Bootstrapping conceptual deduction using physical connection: rethinking frontal cortex

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The age at which infants can demonstrate the ability to deduce abstract rules can be reduced by more than half, from 21 months to 9 months. The key is to introduce a physical connection between the items to be conceptually related. I argue here that making the same change in how items are presented might also help some preschoolers with learning delays, especially some children with autism. I also suggest that the roles of premotor and ventrolateral prefrontal cortices in deducing abstract rules might have been misinterpreted behaviorally and anatomically. The crucial brain region may be the periarcuate, which partially overlaps both premotor and lateral prefrontal cortex. The cognitive ability made possible by this region might be something far more elementary than previously considered: the ability to perceive conceptual connections in the absence of physical connection.

Introduction

Elegant evidence suggests a crucial role for premotor cortex and inferior (ventrolateral) prefrontal cortex in encoding abstract rules [1–4]. The research community has been captivated by evidence that within anterior premotor cortex and perhaps the rear portion of inferior prefrontal cortex there are 'mirror neurons' – neurons that fire when the subject performs a particular action or observes someone else performing that action; [5–9]. I propose that a focus on premotor or ventrolateral (inferior) prefrontal cortex misses the mark, as does a focus on rule learning or even mirror neurons – I propose: (i) that we recognize a coherent region that spans anterior premotor cortex and posterior lateral prefrontal cortex: the periarcuate region (see Box 1), and (ii) that although there is evidence that this region is crucial for deducing abstract rules and that it may contain mirror neurons, the *reason* it is crucial for those functions is because it subserves a more elementary and basic function – that of being able to grasp how physically separate things might be related (i.e. conceptually connected despite their physical independence).

In this article, I propose that infants in the first year of life, and some preschoolers with developmental delays,

can deduce abstract, relational rules long thought beyond their ability. They have appeared unable to do this because behavioral methods have not allowed them to demonstrate this ability. I suggest that instead of having problems deducing abstract concepts, they have a more elementary problem – perceiving conceptual connections between physically unconnected things. If items that infants are meant to relate conceptually are presented physically connected, infants of only 9–12 months *can* grasp abstract, conceptual relations. I predict that this would also be true for some children with developmental disorders, especially some children with autism.

Evidence that infants can deduce abstract relations

Children cannot deduce the abstract rule that underlies the 'delayed nonmatching to sample' (DNMS) task until they are almost 2 years old [1–4], irrespective of whether they are tested only once [1] or daily from 12 months onwards [2]. On each trial a sample object is presented and the child picks it up to reveal a small reward underneath. After a delay, the sample and a novel object are presented. The reward is now under the novel object. No stimulus is used on more than one trial and the right/left positions of the sample and novel object are varied randomly over trials. Subjects are not told that the rule is always to choose the object that does not match the previously presented sample; they must deduce that on the basis of feedback. Because children and monkeys prefer novelty, delayed nonmatching is used rather than delayed matching, which would require that they inhibit their preference and reach back to the familiar, more boring, sample. It takes monkeys 10 times as long to learn delayed matching [5] and children do not succeed at delayed matching until several years after they succeed at delayed nonmatching [6].

Although DNMS was first devised to study animal models of amnesia [7–9], insufficient memory is not why children fail [8,9]. When children first succeed at the training delay for DNMS (typically 5 or 10 s), they also succeed at longer delays in the same session [4]. Their difficulty is not with the delay but in figuring out the abstract rule underlying the task. The age at which children first succeed at this task can be more than halved (from 21 months to 9 months) by introducing a physical connection between the rewards and stimuli. If the reward is attached to the base of the stimulus (still hidden when

Box 1. Equating anatomical terms and regions across primate species

In humans and monkeys the dorsal and ventral portions of Brodmann's Area 6 are termed **premotor cortex** (see Figure I). In monkeys, the area ventral to (below) the principal sulcus extending back to the arcuate sulcus is called **ventrolateral prefrontal cortex** or the **inferior convexity** (Areas 44, 45, and the lateral aspect of 47/12). The area including and, dorsal to (above), the principal sulcus extending back to the arcuate sulcus is called **dorsolateral prefrontal cortex**. The area in the concavity of the arcuate sulcus, where its two arms meet, is the **frontal eye fields** (Area 8).

The human brain has neither a principal nor an arcuate sulcus, but the area homologous to ventrolateral prefrontal cortex in the monkey is the inferior frontal gyrus. By convention that is usually called 'inferior prefrontal cortex' in humans, but is fully homologous to ventrolateral prefrontal cortex in monkeys. The location of

dorsolateral prefrontal cortex in the human brain is roughly the superior and middle frontal gyri.

The area surrounding the arcuate sulcus is called the **periarcuate region**. This spans the posterior portions of ventrolateral and dorsolateral prefrontal cortices, the frontal eye fields, and the anterior portion of premotor cortex. The area in the human brain that roughly corresponds to this periarcuate region in the monkey is an expansion of what has been termed the **inferior frontal junction (IFJ)** [34,35]. It overlaps the posterior portions of inferior and dorsolateral prefrontal cortex, which in humans includes part of Broca's area, and the anterior extent of premotor cortex. Thus, IFJ in humans is contained within the area homologous to the periarcuate in monkeys. It is the periarcuate region (and its human homologue) that is the focus of this article.
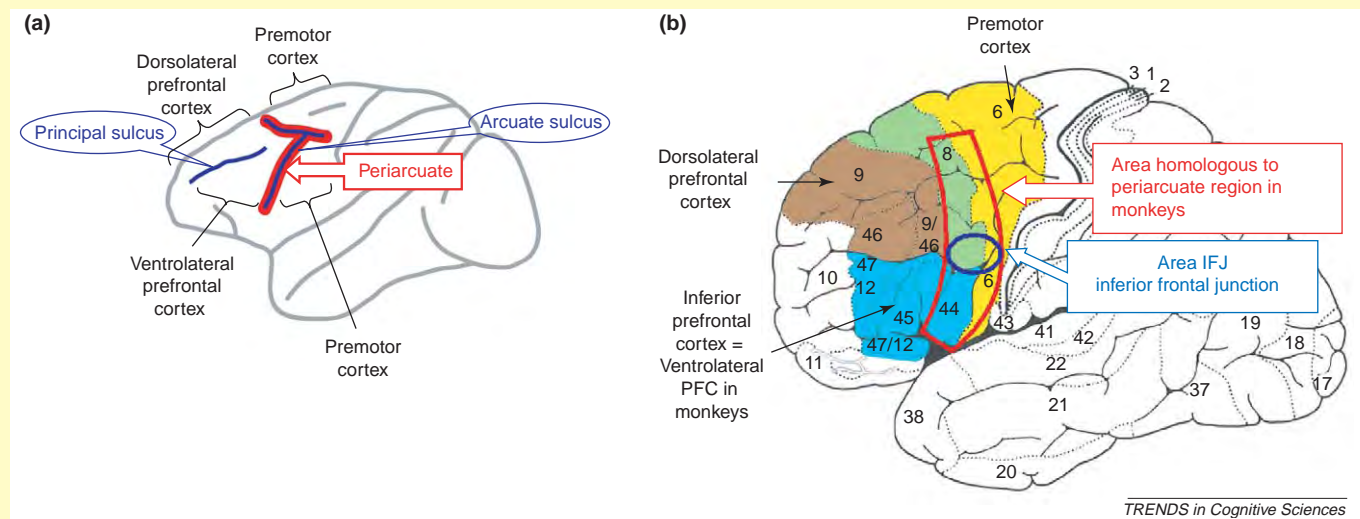
Figure I. Illustration of the lateral surface of the cerebral cortex of a rhesus monkey brain **(a)** and a human brain **(b)**. The area boundaries shown are based on Petrides and Pandya [53]; when Brass *et al.* [34] stated that part of Area 9 falls within IFJ they were using the earlier map of Brodmann. As the human brain does not have an arcuate sulcus, there is no direct equivalent of the periarcuate region, but the homologous area is outlined in red. The region corresponding to the inferior frontal junction (IFJ; outlined in blue) lies within the homologue to the periarcuate region. Locations of the periarcuate and IFJ were verified by Petrides and Brass, respectively.

the stimuli are presented) most infants of 9 or 12 months succeed at the task [10]. This result falsifies the previously held notion that the ability to deduce abstract rules (such as 'Choose the item that does not match the sample') is beyond the ability of infants less than one year old.

Infants of 9 and 12 months also succeed on a 'jack-in-the-box' version of the task *if* stimuli and rewards are attached to the same piece of apparatus, even when the stimuli and rewards are several inches apart and regardless of whether the reward pops up immediately or is delayed [11]. Apparently, when the stimuli and rewards are components of a single thing, the connection between them is understood by infants. Infants fail, however, when each stimulus is directly in front of (but clearly separate from) the box containing its associated pop-up reward, even when the reward appears immediately upon touching the stimulus [11]. Similarly, infants fail the standard DNMS paradigm even if the apparatus is such that they see the reward as soon as they act on the stimulus (K. Shutts *et al.*, unpublished). Thus, in the absence of the perception that stimulus and reward are physically attached or components of a single thing, neither close spatial or temporal proximity, nor their

conjunction, helps infants. When stimulus and reward appear to have a physical connection – whether that connection is direct (via Velcro), or indirect (parts of a larger whole) – neither close spatial or temporal proximity is needed for infants to grasp the relation between stimuli and rewards and deduce the DNMS rule.

The essential competence required for DNMS that seems to elude many children until they are about 21 months old appears to be the ability to grasp the relation between stimulus and reward when there is no obvious physical connection between them. Evidently infants do not understand in the standard DNMS procedure that the stimulus objects are supposed to indicate where the rewards are located and that the rewards are supposed to instruct them about the stimuli. To profit from feedback, infants must relate two objects to one another and must understand that the feedback they receive (reward vs. no reward) is related to which stimulus they have chosen.

A role for physical connection in helping monkeys and children understand conceptual connections

Physical connection has been shown to make a huge difference to non-human primates in their learning of

abstract relations. Fifty years ago, Jarvik [18] asked why it takes chimpanzees hundreds of trials to learn a simple color discrimination (e.g. where a blue plaque always covers one foodwell and a red plaque another, the position of the plaques varies randomly over trials, but food is always only under the red plaque). Jarvik tried a variation: he attached the peanut reward to the underside of a plaque. That produced one-trial learning. As with infants on DNMS, if a physical connection was present, the task was easy; if absent, even if stimuli and rewards were contiguous [19], the task was difficult.

Physical connection can also make a major difference for children. Children of 18–22 months are aided by a landmark in finding a hidden reward if the reward is hidden *in* the landmark (e.g. an armchair), but not if hidden *near* the landmark [20]. DeLoache [21] also varied whether a reward was hidden in one of four distinctive containers, or in a plain box placed beneath the distinctive containers. When these were scrambled, 21-month-olds were 80% correct when the reward was *in* a distinctive container but only 35% correct when a distinctive container marked where the reward was hidden (in the box underneath). Similarly, when rewards are placed inside stimulus boxes, children of 1.5–3.5 years can learn to choose on the basis of relative size in fewer trials than can older children tested with the rewards underneath the stimuli ([22,23]; R.G. Rudel, unpublished doctoral dissertation, New York University, 1955). Finally, DeLoache [24] has elegantly shown that although 2.5-year-olds have difficulty relating a small model of a room to the full-size room (two separate things), they have no difficulty relating those same two spaces if they are told the model and room are really one space that is made to magically change size (i.e. in the child's mind no longer two separate things).

Role of the periarcuate region: grasping conceptual connections without physical connection

Monkeys with lesions of ventrolateral prefrontal cortex, *if and only if* the lesions invade the periarcuate region, show similar performance on DNMS to human infants. They have great difficulty deducing the nonmatching rule even with no delay at all, but once they have grasped the rule they perform well even at long delays [12–15]. They take over 10 times as long to pass the DNMS test post-operatively as they did pre-operatively, but show no evidence of a delay-dependent deficit once they have relearned the DNMS rule. Thus, as with human infants, their difficulty appears to be in acquiring the DNMS rule, not in remembering the sample over a delay.

This pattern of performance is not seen in monkeys with lesions to any other region of the brain, including lesions carefully restricted to ventrolateral prefrontal cortex but sparing the periarcuate. Consistent with this evidence in monkeys, neuroimaging studies implicate the human homologue of this periarcuate region (posterior ventrolateral and anterior premotor cortex) in DNMS and delayed-matching-to-sample (DMS) rule learning in adults [16,17].

I propose that monkeys with lesions invading the periarcuate fail the DNMS task in the same way and

under the same conditions as do human infants because they fail for the same reason – a difficulty in grasping conceptual connections between physically unconnected things. I predict that if they were tested with the rewards attached to the underside of the stimuli, they would succeed at DNMS, just as do human infants.

Evidence from other experimental paradigms
In an elegant series of experiments, Passingham and Halsband [25,26] studied the ability of monkeys with lesions of premotor cortex that, crucially, invaded the periarcuate to learn a visual–motor conditional association: if blue cue, pull a handle; if red, turn the handle. The cue was either:

(a) the color of the handle itself;
(b) the color of the panel in front of the handle (which the monkey had to displace to reach the handle);
(c) the color of the panel behind the handle.

Monkeys with premotor/periarcuate lesions performed superbly in (a), where the color of the handle was the cue for which action to perform on the handle, but were *never* able to demonstrate learning in (b) or (c), where they had to relate a property of one thing to an action for a separate thing. They failed (b) and (c) although they could make the requisite movements and discriminate the color cues, and showed no strong preference for either movement. Whereas Passingham and Halsband focused on premotor cortex, Wang *et al.* [27] have shown that disrupting neural activity in ventrolateral prefrontal cortex (by injecting bicuculline) severely impairs monkeys' ability to master a very similar task with the cue just above the handle. I would argue that the focus of each group is partially correct, but that the crucial region is the transitional area that partially overlaps both premotor and lateral prefrontal cortex – the periarcuate region. In support of this, Petrides [28] showed that no monkey with a periarcuate lesion could learn a conditional association (for one cue, grip a stick; for another cue, press a button), although they could discriminate the stimuli, make the necessary movements, and learn other tasks. Monkeys with lesions elsewhere in prefrontal cortex were unimpaired.

I predict that human infants would fail these tasks in the same ways and under the same conditions as do monkeys with premotor, ventrolateral prefrontal, or periarcuate lesions, because, I suggest, they have the same problem – a difficulty in grasping conceptual connections between physically unconnected things. I further predict that human infants and monkeys with periarcuate lesions would succeed in condition (c) above if the panel behind the handle moved with the handle so that panel and handle were perceived as one physically connected unit.

How should we parcellate the frontal lobe?
In the 1970s and 1980s several behavioral neuroscientists investigated which cognitive functions required the periarcuate region in monkeys (e.g. [28–33]). This line of research lost favor, however, because it was considered more elegant to focus on a defined neural region than on tissue partly in one anatomically defined region and partly

in another. However, I suggest that function might not necessarily respect regional borders assigned on the basis of common neuroanatomy, or on the basis of being located on one side or another of an anatomical landmark.

Recently, Brass, vonCramon and colleagues [34,35] have argued for the existence of a distinct functional and anatomical region located primarily in the depth of the precentral sulcus and inferior frontal sulcus that is a partial human homologue of the periarcuate region. Located 'within a transition zone between premotor and prefrontal cortex' ([34], p. 315), they named it the inferior frontal junction (IFJ), and argue that it 'constitutes a functionally and structurally separable area in the fronto-lateral cortex' ([34], p. 316; and see Box 1). They rely heavily on evidence of the functions it subserves, but note that there is emerging neuroanatomical evidence that the IFJ can also be distinguished by its cytoarchitectonic and receptor properties [36].

If the periarcuate region of the frontal lobe subserves a coherent function, what is that function?
Rule learning: learning conditional associations or abstract rules
Research in the 1970s and 1980s [28–33] documented in many replications and permutations that lesions of the periarcuate, but not of dorsolateral prefrontal cortex, produce deficits in learning conditional associations (in the presence of one cue, Response X is correct but in the presence of another cue, Response Y is correct). The presence of a delay is not necessary to elicit a deficit after lesions invading the periarcuate. Petrides demonstrated similar deficits in learning arbitrary conditional associations (rules) in human adults after frontal lesions [37–39], although those clinical lesions lacked the exquisite spatial precision of the surgical lesions in monkeys.

Since the 1990s, many researchers using single-cell electrophysiology in the intact monkey brain and functional neuroimaging in humans, have similarly concluded, although they do not use the term 'periarcuate', that ventrolateral prefrontal cortex and premotor cortex play important roles in learning and encoding abstract rules and associations. Wallis and Miller [40] found that more cells in the monkey periarcuate (ventro-lateral prefrontal cortex and especially premotor cortex) than in any other frontal region encode the abstract DNMS and DMS rules. Such abstract rules are encoded most strongly in premotor cortex. Matsumoto, Tanaka and colleagues [41] also reported that neurons in ventrolateral prefrontal and premotor cortex show increased activity when monkeys are learning a rule.

In a neuroimaging study using fMRI, Bunge *et al.* [16] found that the approximate human homologue of the periarcuate (spanning inferior prefrontal and premotor cortices) encodes abstract rules, specifically matching and non-matching rules. Similarly, Toni *et al.* [42] demonstrated in a PET study that selecting between actions on the basis of visual associative rules increased activation in ventral prefrontal and dorsal precentral areas (approximating the periarcuate). Combining PET and fMRI in humans with lesion studies in monkeys, Toni, Passingham and colleagues [43] reported converging evidence that

ventral prefrontal cortex is essential for forming associations between visual cues and the actions they specify, and that monkeys with such lesions are impaired at relearning those associations even when there are no working memory demands. These conclusions concerning ventral prefrontal cortex were echoed in another fMRI study, this time of the anterior premotor cortex [44]. Brass, von Cramon, and colleagues have since argued that the IFJ (rather than ventrolateral prefrontal or premotor cortex *per se*) is crucial for the application of abstract rules to guide behavior, for reorganizing stimulus–response associations, and perhaps for cognitive control more generally [34,35].

Imitation and empathy
In the anterior portion of premotor cortex and perhaps the rear portion of inferior prefrontal cortex there are 'mirror neurons': neurons that fire when you perform a particular action *and* when you observe someone else performing that action [45–48]. In the roughly homologous area in the human brain, activation increases during imitation or observation of gestures [46,47,49] and appears sensitive to the goal of the action-to-be-imitated [48]. Such fMRI findings have been confirmed with magnetoencephalography (MEG; [50]) and transcranial magnetic stimulation (TMS; [51]). TMS over the human homologue of the periarcuate (but not over occipital cortex) impairs imitation. Neural activity in this region also increases during observation of emotions [52], giving rise to the notion that this frontal region might be important for the neural basis for empathy.

Grasping conceptual connections in the absence of physical connection
I propose that the reason neurons in the periarcuate region are important for learning abstract rules, and for understanding the relation between others' actions, intentions, or emotions and our own, is because this region underlies our ability to grasp conceptual relations in the absence of a physical relation. I hypothesize that even without a fully functional periarcuate it is still possible in some conditions to deduce abstract rules, for example, where stimulus and reward are physically attached. In other conditions where subjects need to appreciate the relation between two things (e.g. conditional associative learning), the periarcuate should again not be required if the things to be related are physically connected. A focus on premotor or ventrolateral (inferior) prefrontal cortex misses the mark, as does a focus on rule learning, or even on mirror neurons. Rather, I suggest that the periarcuate cortex, which partially overlaps both pre-motor and lateral prefrontal cortex, is the crucial region, and it appears to be necessary for rule learning because it is necessary for something more elementary – perceiving conceptual connections in the absence of physical connections.

Conclusion
The hypothesis advanced here is that infants of less than one year of age, and some preschoolers with

Box 2. A bolder hypothesis concerning children with developmental delays, especially some children with autism

Many young children with developmental delays have difficulty learning abstract principles or grasping the relation between symbol and referent. I propose that a subset of those children may have an anomaly in the human homologue of the periarcuate. Physically connecting the elements to be conceptually connected might enable such children to grasp concepts and abstract rules more easily. This might be especially likely to help a subset of learning-delayed children with autism. They are particularly prone to see things as unrelated to each other. Indeed, Frith [54] hypothesized that a core problem in autism is a deficit in 'central coherence'; that is, a tendency to see things in isolation, rather than in relation to one another or to the surrounding context. For example, persons with autism (a) tend to outperform controls on tasks where focusing on the relation between items is misleading, and (b) tend not to show the typical cost of trying to hold isolated elements in mind rather than a coherent whole (e.g. [55–58]).

Bíró and Russell [59] found that teenagers with autism could readily learn to depress the lever on a box to make a ball drop down (just as infants can perceive the connection between DNMS stimuli and rewards when they are components of a single thing), but they were impaired in learning that putting a cup in front of the box (i.e. not connected to the box) would cause the ball to drop down. Children 3–5.5 years of age with autism show the same pattern of performance on DNMS as do (a) normally-developing infants and (b) monkeys with ventrolateral-prefrontal/periarcuate lesions: that is, great difficulty in deducing the DNMS rule even with minimal delays, but having deduced it, excellent performance at longer delays [60,61]. Similarly, if 5-year-old children with autism are told the DMS rule, all who pass the zero-delay training perform well when a delay is introduced [62]. Thus,

the problem for children with autism is not in overcoming a delay, but in grasping the abstract rule. It is an intriguing possibility that some of the children with autism who seem unable to deduce the DNMS rule using the standard procedure might succeed under the same conditions as do infants – conditions of physical connection (e.g. the 'stuck with velcro' condition).

By 2 years of age, imitation deficits discriminate children with autism from those with other developmental disorders [63–65]. The mirror neuron system may be impaired in autism [64]. Even high-functioning individuals with autism show delayed and diminished activation in Broca's area during imitation [66], and acquisition of spoken language (dependent on Broca's area) can be severely delayed or disrupted, thus implicating the periarcuate as one site of possible abnormality in some individuals with autism. Adults with autism generally have good knowledge of the meanings of isolated words [67], but relational semantics, particularly abstract language processing, is weak [68].

Perhaps one reason (although not the only reason) that some people with autism have difficulties in the social domain is because in social interactions things that need to be related are rarely physically connected. Hence, it might be difficult for persons with autism to appreciate the relation between their actions and the responses of others. Imitation and understanding other minds also involve relating physically separate things.

I suggest that some children with developmental delays, especially a subset of those children with autism, have only *seemed* unable to deduce abstract rules. I hypothesize that they might make the connection between a reward object and stimulus object if the two are physically connected.

developmental delays, especially such children with autism, would be able to grasp abstract relations and conditional associations if the objects to be conceptually connected are presented physically connected. Most behavioral training with children with developmental delays has not considered whether physical connection matters. Making such a simple change in training methods could enable children to grasp concepts previously thought to be well beyond their ability.

Moreover, recent evidence suggests that the periarcuate region of the frontal lobe (and its human homologue) might be a coherent functional region. Those who argue for the role of premotor cortex or ventrolateral prefrontal cortex in rule-learning might both be partially correct, as the periarcuate overlaps those two regions. However, the fundamental ability subserved here might be more basic than rule-learning: the ability to perceive connections between physically separate things. The human homologue of the periarcuate could be sufficiently immature in infants of 9–12 months that a physical connection between items to be related is necessary, and sufficiently mature (although still not fully mature) by 21 months that a physical connection is no longer needed. If there is a biological abnormality in this region of the frontal lobe in a subset of developmentally delayed children, especially a subset of those with autism (see Box 2), they, too, should be able to deduce abstract rules if there is a physical connection between the items to be related.

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