidence of an earlier, implicit understanding does not solve but rather exacerbates the puzzle about Onishi and Baillargeon's finding with infants: Where would the implicit understanding be hiding between 15 months and 3 years?

By adopting particular assumptions about how infants encode events and behavior, we propose two explanations for the apparent early competence of infants that imply an evolutionary, innate bias for understanding the mind. Infants encode events and behavior the way they do because this encoding captures something useful about how people tend to act only because people are endowed with minds. Yet there is no need to assume an understanding on the infant's part that a mind mediates a particular behavior.

Our first account of Onishi and Baillargeon's data is based on neuronal activation as babies process the events of the nonverbal false-belief task (see the figure). Our suggestion is that babies create three-way actor-object-location associations. During the familiarization phase of the test, an adult actor watched by the infants last observes the object (water melon slice) in the yellow box under two conditions (right column) and in the green box under another two conditions (left column). Neurons remember this information both in an active manner (through sustained firing in the prefrontal cortex) and in a latent manner (through altered firing thresholds in nonfrontal regions) (*7*). If an association of elements "actor-object-yellow box" is still sustained in the frontal cortex when babies are exposed to the test stimuli, a consistent test combination will need less processing and, consequently, a shorter "looking" time than a new combination of elements (e.g., actor-object-green box). In the latter case, babies might need longer looking times because, when they examine the new combination, they must form a new association.

A similar increase in looking times may also stem from changes in latent activation in nonfrontal regions, where neurons code for the recency of exposure and increase their firing when a nonrecent stimulus is presented. Even rats are able to represent new arrangements of three familiar stimuli, resulting in increased neuronal activation in the postrhinal cortex and hippocampus and less activation in the dentate gyrus and subiculum (*8*). New arrangements of "actor-object-location (yellow box versus green box)" could result in longer observation times because of the differential activation of neurons that code for the recency of stimuli. Both of these explanations have a clear testable prediction that differs from explanations based on understanding belief: The actor's intentional search for the object in a box in the test phase is not critical. The actor could do something equally interesting (but nonintentional) at either box, and this would also result in the same pattern of differential looking in infants.

For our second account of Onishi and Baillargeon's findings, we acknowledge their suggestion that infants expect the observed person to act in a particular way. However, we propose that this can be based on behavior rules. Infants may have noticed (or are innately predisposed to assume) that people look for an object where they last saw it and not necessarily where the object actually is. Again, such a rule captures something implicit about the mind, because the rule only applies as a result of the mind mediating between seeing and acting. Nonetheless, infants can simply know the rule without any conception that the mind is the mediator. For instance, O'Neill (*9*) found that when requesting an object, 2-year-olds gesture more to the object's location if a parent had not witnessed its placement on a shelf. This finding is compatible with a 2-year-old's understanding of the parent's need for knowledge. It is also equally compatible with a 2-year-old's understanding of the link between the behavior of not having looked at the object in its new location and the likely action of looking in the wrong place (which needs to be prevented by gesturing to the right location).

Povinelli and Vonk (*10*) recently argued that extant evidence for the social intelligence of primates leaves open the question of whether they merely know about behavior or whether they also know about the mental states that mediate behavior. No explanatory power or theoretical parsimony is gained by assuming that animals know about the mind. This criticism also applies to the traditional verbal false-belief task (featuring Max) that children do not pass until 4 years of age. So, it is important to realize that claims about 4-year-olds' understanding of belief cannot be based solely on their positive response to this particular test. The conclusions drawn from the false belief task are warranted only because understanding of false belief around 4 years can be demonstrated in a

variety of belief-inducing situations [in which behavior rules would lead to contradictory predictions of actions (*11*)]. Only the assumption that children acquire an understanding of belief at this point can explain why they start to make correct predictions of actions in these different situations at the same time. Demonstration of such flexible use of belief understanding is missing from studies of both primates and infants (and from studies of the implicit understanding of 3-year-olds).

Assuming that primates have a genetic predisposition to acquiring behavior rules, we can concoct a plausible story about human development. Inheriting from our evolutionary ancestors this predisposition, infants start with a "core theory" (*12*)—that is, knowledge that stays close to the perceptible. Then, children develop a deeper mental understanding of behavior through enculturation into a language community. This contention is supported by increasing evidence that the explicit understanding of belief around 4 years of age strongly relates to language development. Most notably, deaf children raised by hearing parents suffer from a language delay of several years that is also reflected in their late understanding of false beliefs. Thus, we can conclude that the acquisition of our adult theory of mind has a strong evolutionary basis and is deepened by universal aspects of culture, and by linguistic communication in particular.

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CHEMISTRY

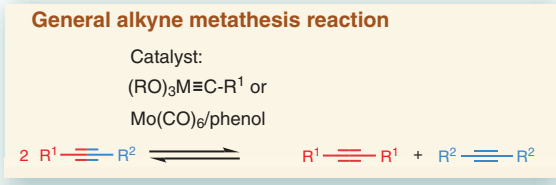
How Are Alkynes Scrambled?

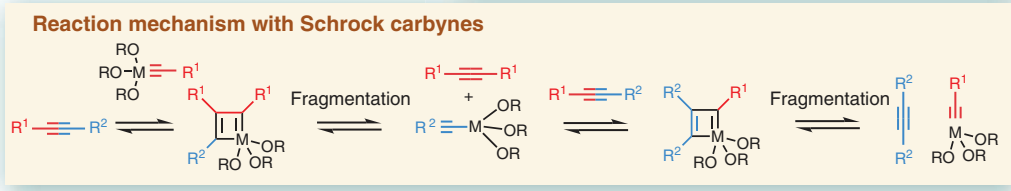
Uwe H. F. Bunz

In a metathesis reaction, two molecules exchange atoms or groups of atoms. For example, two alkynes—hydrocarbons that contain a carbon-carbon triple bond—may swap their substituents (see the first figure, top panel). Such alkyne metathesis reactions, discovered by Mortreux in 1974 (*1*), are very useful for synthesizing complex natural products (*2*), semiconducting polymers, and macrocyclic compounds (*3*, *4*). On page 234 of this issue, Bino *et al.* (*5*) shed light on how some of these reactions are catalyzed.

Mortreux found that treating a disubstituted alkyne with a mixture of two compounds—molybdenum hexacarbonyl [$Mo(CO)_6$] and a phenol derivative called resorcinol—led to the formation of an "in situ" catalyst and yielded a statistical mixture of three alkynes, with their substituents scrambled (*1*). Variants of this catalyst system containing more acidic phenols have been used successfully in the synthesis of polymers and natural products (*1*–*4*, *6*, *7*). However, the chemical nature of the in situ catalysts remains unknown.

In an effort to understand how alkyne metathesis reactions are catalyzed, Schrock and co-workers (*8*, *9*) have produced tungsten and molybdenum carbynes of the type $(RO)_3M{\equiv}C\text{-}CMe_3$, where M is W or Mo and R is Me_3C or aryl (see the first figure, top panel). These complexes, which are air sensitive and are now commercially available, are highly active, structurally defined catalysts for alkyne metathesis. In the case of tungsten carbynes, the reaction proceeds via two cyclic intermediates, which each fragment into a metal carbyne and an alkyne (see the first figure, bottom panel) (*8*, *9*). If one of the product alkynes is removed from the reaction mixture—for example, by distilling off the alkyne with the lower boiling point—the metathesis reaction will yield only the desired metathesis product.





Alkyne metathesis and its mechanism. (Top) Two types of compounds—the original Mortreux-type in situ catalysts and the carbynes pioneered by Schrock and co-workers—are known to catalyze alkyne metathesis. **(Bottom)** In the case of carbynes, insights have been gained into the catalytic intermediates. R^1 and R^2 are organic residues, M is tungsten or molybdenum, and RO are bulky alkoxide or aroxide ligands.

Zhang and Moore have obtained variants of the Schrock carbynes (*10*, *11*) by reaction of the molybdenum complex $(R_2N)_3Mo{\equiv}C\text{-}Et$ (*1*, *12*) with 4-nitrophenol. The resulting carbyne, $(O_2N\text{-}C_6H_4\text{-}O)_3Mo{\equiv}C\text{-}Et$, is the most active alkyne metathesis catalyst reported so far and tolerates sulfur atoms adjacent to the catalytic center: It catalyzes the conversion of thiophene-containing monomers into organic semiconductors. This is an important achievement in the field of alkyne metathesis; none of the earlier alkyne metathesis catalysts are able to perform this transformation.

Nevertheless, the simpler Mortreux-type in situ catalysts are powerful for synthetic applications, provided the substrates are sufficiently robust and do not contain nitrogen or sulfur functionalities in close proximity to the alkyne unit. But despite their usefulness, there is no mechanistic understanding of this reaction. It has been suggested that it may proceed via an intermediate resembling the carbyne complexes discussed above, but it remains unclear how these carbynes would form from molybdenum hexacarbonyl and phenols. Bino *et al.* (*5*) bridge this chasm in understanding and shed some light on possible intermediates of alkyne metathesis with in situ catalysts.

Reaction of molybdenum hexacarbonyl

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