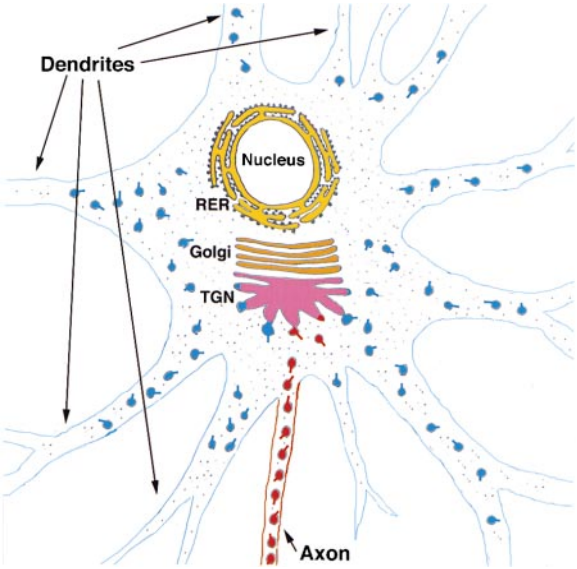

Cartoon of a Prototypical Neuron Showing the Components of the Endomembrane Pathway for Membrane Protein Biosynthesis

Sorting of membrane proteins into distinct populations of transport vesicles destined for the axon (red) and for the somatodendritic (blue) compartments occurs in the TGN (purple). Sorting of mGluR isoforms is directed by signals in the cytoplasmic tail, as indicated in the cartoon.

One major question that arises from these studies relates to general principles of axonal versus somatodendritic protein sorting in neurons. As discussed by Stowell and Craig, the exclusive axonal targeting that is widespread in nature has been difficult to reproduce when recombinant proteins are expressed in cultured neurons. mGluR7 is found predominantly in axons in situ, for example. These authors point to the fact that generating and maintaining an exclusive axonal localization may involve more than selective axonal targeting, and propose that axonal membrane proteins may initially be uniformly distributed and only achieve polarity through localized differential turnover. As such, the short incubation times dictated by transient protein expression in cultured neurons may not be sufficient to generate the proper localization. Given this, one would expect that any endogenous membrane protein destined for axonal localization in cultured hippocampal neurons would initially be expressed uniformly, followed by enrichment in the axon through selective turnover. Future studies on the dynamics of the targeting of mGluR7 or other axonal membrane proteins may clarify these issues and solve the discrepancy between in situ and in vitro localization of axonal membrane proteins. However, identification of cellular proteins that exhibit differential interaction with the distinct targeting signals on the cytoplasmic domains of mGluRs characterized by Stowell and Craig may allow for the identification of components of the polarized protein trafficking machinery in neurons that have remained so elusive in epithelial cells.

It is surprising that both of the sorting signals identified by Stowell and Craig are found in the cytoplasmic tail of the mGluRs. Taken together with recent observations that synaptobrevin contains a cytoplasmic axonal targeting motif (West et al., 1997), these findings suggest that, unlike apical targeting in epithelial cells, the axonal targeting machinery of neurons can utilize cytoplasmic sorting signals. It is interesting to note that the cytoplasmic tail of G protein–coupled receptors such as the mGluRs also plays an important modulatory role and is the site for modification by phosphorylation and for interaction with arrestin and other cellular proteins. This raises the possibility that the targeting of mGluRs in neurons could be dynamically modulated via such modifications in this region critical for targeting, and may provide a mechanism to generate the observed cellular variability in mGluR localization.

James S. Trimmer
Department of Biochemistry and Cell Biology
Institute for Cell and Developmental Biology
State University of New York
Stony Brook, New York 11794

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Trying versus Succeeding: Event-Related Designs Dissociate Memory Processes

We have all experienced the frustration of trying to remember a name or fact that feels as if it is at the tip of our tongue but remains inaccessible despite our best efforts to retrieve it. This common occurrence provides a heuristic demonstration that acts of remembering can be separated into two types of processes—one associated with the *effort* of retrieving and one associated with *success* in retrieving. In the instance of the "tip-of-the-tongue" phenomenon, effort is exerted but information is not successfully retrieved. While this exact experience is not the focus of the study by Ranganath and Paller in this issue of *Neuron* (1999), the phenomenon illustrates the issue that is explored; namely, understanding how and where the processes associated with retrieval effort and retrieval success occur in the brain. Ranganath and Paller have shed new light on the question of what brain regions are involved in effort and success during episodic memory (e.g., see Tulving, 1983) by mapping event-related potentials (ERPs).

Ranganath and Paller (1999) cleverly designed a behavioral procedure to encourage varied levels of retrieval effort, while simultaneously monitoring whether or not information was successfully retrieved. They employed a recognition memory task where subjects attempted to discriminate between studied and novel pictures (line drawings of common objects). In the "specific test" condition, subjects were only to say that an item was old if it appeared exactly as it did when studied. While some of the old test items were identical to those presented during the study period, others had been subtly changed in size and shape (the pictures were scaled, altering their height and width). In this manner, the specific test required considerable retrieval effort to be exerted; to remember accurately, subjects were required to develop a strategy that made use of very specific perceptual details. The second condition, the "general test," demanded considerably less effort. Subjects were required to endorse an item as old regardless of a change in exact perceptual details. ERPs were compared both within and across the different testing conditions. By isolating electrophysiological correlates of successfully retrieved items, in the context of varied retrieval demands, Ranganath and Paller were able to dissociate neural correlates of retrieval effort from those of success. They found that scalp potentials localized over left frontal cortex tracked the strategic demands of the retrieval task independent of whether information was successfully recognized. By contrast, differences between old and new items were found in scalp potentials over right frontal cortex, suggesting a complementary correlate of retrieval success.

To fully appreciate the significance of Ranganath and Paller's study, it is necessary to consider the origins of the debate over localization of retrieval effort versus retrieval success. The issue arises because of a controversy concerning the role of the prefrontal cortex in memory retrieval. A host of neuroimaging studies have revealed that certain areas of prefrontal cortex are involved in memory retrieval (reviewed by Buckner, 1996; Fletcher et al., 1997; Tulving et al., 1994). In particular, activity in areas of right anterior and dorsolateral prefrontal cortex have been consistently reported across a variety of memory tasks and materials (e.g., for recognition and cued recall, and for words and pictures). The question is: does this activity represent retrieval effort, retrieval success, or both?

The difficulty in resolving this debate is exemplified by comparing two studies employing positron emission tomography (PET) that were conceptually similar yet produced findings that led to opposing conclusions. In the first case, Nyberg et al. (1995) employed a simple recognition memory test in which subjects studied a list of words and were then asked to discriminate between old (studied) and new (unstudied) items. Brain activity was measured during the recognition test, with the key manipulation being a contrast between two experimental conditions in which all the test items were either old (attempt and success in retrieval) or new (attempt to retrieve but with no success), respectively. Relative to a control condition (silent reading), the right prefrontal cortex was found to be active for both memory conditions, with little difference between them. That is, the prefrontal cortex was active both when all test items were old and when all test items were new. Consequently, Nyberg et al. (1995) concluded that activity in the prefrontal lobes was related to the effort or attempt to retrieve, regardless of whether retrieval was successful.

In the second case, Rugg et al. (1996) also employed a recognition memory test and again contrasted activity in two experimental conditions. In this study, the key manipulation between the experimental conditions was to vary the proportion of old and new items in each test list, such that there was either a high (4:1) or low (1:4) ratio of old to new test items. Significantly, the critical test conditions were *embedded* within a much longer test list, in the hope that subjects would be unlikely to notice the different ratios of old to new test items and would therefore be unlikely to vary their retrieval effort. Thus, subjects were tested on a long list of items, but brain scans were only taken during the critical test conditions where the proportion of old to new items had been manipulated. Relative to a control condition (in which all items were new) significant prefrontal activity was found in both memory conditions, with greater activity occurring when more old items were present. Thus, Rugg et al. (1996) found that prefrontal activity varied as a function of the number of old items presented, suggesting that the prefrontal lobes are sensitive to whether retrieval is actually successful.

How can two studies both designed to answer the same question, using the same technique and similar experimental protocols, come to such radically different conclusions? The answer lies primarily in the technique itself, namely PET. An inherent feature of PET studies is the fact that they are limited to the use of blocked designs. Within a blocked design, brain activity is measured in distinct experimental conditions, periods of time during which a series of sequential experimental trials are presented. This produces a measure of brain activity that is averaged across the entire series of trials (or block) regardless of variation in the types of stimuli presented or subjects' responses to those stimuli. Consequently, experimental manipulations are limited to changes across different blocks of stimuli, for example old versus new test items in the Nyberg et al. (1995) study and varied proportions of old and new test items in the Rugg et al. (1996) study. While these manipulations were designed to encourage retrieval success in one condition and discourage it in the other, the blocked design of PET did not allow either study to compare activation specifically for trials in which retrieval was successful with those in which it was not: because of the averaging across experimental conditions in a blocked design, retrieval effort and retrieval success could not be clearly separated. By contrast, the ERP technique employed by Ranganath and Paller allows the use of event-related designs. In event-related studies, data can be separated post hoc according to the different classes of experimental stimuli that were presented *and* the different responses made by each subject (i.e., contingent upon subject's performance).

The experiment presented by Ranganath and Paller illustrates the advantage of event-related techniques nicely (see also Johnson et al., 1997; Schacter et al., 1997; Donaldson and Rugg, 1999; Duzel et al., 1999; and Wilding, 1999, for related manipulations). The strength of

the approach used by Ranganath and Paller is not simply in their use of separate blocked recognition conditions to encourage varied retrieval strategies. Rather, the analysis possible in their study relied both on a manipulation of retrieval demands across blocks of trials *and* the use of event-related procedures to isolate correlates of individual recognition events. By crossing the two levels of analysis—examining the effects concerned with the overall strategy (across blocks) and those concerned with individual items (within each block in an event-related manner)—they were able to distinguish between the neural correlates of retrieval effort and success.

David I. Donaldson and Randy L. Buckner
Department of Psychology
Washington University
St. Louis, Missouri 63130

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How Hallucinations Make Themselves Heard

Schizophrenia is a common disorder with a lifetime risk of about 1%. The age of onset is typically in the mid twenties and many sufferers never fully recover. The effects of the illness can be devastating for the sufferer and for his or her family. Although there is evidence of structural and functional brain abnormalities in schizophrenia, the causes of the disorder remain unknown (Straube and Oades, 1992). Auditory hallucinations are the most common symptom of this disorder, being reported by about 65% of patients with schizophrenia (David, 1994). The patient does not hear just sounds but fully formed verbal communications that appear to emanate from a particular speaker or group of speakers. These speakers often seem omniscient (they can read the patient's thoughts) and are usually hostile, as in the following example:

> Days later while in the Metropolis again, I was once more startled by these same pursuers, who had threatened me several days before. It was night-time. As before, I could catch part of their talk, but, in the theatre crowds, I could see them nowhere. I heard one of them, a woman, say: "You can't get away from us; we'll lay for you and get you after a while!" To add to the mystery, one of these "pursuers" repeated my thoughts aloud verbatim. I tried to elude these pursuers as before, but this time I tried to escape from them by means of subway trains, darting up and down subway exits and entrances, jumping on and off trains, until after midnight. But, at every station where I got off a train, I heard the voices of these pursuers as close as ever (L. Percy King, from a letter written in the 1940s protesting the writer's imprisonment in a mental hospital).

Hallucinations can cause considerable distress because the voices continually criticize the patient and may command the patient to act against his or her wishes:

> Only a short time before I was confined to my bed I began to hear voices, at first only close to my ear, afterwards in my head, or as if one was whispering in my ear—or in various parts of the room... These voices commanded me to do, and made me believe a number of false and terrible things (from John Percival, Esq., *A Narrative of the Treatment Experienced by a Gentleman, During a State of Mental Derangement* [1840]; examples quoted in Peterson, 1982).

How is it that, in the absence of any sensory input, the hallucinating patient can have an experience that is indistinguishable from a real, external voice? Discovering the physiological basis of hallucinations would provide a major insight into the neural basis of phenomenological consciousness as well as pointing toward possible physiological mechanisms underlying hallucinations. The new generation of brain imaging techniques provide the opportunity to localize any brain activity associated with the occurrence of hallucinations. Functional magnetic resonance imaging (fMRI) is particularly suited to this purpose; since its temporal resolution is relatively high (in the order of seconds), scanning can be carried on continuously and can be repeated over a number of sessions. It would seem at first sight an easy matter to scan patients while they indicated when hallucinations were occurring. In practice, suitable patients are difficult to find. Furthermore, the timing of the hallucinations is not under the control of the patient or the experimenter and the temporal sequence of the hallucinations that happen to occur must be appropriate to the scanning protocol. Additionally, many patients are unwilling to give detailed information about when the hallucinations are occurring.

In this issue of *Neuron*, Dierks and his colleagues (1999) report results from a series of three suitable patients in whom fMRI was used to identify brain activity during hallucinations. These patients were identified by screening all the patients with a history of hallucinations