

NEUROSCIENCE

Escaping Attention

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Cognitive neuroscience continues to unravel complex perceptual and cognitive processes of the human brain, in part by combining functional and anatomical aspects into network models. For example, the “dual-route” computational model of reading aloud (lexical and nonlexical routes from print to speech) has provided insights into how the process works and where its pathological variants, such as dyslexia (1), may originate. As well, the standard model for how we recognize other people’s faces (2) has emerged from behavioral studies and sparse neuropsychological evidence available in the 1980s, and by more recent functional magnetic imaging studies of brain activity (3) and genetic analysis (4–6). Still, we are only beginning to understand the brain’s cognitive function. One limitation is that static functional models of cognition remain a rough approximation of the brain’s dynamic processing power. Another challenge is that some cognitive dysfunctions may not be so obvious.

Cognitive deficits in basic human skills are expected to draw attention. But, for example, dysfunction in a socially important cognitive task, such as recognizing people’s faces, may not be apparent. The congenital type of prosopagnosia (7, 8) or “face blindness”—the impaired ability to recognize faces on an individual level—was considered to be a rare condition. Surprisingly, though, it has recently been found to affect about 2.5% of the general population in Germany (8, 9), despite the fact that it is generally not noticed in society. Other cognitive dysfunctions may have gone unnoticed as well, including voice agnosia (impaired ability to recognize people by their voices) or a hereditary type of color agnosia (impaired ability to recognize colors, even though the eyes distinguish them) (10, 11). What might account for such invisibility?

It is difficult to define common features of conditions whose primary characteristic is that they have escaped attention. Therefore, a more informative question to ask may be, “What kinds of dysfunctions will most probably be found?” One consideration is that some cognitive requirements are culture-dependent. In a primitive, mostly illiterate society, a cognitive deficit would become

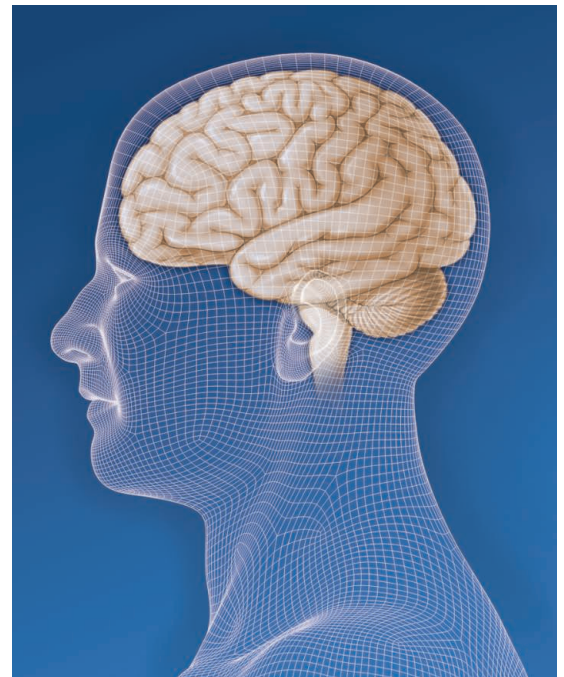
apparent if, for instance, it prevents a person from becoming an expert archer. By contrast, dyslexia might never be noticed in these societies. Even in literate cultures, conditions differ: Dyslexic persons in China show a different pattern of brain activity in a reading task than do European dyslexics (12), and hence its detection might be culture-dependent. Moreover, skills can only be compared if they are practiced by a substantial number of people in a given cultural context. Otherwise, performance depends on the individuals’ arbitrary state of training. As well, a sudden loss or decrease of a cognitive skill after a traumatic incident (such as a stroke or severe brain tissue damage) is not easily overlooked.

Yet cognitive dysfunctions that meet some of these conditions still may not be detected easily. For example, people may try to hide socially disabling or embarrassing impairments. Congenital prosopagnosia [being “face blind” from birth (7)] would be expected to lead to severe social restrictions, but, in fact, in most affected people it does not. Face recognition is only a subtask of the socially important task of person recognition. Impaired face recognition can, to a certain degree, be compensated for by other means, such as voice recognition or recognition of outer facial features such as hairstyle (8). In fact, most cognitive tasks are composed of subtasks that can be compensated for or substituted to some extent. A color-agnosic person may infer color by comparing the surface properties of a presented object with that of a known object (10). People with congenital agnosias have never known normal cognition, and therefore, they may have difficulty understanding or communicating the nature of their deficits. If a prosopagnosic, for example, complains to his doctor that he can’t recognize people, the doctor may assume that the patient can’t remember names, which is a very common memory problem.

A more general factor that may limit the discovery of cognitive deficits is the structure of cognitive tests. The human cognitive system adapts continuously. Thus, an assess-

Some cognitive disorders can be overlooked.

ment at a given point in time may not take into account flexibilities in reaction time, learning and processing speeds, or problem-solving techniques. For instance, a large meta-analysis of 107 samples—with a total of 134,436 participants given a cognitive ability test—revealed retest performance improvement of about one-half of the standard deviation from the first to the third test (13). The effect was larger when identical tests were used and



has also been observed for the quite complex Wechsler Adult Intelligence Scale (WAIS) test (14). Although the ability to adapt quickly to new challenges is a much sought-after skill in many professions, retest gains are treated as unwanted effects in many selection tests. Also, those skills for which a person is not specifically trained will only be developed to the socially accepted minimum. Thus, a standard cognitive test might miss a deficit in such a skill when cognitive dynamics are neglected.

Performances of many cognitive functions are distributed across a population in a normal (Gaussian) way, and thus “low performers” may be thought of as ordinary “tail-enders” in the distribution. There are also questions about the adequacy and scope of some contemporary cognition tests. For example, a

type of hereditary color agnosia cannot be detected by the standard Ishihara color test for color blindness or the Farnsworth-Munsell 100-hue test for color matching (10). Tests for “general intelligence” (such as the Stanford-Binet and WAIS tests) do not reflect the function of a broad range of brain regions but mainly recruit a specific system in the frontal lobes (15).

Considering all these factors, some common cognitive dysfunctions may still await discovery. In Piaget’s model of human cognitive development (genetic epistemology), children learn by assimilation, the fitting of the perception of a new event or object to existing schemes, and by accommodation, the adaptation of cognitive schemes to new percepts. With one or more dysfunctional cognitive skills, cognition may still reach a sufficient functional level, but the cognitive

network will become stretched and bent in the process. Therefore, any congenital functional or anatomical differences, as in congenital prosopagnosia or protanopia (red-green color blindness), will cause the neural networks to develop and connect in specifically different ways and lead to typical behavioral changes.

These processes and the underlying functional and anatomical dynamics are an extremely promising field for further research. As well, cognitive tests could evolve in ways such as defining the scope of tests more precisely. The human cognitive system is praised for its enormous adaptability. To help affected persons and to acquire a more comprehensive understanding of the brain, greater attention needs to be directed toward the structures, dynamics, and limits of these adaptive processes.

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MOLECULAR BIOLOGY

Syntheses That Stay Together

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An old principle of macromolecular biosynthesis in bacteria is that the speed of protein synthesis (translation) matches that of messenger RNA (mRNA) synthesis (transcription), but how this integration occurs has not been clearly defined. An obvious conjecture is that ribosomes move along the emerging mRNA at whatever speed RNA polymerase goes so that translation and transcription remain coordinated, as it is known to do when conditions change (1). However, on page 504 (2) and 501 (3) of this issue, Proshkin *et al.* and Burmann *et al.*, respectively, suggest the opposite: Efficient binding and progression of ribosomes along mRNA increase the speed of RNA polymerase, whereas the absence of ribosomes allows the polymerase to slow and wait for ribosomes to catch up.

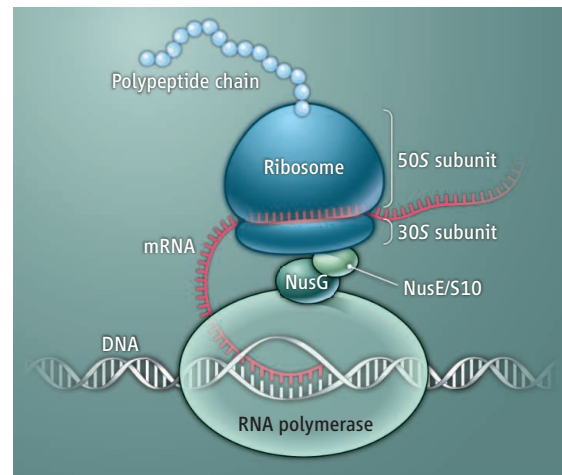
Proshkin *et al.* measured the rate of RNA polymerase progression along DNA in bacteria when translation was slowed in any of three ways: treatment with an antibiotic, expression of a mutated ribosomal protein, and an increase in the abundance of rare codons in the transcribed DNA. In each case, transcription slowed correspondingly. Furthermore, a ribosomal mutation that increased the rate of translation accelerated transcription.

What connection between RNA polymerase and ribosome underlies this unexpected effect? Proshkin *et al.* suggest that it depends on the polymerase’s ability to “backtrack,” in which it momentarily stops elongating mRNA and spools backward instead (4, 5). Consequently, the newly synthesized mRNA end is extruded from the “secondary” channel of RNA polymerase and the

The rate of mRNA translation determines the rate of mRNA synthesis in bacteria through direct coupling of the respective molecular machinery.

upstream segment of mRNA is drawn back into the usual exit pore of the enzyme. RNA polymerase moves relatively freely between these isomeric states, although backtracking is favored when the mRNA-DNA hybrid is stronger in the backtracked position than in the forward position. Backtracking also is the response of polymerase to a physical barrier in its path, such as a DNA binding protein, even in the absence of an energetically favorable hybrid. A reasonable proposition is that temporary barriers in the chromosome make backtracking frequent enough to slow the overall rate of transcription. But backtracking is inhibited if another molecule binds to upstream mRNA and prevents its retraction into the enzyme (6). Along these lines, Proshkin *et al.* propose that a ribosome closely following RNA polymerase restrains the emerging mRNA. This would inhibit backtracking and favor net forward movement of the polymerase.

How does this mechanism relate to the fundamental regulatory step in which gene expression varies with the rate of ribosome access to its binding site at the beginning of the mRNA (7)?



Coupled syntheses. A model for the coupling of translation and transcription in bacteria is shown. The first ribosome translating a mRNA associates with RNA polymerase through the NusE-NusG-polymerase interaction. This prevents retraction of the emerging mRNA into RNA polymerase, and thus inhibits backtracking-associated pauses that slow RNA polymerase in the absence of the ribosome.

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