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ORIGINAL PAPER

Reducing mind to molecular pathways: explicating the reductionism implicit in current cellular and molecular neuroscience

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Abstract As opposed to the dismissive attitude toward reductionism that is popular in current philosophy of mind, a "ruthless reductionism" is alive and thriving in "molecular and cellular cognition"—a field of research within cellular and molecular neuroscience, the current mainstream of the discipline. Basic experimental practices and emerging results from this field imply that two common assertions by philosophers and cognitive scientists are false: (1) that we do not know much about how the brain works, and (2) that lower-level neuroscience cannot explain cognition and complex behavior directly. These experimental practices involve intervening directly with molecular components of sub-cellular and gene expression pathways in neurons and then measuring specific behaviors. These behaviors are tracked using tests that are widely accepted by experimental psychologists to study the psychological phenomenon at issue (e.g., memory, attention, and perception). Here I illustrate these practices and their importance for explanation and reduction in current mainstream neuroscience by describing recent work on social recognition memory in mammals.

Keywords Reduction · Long-term potentiation (LTP) · Social recognition memory consolidation · Molecular mechanism

1 Psychoneural reduction: Two competing attitudes

Something called *naturalism* is fashionable in current philosophy of mind. Its proponents claim that psychological kinds are part of "the natural world" and ultimately are explicable by "natural science." However, most naturalistic philosophers explicitly reject *reductionism*. Reductionists remain few and far between in current philosophy

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of mind. More than one decade ago, LePore and Loewer (1989) spoke for the orthodoxy, writing:

> Recent discussions of content properties have focused on a number of features which these properties are claimed to possess and which have been thought to show either that they are not reducible to the physical properties which ground causal relations . . . or not reducible to physical properties at all. . . . It is practically received wisdom among philosophers of mind that psychological properties (including content properties) are not identical to neurophysiological or other physical properties. (p. 179)

Even Jaegwon Kim, a noted reductionist among philosophers, has remarked on the unpopularity of the position: "Being a reductionist is a bit like being a logical positivist or a member of the Old Left—an aura of doctrinaire naiveté hangs over him" (1993, p 266).

However, this attitude is completely at odds with that among neuroscientists, especially among the cellular and molecular neuroscientists who now constitute the discipline's mainstream.[1] Recently, in the introduction to the 4th Edition of their monumentally influential textbook, *Principles of Neural Science*, Eric Kandel, James Schwartz, and Thomas Jessell announce accomplished mind-to-molecules "linkages":

> This book . . . describes how neural science is attempting to link molecules to mind—how proteins responsible for the activities of individual nerve cells are related to the complexities of neural processes. Today it is possible to link the molecular dynamics of individual nerve cells to representations of perceptual and motor acts in the brain and to relate these internal mechanisms to observable behavior. (2000, pp. 3–4)

These "links" are nothing less than *reductions* of psychological concepts and kinds to molecular-biological mechanisms and pathways.

Many philosophers (and cognitive scientists) are baffled by such claims. Set aside (for this paper) familiar worries about "the multiple realization of psychological on physical kinds" and "the hard problem of consciousness."[2] Many philosophers will still wonder how current neuroscience proposes to step across so many "levels" in a single bound. Between the behavioral and the molecular-biological levels lie (at least) the cellular, the neuroanatomical, the circuit (neuron networks), the regional, the systems (including the motor system, to generate measurable behavior), and perhaps even the information-bearing and -processing. Must not reductive "bridges" be laid between all these intermediaries before we can claim "mind-to-molecular pathway reductions"? And is not *cognitive neuroscience*—the branch of the discipline that at least some philosophers can claim familiarity with—having enough trouble "bridging" the higher levels to warrant reasonable worries about whether neuroscience will ever pull off the entire reduction?

Figure 1 illustrates this "multitude of levels" picture of the mind-brain scientific endeavor and the step-by-step task thought to confront reductionists. This figure

[1] I give a quantitative argument for the dominance of cellular and molecular neuroscience, based on self-identifications of areas of specialization and categories of abstract submission for the annual meeting among the 31,000+ Society for Neuroscience members, in Bickle (2003, Ch. 1, Sect. 1). This information was drawn from the Society for Neuroscience web site (www.sfn.org).

[2] Set aside these worries, but do not forget about them. I address the "multiple realization" worry from the perspective of current molecular neuroscience in Bickle (2003, Ch. 3, Sect. 4–6), and issues concerning consciousness from the perspective of current cellular neuroscience in Bickle (2003, Ch. 4).

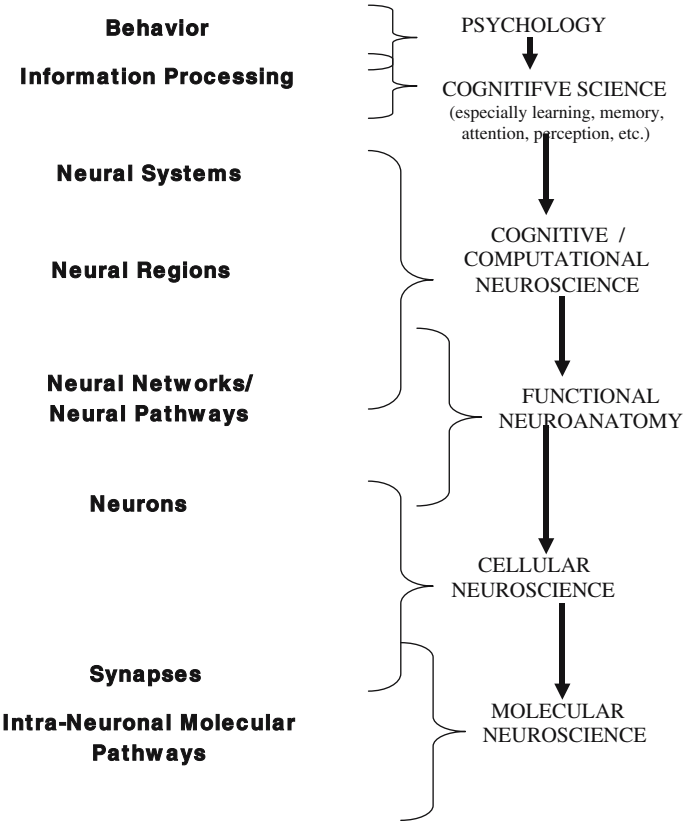

Fig. 1 Schematic illustration of the currently standard view of levels of organization within the nervous system, relationships to higher levels of organization (behavior, information processing), and the scopes of the mind-brain sciences addressing these levels. Allied with this standard view is a "step-by-step" view of psychoneural reduction (downward arrows), in which reduction succeeds only when features of a higher level of organization (via their affiliated scientific theories) are linked to features at the next level down

should be crashingly familiar since it is now part of the accepted background in current philosophy of mind (at least in the "analytic" tradition) and cognitive science. And since cognitive neuroscience is having enough trouble bridging a gap high in the hierarchy, there seems little reason for philosophers (and cognitive scientists) to attend to lower-level neuroscience—except, perhaps, for heuristic or methodological or pragmatic reasons.

It is interesting to note that even the originator of "neurophilosophy," Patricia Churchland—hardly an enemy of reductionism—shared this "multitude of levels" view and the accompanying attitude about the fields of neuroscience that reductionists should attend. (Indeed, Churchland and Sejnowski [1992] wrote one of the earliest primers in computational cognitive neuroscience.) For Churchland (even back in 1986), the reduction of neurophysiology to molecular biology and biochemistry was not in serious doubt: "Researchers have begun to reduce electrophysiologically defined properties, such as spiking and synaptic potentials to the basic molecular biochemistry of cell membranes" (1986, 59). What remained in doubt—and what Churchland undertook to provide in *Neurophilosophy*, based on both a philosophy

of science and emerging ideas in cognitive neuroscience—was the "link" that bridged neurophysiology and functional neuroanatomy with "higher functions":

> Fine-grained detail has accumulated concerning such things as the molecular structure, location, synthesis, blocking agents, and enhancing agents of the various neurochemicals, but there is still nothing remotely resembling a comprehensive *theory* of what they do or of how the known psychological effects result from tinkering with them. ... Until we have higher-level concepts to describe what configurations of neurons are doing, we have no means of bridging the gap between molecular descriptions and molar ["systems-level"] descriptions. (1986, 82)

Philosophers of neuroscience have followed Churchland's lead. They have virtually ignored developments in cellular and molecular neuroscience over the past two decades and have instead sought "psychoneural links" at the levels of neuronal regions, ensembles, their connectivities, and their "systems" properties and dynamics (e.g., Bechtel, Mandik, Mundale & Stufflebeam, 2001).

One central contention of this paper can now be stated succinctly. As long as philosophers (and cognitive scientists) ignore developments in cellular and molecular neuroscience, they will continue to either voice anti-reductionist worries or look for mind-to-brain linkages in the higher-level reaches of cognitive neuroscience. But molecular neuroscientists have developed experimental practices that bridge the behavioral to the molecular pathway levels *directly*; and these practices are common to all recent empirical successes that forge the "links" alluded to in the passage quoted above from Kandel, Schwartz, and Jessell's (2000). My purpose in this paper is to make these practices explicit by presenting one elegant example of recent research employing them and then highlighting features of this example that speak to some philosophical concerns about "reductionism."

Obviously, more than one example from cellular and molecular neuroscience is necessary to defend my general claim. More are already on offer. In my (2003) I present many examples and a lot more experimental detail, ranging from hippocampal-dependent contextual fear conditioning through single-cell physiological investigations of working memory and selective visual attention, to effects of microstimulation in visual and somatosensory cortex. All of these examples mobilize the experimental practices I am about to illustrate and describe, in that they intervene directly at the cellular or molecular levels and track specific behaviors in well-accepted experimental protocols for studying the psychological kind at issue. But even those who remain unconvinced about the general plausibility of the reductionism made explicit here will still benefit from learning about the single case in this paper or the multiple cases in the above-cited book. The ignorance of philosophers of mind and cognitive scientists about the practices and results of current cellular and molecular neuroscience detracts from the credibility of claims they make about the entire discipline. These case studies at least bring to light the way neuroscience is currently done "on the bench."

2 Some basic scientific background: Molecular mechanisms of long-term potentiation in mammals

We begin with some necessary scientific background. Since its explicit discovery in 1973, *long-term potentiation* (LTP) has held promise as one neurobiological mechanism

for memory consolidation.[3] LTP is easy to induce and measure physiologically. With the development of improved electrodes and electrophysiological techniques over the past three decades, a popular neural site for studying LTP is the Schaffer collateral pathway, a bundle of axons internal to the mammalian hippocampus. The hippocampus itself is a bilateral structure in the medial temporal lobe whose implication in memory consolidation has been known for nearly a half-century (Squire, 1987). ("Consolidation" is the conversion of labile, easily disrupted short-term memories into their stable long-term form.) The Schaffer collateral pathway projects from neurons in the CA3 region onto neurons in the CA1 region. The experimental work revealing the cellular and molecular mechanisms of LTP was done primarily using viable tissue slices, 300–400 microns thick, cut from the hippocampi of young laboratory rats and maintained on slides in a nutrient bath. A stimulating electrode is inserted into the Schaffer collateral bundle projecting from CA3 neurons of the slice and a recording electrode is inserted into the CA1 region. Baseline responses of CA1 neurons are first recorded, either as amplitude of membrane voltage depolarization or time to maximum amplitude of *excitatory post-synaptic potentials* (EPSPs), or as frequency or time to maximum frequency of action potentials, in neurons nearby the recording electrode. Then either a single burst of electric pulse or a chain of pulses is delivered through the stimulating electrode, inducing strong activity (i.e., a high frequency of action potentials) in Schaffer collateral axons near the stimulating electrode. The result of this strong afferent (incoming) stimulation "potentiates" specific synapses between affected axons and their CA1 neuron targets. In other words, in CA1 neurons with potentiated synapses, subsequent pre-synaptic activity produces EPSPs with greater amplitudes and shorter onset times to maximum amplitude, and action potentials at a higher frequency and with shorter times to maximum frequency, compared to (pre-potentiation) baseline values. This effect maintains for durations depending on the potentiating current. Single bursts through the stimulating electrode potentiate affected Schaffer collateral-CA1 synapses for up to 2 or 3 h. Multiple bursts have potentiated synapses for days, even weeks, in vivo (in the living animal, a variety of chronic physiological recording techniques).

One feature that gave this laboratory trick for inducing LTP some real-life explanatory potential was the early discovery that stimuli at the theta frequency are optimal for inducing long-term LTP. Theta is a 5–7 Hz electroencephalogram (EEG) wave that appears when animals are engaged in "voluntary," especially exploratory behaviors (Vanderwolf, 1969). In rats, theta is correlated with sniffing rates, which suggests that it is a "stimulus sampling" mode of hippocampal function (Macrides, Eichenbaum, & Forbes, 1982). Based on such behavioral discoveries, Larson, Wong, and Lynch (1986) induced stimulation trains in tissue slices that mimicked hippocampal theta bursting—short bursts delivered through the stimulating electrode every 200 milliseconds—and produced optimal LTP in affected CA1 neurons. Further studies using freely moving rats implanted with chronic stimulating and recording electrodes showed that LTP induced in vivo by theta frequency stimulation was stable for weeks (Staubli & Lynch, 1987).

[3] Lynch (1986) is a useful early statement of this promise. Two often-cited criticisms are Gallistel (1995) and Shors and Matzel (1997) (the latter published with numerous commentaries and the authors' replies). The literature on the LTP-memory hypothesis is huge. Craver (2003) is an excellent introduction for philosophers to the historical details. I give a mostly up-to-date review of (part of) the empirical search for the molecular mechanisms of LTP in my (2003, Ch. 2 and 3).

Long-term potentiation quickly became a popular experimental target when the "molecular wave" began washing over neuroscience two decades ago. An influential account of its molecular mechanisms is now in place. Their initial elucidations are from work on invertebrates, and early experiments on late-phase (L-) LTP were done using hippocampal slices (Frey, Huang, & Kandel, 1993). These experiments confirmed that L-LTP requires multiple-spaced pulse trains through the stimulating electrode for induction, begins only after the first 1-3 h following stimulation, lasts for at least 10 h, and requires new protein synthesis (Hiang, Li, & Kandel, 1994).

Multiple pulse stimuli through the stimulating electrode in the Schaffer collateral pathway activate interneurons that synapse on the same neurons that receive excitatory projections from the Schaffer collateral axons. The Schaffer collateral axons release glutamate, an amino acid, as their neurotransmitter. Fibers from the mesolimbic dopaminergic pathway innervate the hippocampus and release dopamine, a catecholamine, onto the same CA1 pyramidal cells that receive glutamatergic inputs from the Schaffer collateral axons (Fig. 2). Dopamine binding activates a G-protein complex that primes adenylyl cyclase molecules in the post-synaptic dendritic spine to increase the conversion of adenosine triphospate (ATP, a principal energy-carrying molecule in cells) into cyclic adenosine monophospate (cAMP). This quickly raises the number of cAMP molecules present in the spine. cAMP is the classic "second messenger" substance in molecular biology, which induces activity throughout the cell. In the case of LTP, cAMP molecules quickly bind to sites on the regulatory subunits of cAMP-dependent protein kinase A molecules (PKA), freeing the PKA catalytic subunits.

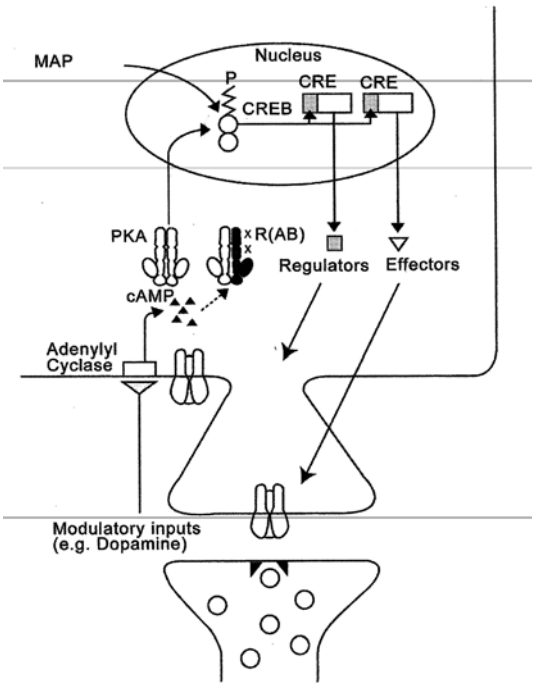

Fig. 2 Steps in the molecular mechanisms inducing L-LTP at an individual synapse. See text for discussion. Reprinted from Abel et al., (1997), with permission from Elsevier Science

During early phase (E-) LTP, induced experimentally by a single electric bursts through the stimulating electrode, freed catalytic PKA subunits turn off an inhibitory pathway that normally blocks the activity of phosphorylated calcium-calmodulin kinase II (CaMKII).[4] This enables phosphorylated CaMKII molecules to bind to α-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid (AMPA) receptors, the principal excitatory receptors that bind glutamate. (This CaMKII-AMPA binding takes place through interactions with nearby activated N-methyl-D-aspartate (NMDA) receptors, whose role in LTP induction has been studied for more than two decades.) It was previously thought that CaMKII binding changes the configuration (shape) of AMPA proteins to greatly increase (i.e., nearly triple) their conductance capacity for sodium (Na+) ion influx. More recent experimental evidence suggests that increased activity of CaMKII induces the delivery of AMPA receptors into activated synapses by a mechanism that associates a particular subunit of the AMPA protein (the GluR1 subunit) with a class of proteins containing a specific domain (the PDZ) domain) (Hayashi et al., 2000). But during the "consolidation" to late phase (L-) LTP, the huge rise in freed catalytic PKA subunits (driven by the multiple pulse stimulations through the stimulating electrode and the combined release of glutamate and dopamine from pre-synaptic neurons) enables them quickly to translocate to the neuron's nucleus, where they bind to and phosphorylate various isoforms of cyclic AMP response element binding protein (CREB), enabling one form of CREB molecules to serve as gene expression enhancers or activators for two important classes of immediate early genes.

Some non-scientists might here need a brief primer on molecular genetics. I will provide this in one paragraph (!) with the aid of one illustration (Fig. 3).[5] Molecular biologists divide a gene into two separate functional regions, the coding region and the control region. The coding region contains nucleotide sequences of the deoxyribonucleic acid (DNA) that express specific proteins—the instructions for protein synthesis, transcribed onto messenger ribonucleic acids (mRNAs) which then translocate out of the cell nucleus and onto the protein synthesis machinery in the cytoplasm. (This region is what most non-specialists think of as a "gene.") The control region, which has been a principal focus of molecular genetics over the past two decades, contains the molecular machinery for turning on and off the gene's expression. The control region itself is divided into two functional parts, response elements and the promoter region. Response elements are nucleotide sequences containing binding sites for response element binding proteins. The promoter region, typically located downstream from the response elements and adjacent to the gene's coding region, consists of nucleotide sequences containing binding sites for molecules that bind RNA polymerases. The latter transcribe the gene's coding region into mRNAs (Fig. 3a). When a polymerase molecule is bound at the promoter region and *enhancer* or *activator* response element binding proteins are bound to response elements, the shape of the DNA molecule in the control region changes to bring the bound response element binding proteins

[4] *Phosphorylation* is an important molecular-biological event in which a phosphate group (PO_4) is attached to a molecule. In the case of proteins, phosphorylation changes their tertiary conformations to change their molecular-biological interactions.

[5] For those interested in really learning the science, Lodish, Berk, Zipursky, Baltimore and Darnell (2000) is an excellent recent text—but the field moves fast! (The entire text is available on line at www.ncbi.nih.gov.)

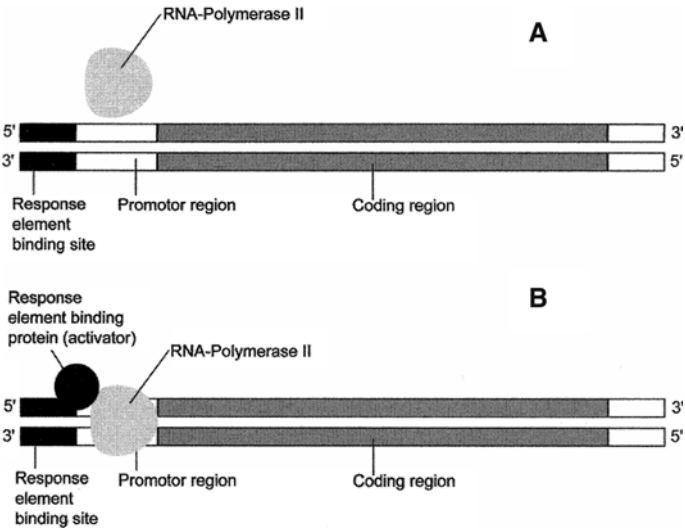

Fig. 3 Basic functional constituents of a gene and mRNA transcription. (**A**) No mRNA transcription initiated since no activator binding protein is bound to a response element binding site on the gene's regulatory region. (**B**) mRNA transcription initiated by activator binding protein bound to response element binding site. See text for discussion. Reprinted from J. Bickle (2003), Fig. 2.7, p. 72, with permission from Kluwer Academic Publishers

into interaction with the RNA polymerase. This interaction initiates gene transcription (Fig. 3b). When *repressor* response element binding proteins bind to response elements, the shape of the DNA molecule is affected to keep the response element binding proteins from interacting with the RNA polymerase. This inhibits or blocks gene transcription and expression. Molecularly speaking, gene expression in a cell over time (and hence protein synthesis) is an interplay of the availability and binding of response element binding proteins at response element sites (And, of course, these response element binding proteins are themselves the products of gene expression "upstream," and hence of other response element binding proteins, . . .).

Before that brief foray into molecular genetics, I noted that one isoform of cAMP response element binding protein (CREB), phosphorylated by the freed catalytic PKA subunits that have translocated to the neuron's nucleus (P-CREB), serves as an activator for two immediate early genes. Which two? First, P-CREB activates expression of the gene, *ubiquitin carboxyl-terminal hydrolase (uch)*, and the synthesis of the protein of the same name (Fig. 4). This protein translocates back through the neuron, binding to proteasome complexes that in turn destroy free regulatory subunits of PKA molecules. This gene-driven "feedback" mechanism keeps the freed catalytic PKA subunits in a persistently active state, to maintain high enough numbers to continue translocating to the neuron's nucleus, phosphorylating CREB molecules and initiating further gene expression (Chain et al., 1999). Second, phosphorylated CREB molecules activate expression of the gene, *CCAAT enhancer binding protein (C/EBP)*, and the synthesis of that protein. C/EBP itself is a gene transcription enhancer, binding "downstream" at numerous sites to initiate gene expression for a variety of proteins that in turn translocate back to the neuron's dendrites and literally reshape the cytoskeleton of spine scaffolding. These proteins increase the number of active receptor proteins in the post-synaptic densities of potentiated synapses and even

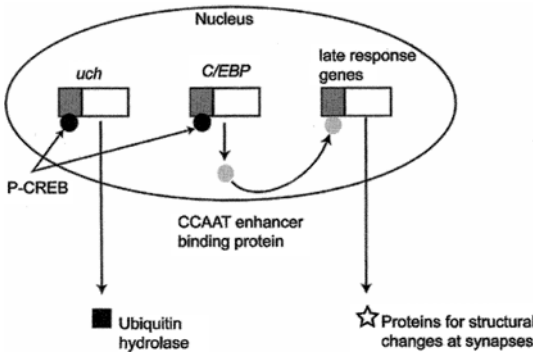

Fig. 4 Specific gene targets of one isoform of phosphorylated CREB. The *uch* gene expresses the protein, ubiquitin carboxyl-terminal hydrolase, a key constituent of a proteasome that destroys free PKA regulatory subunits, keeping the catalytic PKA subunits in their persistently active state. The *C/EBP* gene expresses the protein, CCAAT enhancer binding protein, itself an activator for late-response genes expressing proteins that more permanently alter (potentiate) postsynaptic structure and function. See text for details. Reprinted from J. Bickle (2003), Fig. 2.8, p. 73, with permission from Kluwer Academic Publishers

build new synapses in these affected dendritic spines (Taubenfeld et al., 2001). The result of this activity-driven gene expression is potentiated synapses—synapses more efficacious at generating excitatory post-synaptic potentials (EPSPs) to subsequent glutamate release and hence more likely to generate action potentials to subsequent afferent stimuli from Schaffer collateral axons. Only now, due to the gene expression and protein synthesis, the potentiation is more permanent. A *structural* change in the molecular make-up of post-synaptic dendritic spines has ensued. Each step in this molecular pathway and its functional significance for permanently potentiated post-synaptic activity to pre-synaptic afferent stimulation has been carefully documented and controlled in in vitro studies.[6]

These same synaptic changes driven by new gene expression and protein synthesis are also occurring in synapses further downstream in the pathways from CA1 hippocampal cells to a variety of cortical sites. Ultimately these lasting synaptic potentiations reach motor neurons whose activation orchestrates organized sequences of muscle contractions and relaxations against the body's skeletal frame—all the way down, that is, to the mechanisms generating *behavior*. These molecular processes in neurons throughout neuronal circuitries provide a plausible mechanism for how memory consolidation works and how subsequent behavior is affected for as long as these activity-driven, gene expression- and protein synthesis-governed changes persist. Activation of these potentiated neurons anywhere in these circuitries will now produce activity ultimately in the motor neurons that drive the learned, remembered behavior. Small wonder that LTP continues to generate excitement among neuroscientists interested in the cellular and molecular mechanisms of memory consolidation and, potentially, their behavioral effects.

[6] Again, for a more complete description of these mechanisms and the methodologies used to discover them, see Bickle (2003), Ch. 2, Sect. 4.2.

3 Forging mind-to-molecular pathway linkages experimentally

But are these molecular mechanisms actually the ones of *memory consolidation*? Are they the molecular mechanisms of consolidation for forms of memory with a "cognitive" flavor—forms prominent in and specific to mammals? Do they actually have effects on motor circuits and hence behavior? And most importantly, can these questions be answered experimentally?

A convincing approach would be to intervene directly with these intracellular molecular pathways in a controlled fashion and then measure the behavioral effects using well-accepted tasks from experimental psychology for the form of memory at issue. Over the past decade, advances in biotechnology have enabled experimenters to do this by manipulating gene expression and protein synthesis in mice. One can either "knock out" specific genes that express protein components of these molecular pathways or insert specific "transgenes" to overexpress these components. Increased knowledge of mammalian genomes and better biotechnological tools have made possible the mutation of specific genes (and their protein products) and the times at which their expression can be turned on or off. (Much of this specificity has to do with the use of specific promoter regions and molecules.) A quick glance through a recent issue of *Cell*, *Neuron*, or the *Journal of Neuroscience* (not to mention the neuroscience sections of *Science*, *Nature*, and *Proceedings of the National Academy of Sciences*) reveals that work with bioengineered genetic mutants now dominates cutting-edge neuroscientific research.[7]

A recent study by Alcino Silva and his colleagues (Kogan, Frankland, & Silva, 2000) elegantly displays this popular experimental strategy. Working with CREB$^{\alpha\delta-}$ knock-outs—mice specially bred so that the activator α and δ isoforms of the CREB molecule are not expressed in cells throughout the body—they have demonstrated that this intervention induces long-term amnesia for social recognition memory while leaving intact initial learning and short-term social recognition memory. That is, this intervention induces a specific disruption in the "consolidation switch" for social recognition memory.

The molecular intervention begins by inserting a targeting vector into mouse embryonic stem (ES) cells, with a promoterless neomycin-resistant gene (*Neo*) inserted into a specific point in the nucleotide sequence for the CREB isoforms. The *Neo* gene insertion serves two purposes. First, it is part of the selection process for the mutant DNA clones. After gene insertion the ES cells are then cultured on a mitomycin (antibiotic) solution. Only those DNA clones carrying the *Neo* (antibiotic-resistant) insertion survive the treatment. ES cells from successful clones are then injected into blastocytes derived from wild-type laboratory mice. Breeding for offspring homozygous for the mutated CREB gene then proceeds as usual.[8] Second, the *Neo* gene inserted into the *CREB* sequence disrupts CREB $\alpha\delta$ expression. Standard protein analysis reveals no CREB$\alpha\delta$ expression in homo-

[7] For a primer for non-scientists on how to create knock-out and transgenic animals, see Bickle (2003), Ch. 2, Sect. 5.2.

[8] The blastocytes are transferred to females of a different rat strain and chimeric offspring (those containing one copy of the mutated gene) are identifiable by their hair color. Chimeric males are then mated with wild-type females of the original lab mouse strain. Offspring heterozygous for the mutated gene are then mated to produce offspring homozygous (-/-) for the mutated gene. Due to the low viability of their particular strain of lab mouse homozygous for the α and δ CREB isoform mutation, Silva and his colleagues crossed the original heterozygotes for the mutation with another

zygous CREB mutants (Hummler et al., 1994). Nevertheless, mutants that survive into adulthood show no developmental or phenotypic abnormalities (Kogan et al., 1997). Previous results suggest that this is due to an overcompensation by a related protein product, cAMP response element modulation protein (CREM) (Hummler et al., 1994).

Using a hippocampus-dependent fear-conditioning memory task (memory for a novel environmental context-foot shock association), Silva and his colleagues had previously shown that CREB$^{\alpha\delta-}$ mutant mice were impaired in long-term memory of the context-shock association when tested 24 h after initial exposure and subsequent foot shock. Nevertheless, they were intact (compared to wild-type controls) on immediate effect of the shock (measured as time spent "freezing" immediately after the shock) and on short-term memory when tested in the conditioned environment 1 h later (Bourtchouladze, Frenguelli, Blendy, Cioffi, Schutz & Silva, 1994).[9] More recently, they have used these engineered mutant mice to investigate the molecular mechanisms of social recognition memory consolidation. Social recognition memory has become the "gold standard" for investigating scientifically a variety of social phenomena. In a recent review paper, Ferguson, Young, and Insel write:

> Across species, the ability to recognize a familiar individual forms the foundation upon which all social relationships are built. . . . In some cases . . . it may be necessary to remember specific details of individual social status or kinship. The ability to encode and recall very specific, individual information of this second type is required of almost all organisms living in complex social systems. . . . Whatever the sensory source of the information, the consequences of individual recognition are profound for reproduction and species survival. Kin recognition, pair bond formation, selective pregnancy termination, and dominance hierarchies all depend upon the long-term capacity of individuals to differentiate among familiar, previously encountered conspecifics. (2002, 200–201).

How is social recognition memory best investigated experimentally? Ferguson, Young, and Insel report: "In the laboratory, social memory can be assessed reliably by measuring the reduction in investigation [time] of a familiar partner relative to novel conspecifics" (2002, 200).

Since the mid-1980s, specific protocols employing this strategy have often been derived from Thor and Holloway (1982). Their task was developed and widely explored by experimental psychologists before being co-opted by neuroscientists. A typical study proceeds as follows. A novel juvenile male rodent is placed into the cage of an adult male of the same species for two minutes. Experimenters score the amount of time the adult spends in stereotypic examination of the novel juvenile. The juvenile is removed and an intertrial delay period ensues, characteristically 30 min to 1 h for short-term social recognition memory and 24 h for long-term. Either the familiar juvenile or a novel juvenile is then placed into the adult's cage and the adult is scored for the amount of time he spends in stereotypic investigation. Given the experimental psychology background of this protocol, all plausible behavioral controls have been investigated. The duration of investigation time by the adult on

Footnote 8 continued
strain of lab mouse and then crossed heterozygotes in the offspring to produce more viable CREB$^{\alpha\delta-}$ homozygotes.

[9] Notice that this result controls for potential confounds like perceptual, motor, or motivational deficits.

each trial is assumed to provide a quantitative measure of familiarity with the juvenile. This assumption is not without controversy—inattention can be motivated in many ways![10] Nevertheless, as Ferguson, Young, and Insel attest in the quote above, it remains the dominant quantified laboratory behavioral measure for social recognition memory.

Silva and his collaborators employed this behavioral paradigm with their CREB$^{\alpha\delta-}$ mutant mice and a variety of other experimental and control groups (Kogan et al., 2000). First, they acquired an expected but not previously demonstrated result. Adult CREB$^{\alpha\delta-}$ mutants displayed normal short-term social recognition memory for a juvenile conspecific presented earlier. Thirty minutes after initial exposure to it, they spent the same amount of time (statistically) in stereotypic investigative interaction with the juvenile as did wild-type control adults (Fig. 5a). However, CREB$^{\alpha\delta-}$ mutants were seriously impaired in long-term social recognition memory. In fact, the mutants spent the same amount of time (statistically) investigating the same juvenile 24 h after initial exposure as they did during the initial exposure. This result indicates complete long-term amnesia despite intact short-term recognition (Fig. 5b). This result is in keeping with Silva and colleagues' dissociation between intact short-term memory and impaired long-term memory in the CREB$^{\alpha\delta-}$ mutant mice for a variety of other tasks (e.g., Kogan et al., 1997), and with other researchers' genetic manipulations of the cAMP-PKA-CREB pathway and subsequent behavioral results (e.g., Abel, Nguyen, Barad, Deuel, Kandel & Bourtchouladze, 1997).

We saw in the previous section a sketch of the current model of how activity in the cAMP-PKA-CREB pathway leads to gene expression and protein synthesis producing permanently restructured potentiated synapses. We have now seen how direct intervention in this pathway leads to experimental confirmation of the hypothesis that it is a molecular mechanism of the consolidation switch for a cognitively robust kind of memory. As an experimental control to the study just described, Silva and his collaborators injected one group of wild-type adult mice with anisomycin, a general protein synthesis inhibitor, and another group with an equivalent volume of saline,

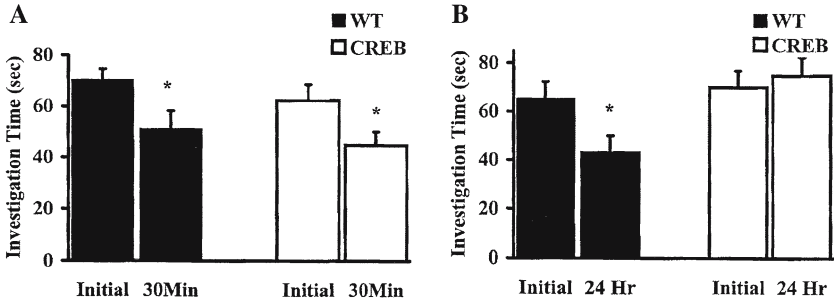

Fig. 5 Long-term but not short-term social recognition memory is impaired in CREB$^{\alpha\delta-}$ mutant mice. (**A**) Familiar juveniles were re-exposed to wild type (WT) or CREB$^{\alpha\delta-}$ mutant (CREB) mice 30 min after initial interaction. * indicates significant reduction in investigation duration in both groups ($P < 0.05$ compared to Initial). (**B**) Familiar juveniles were re-exposed to WT or CREB$^{\alpha\delta-}$ mutant mice 24 h after initial exposure. * indicates significant reduction in investigation duration only for WT mice ($P < 0.01$, compared to Initial). Reprinted from Kogan, Frankland, and Silva (2000), Fig. 6, p. 53, with permission from Wiley-Liss, Inc

[10] Thanks to Robert Richardson for reminding me about this controversy.

30 min prior to the initial exposure to the juvenile. As expected, short-term social recognition memory was not affected by the protein synthesis inhibitor but long-term social recognition memory was. Anisomycin-treated mice displayed a statistically similar decrease in investigative behavior when the previously presented juvenile was re-introduced 30 min later as did controls. But they showed no decrease in investigation time compared to initial exposure (unlike the controls) when the juvenile was re-introduced 24 h later (Fig. 6a, b). Compare the graphs in Figs. 5b, 6b. The values for the CREB$^{\alpha\delta-}$ mutants and anisomycin-treated wild-types are statistically similar, strongly suggesting that CREB pathway disruption is the key effect of the protein synthesis inhibitor for blocking long-term synaptic potentiation and social recognition memory consolidation.

Many studies have shown cognitive and behavioral deficits in mice reared in socially isolated environments, compared to mice raised in group environments.[11] To assess possible effects of social isolation on social recognition memory, Silva and his collaborators housed one group of adult wild-type mice in individual cages for three weeks prior to the experiment. The control group was drawn from adult wild-type mice who remained housed in a group setting. The behavioral task was as described above. Long-term social recognition memory, but not short-term, was impaired in socially isolated mice, indicating once again a deficit in memory consolidation (Fig. 7a, b). Again, compare Figs. 5 and 7. The effects of the CREB$^{\alpha\delta-}$ mutation and social isolation on social recognition memory consolidation are statistically similar. This raises the intriguing possibility that CREB α and δ isoform availability in various neurons is a molecular mechanism through which a cause as "high level" and "external" as a mammal's environmental interactions with conspecifics affects a central kind of cognition and behavior (social recognition memory). Is the cAMP-PKA-CREB pathway, internal to specific individual neurons, the point where "the rubber meets the road," causally speaking, for effects beginning from so distal and abstract a cause as a mammal's social environment? Is this molecular pathway embedded in neural circuits from hippocampus and cortex to motor peripheries the "internal" mechanism

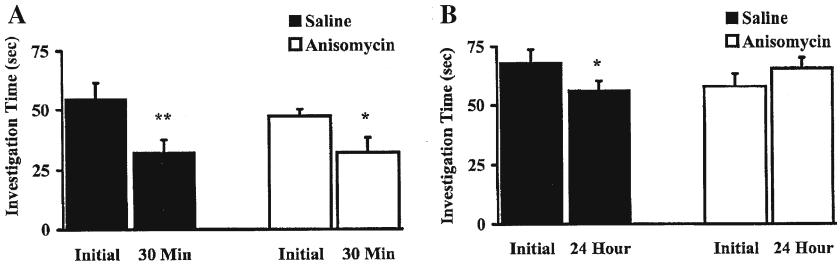

Fig. 6 Long-term but not short-term social recognition memory is impaired in WT mice by a protein synthesis inhibitor, anisomycin, injected 30 min prior to the first exposure to the juvenile mouse. (**A**) Familiar juveniles were re-exposed to saline- or anisomycin-injected mice 30 min after initial interaction. * indicates significant reduction in investigation duration in anisomycin-injected mice ($P < 0.05$, compared to Initial); ** indicates significant reduction in investigation duration in saline-injected mice ($P < 0.01$, compared to Initial). (**B**) Familiar juveniles were re-exposed to saline- or anisomycin-injected mice 24 h after initial interaction. * indicates significant reduction in investigation duration only for saline-injected mice ($P < 0.05$, compared to Initial). Reprinted from Kogan, Frankland, and Silva (2000), Fig. 5, p. 53, with permission from Wiley-Liss, Inc

[11] See the references cited in Kogan et al., (2000, p. 54).

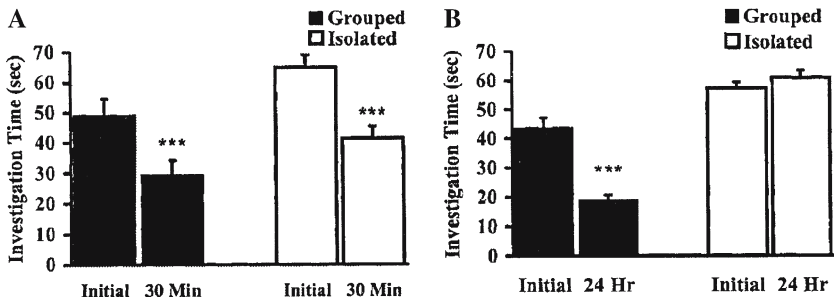

Fig. 7 Long-term but not short-term social recognition memory is impaired in socially isolated mice. (**A**) Familiar juveniles were re-exposed to group caged or chronically isolated (for three weeks prior) WT mice 30 min after initial interaction. *** indicates significant reduction in investigation duration in both groups ($P < 0.01$ compared to Initial). (**B**) Familiar juveniles were re-exposed to group caged or chronically isolated WT mice 24 h after initial exposure. *** indicates significant reduction in investigation duration only for group caged mice ($P < 0.01$, compared to Initial). Reprinted from Kogan, Frankland, and Silva (2000), Fig. 2, p. 53, with permission from Wiley-Liss, Inc

of so "external" a cause? By intervening into this intra-neuron molecular pathway, are we inducing "social isolation" artificially? Could we overcome the cognitive and behavioral deficits of social isolation (at least with regard to social recognition memory consolidation) by intervening to *increase* the availability of CREB α and δ isoforms in the appropriate neurons—perhaps using transgenic biotechnologies? The Silva lab data from this study, though of course not conclusive, suggests positive *empirical* answers to these intriguing questions.

Silva and his collaborators note that the results graphed in Fig. 5 above are in keeping with previous results using biotechnological and pharmacological interventions into the cAMP-PKA-CREB molecular pathway and subsequent measurements of behavior in tests routinely employed to study memory consolidation:

> Studies in *Aplysia*, *Drosophila*, rats, and mice showed that CREB-mediated transcription is a requirement for the induction of long-term memory. ... We previously demonstrated that CREB$^{\alpha\delta-}$ mutant mice have intact short-term, but impaired long-term memory in several hippocampus-dependent tasks. (Kogan et al., 2000, 54).[12]

They also see their new results as further experimental verification that the cAMP-PKA-CREB intra-neuron pathway is a molecular mechanism for hippocampus-dependent memory consolidation in mammals:

> CREB may be a gain control device that regulates the expression of genes necessary for memory consolidation. Additionally, CREB appears to regulate both the number and timing of the training trials required for long-term memory formation. ... Our findings that long-term social memory is also dependent on CREB function parallels our previous findings with other hippocampus-dependent tasks, including the social transmission of food preference, water maze, and contextual fear conditioning. (Kogan et al., 2000, 54).

[12] See Bickle (2003), Ch. 3, for a presentation of recent research on *Aplysia* (sea slug) and *Drosophila* (fruit fly) memory consolidation, along with implications contrary to the multiple realization argument against psychoneural reductionism (an argument that remains central to orthodox contemporary philosophy of mind).

They also do not balk at speculating on the relevance of their results for the search for molecular mechanisms of human memory consolidation: "Finally, social memory requires the hippocampus in both mice and humans, which suggests that social recognition studies in mice may be relevant to the study of human memory mechanisms" (Kogan et al., 2000, 55). "Molecular and cellular cognition," as Silva and his colleagues call their field (http://www.molcellcog.org), is alive and thriving in "ruthlessly reductive" cellular and molecular neuroscience.

4 "Intervene molecularly and track behaviorally": The nature of reduction in current neuroscience

Silva and his colleagues' recent study is but a single example, albeit an impressive one, of a general methodology that is now prevalent in current neuroscience.[13] My next task is to articulate this methodology explicitly, since it reflects what "reductionism" amounts to within the current discipline. And this description looks quite different from the "theories of intertheoretic reduction" that pervade contemporary philosophy of science. It also presents a very different picture of how to carry out a reduction of psychology to neuroscience, of mind to brain, than the one now standard in philosophy of science (discussed and illustrated in Sect. 1 above).

I begin with two popular claims about neuroscience and its explanatory potential, shared uncritically by the current orthodoxies in both philosophy of mind and cognitive science. Both claims will strike many readers as obvious:

- "We don't know much about how the brain works."
- "Lower level neuroscience can't explain cognition and behavior directly. For that, we need higher-level theorizing—we need *cognitive* neuroscience."

The second claim is so enshrined that it lies behind the scientific focus in current philosophy of neuroscience (Sect. 1 above). However, in cellular and molecular cognition, the approach instead is to "intervene cellularly/molecularly and track behaviorally," i.e.,

- intervene *causally* at the level of cellular activity or molecular pathways within specific neurons (e.g., via genetically engineered mutant animals, as in the case study described in the previous section);
- then track the effects of these interventions under controlled experimental conditions using behavioral protocols well accepted within experimental psychology.

This methodology constitutes an implicit condition on *explanation* in this field. One only claims a successful *explanation*, a successful *search for a cellular or molecular mechanism*, or a successful *reduction*, of a psychological kind when one successfully intervenes at the lower level and then measures a statistically significant behavioral difference.[14] In the study from Silva's lab, the intervention is at CREB α and δ isoform sites in the activity-driven intraneuronal cAMP-PKA-CREB-gene expression-protein synthesis pathway. The behavioral tracking is in the widely accepted Thor and

[13] As already mentioned, Bickle (2003), Chs. 2 through 4, describes a number of other (equally impressive) examples.

[14] Readers should *not* interpret this sentence as my asserting that these practices (explanation, investigation, reduction) are *equivalent*. I am only claiming that the "intervene cellularly/molecularly and track behaviorally" strategy is central to all of them in current molecular and cellular cognition.

Holloway protocol for studying social recognition memory. (Recall that social recognition memory was claimed to be the foundation of all mammalian social behaviors in the passage cited at the beginning of Sect. 3 above from Ferguson et al., 2002.) Silva and his collaborators found significant behavioral differences in long-term but not short-term social recognition memory.

When this strategy is successful, the cellular or molecular events in specific neurons into which experimenters have intervened, in conjunction with the neuronal circuits in which the affected neurons are embedded, leading ultimately to the neuromuscular junctions bridging nervous and muscle tissue, *directly explain* the behavioral data. These explanations *set aside* intervening explanatory levels, including the psychological, the cognitive/information processing, even the cognitive-neuroscientific. The level relations illustrated in Fig. 1 above are replaced in the explanatory practices of cellular and molecular cognition by the picture in Fig. 8.

Accordingly, establishing reductive links across levels is no longer the step-by-step mapping of features of a higher level onto features at the next level down. The *explanatory* relevance of intervening levels is no longer needed when the "intervene cellularly/molecularly and track behaviorally" approach succeeds. These successes *amount to* reductions of mind to molecular pathways in neurons and their embedding

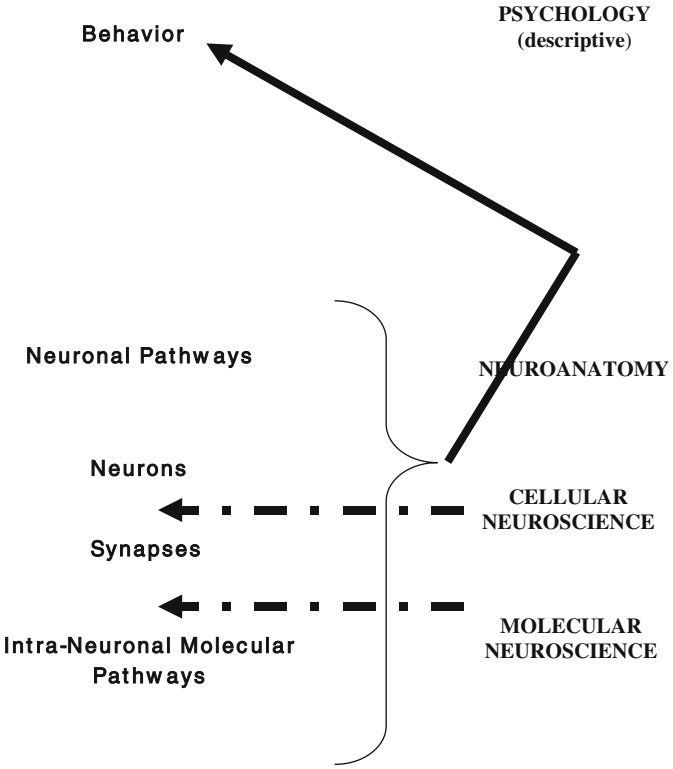

Fig. 8 Schematic illustration of the "intervene cellularly/molecularly and track behaviorally" account of reduction from cellular and molecular cognition and scopes of the mind-brain sciences addressing these levels. Dashed arrows represent levels of experimental intervention; solid arrow represents the level at which these interventions are measured. Psychology is a descriptive endeavor generating behavioral data, rather than explanatory. Contrast with Fig. 1

anatomical circuits. This is what reduction *is* in "ruthlessly reductionistic" current neuroscience.

Philosophers of mind/psychology/neuroscience and cognitive scientists may not recognize the explanatory practices pictured here. But this reaction only reflects unfamiliarity with state-of-the-art neuroscience—with the experiments and questions that dominate the attention of the majority of professional neuroscientists.

What then of the first orthodox claim listed above—the pitying lament from philosophers of mind, psychologists, and cognitive scientists that "we just don't know much about how the brain works"? On one interpretation of 'we,' this claim is true: *they* tend not to know much about how the brain works![15] But in current cellular and molecular neuroscience, not only *do* we know *a lot* about how the components of nervous tissue work and interact; we also know how to manipulate these mechanisms, causally and directly, to generate novel behavioral data and significant dissociations in experimental tasks long accepted by behavioral scientists. This leads to a methodological recommendation for philosophers and cognitive scientists who seek to keep up with cutting-edge neuroscience. Occasionally set aside issues of *Behavioral and Brain Sciences* and the *Journal of Cognitive Neuroscience*, and peruse issues of *Cell*, *Neuron*, and the *Journal of Neurophysiology*.

The experimental methodology, the scientific results, and the philosophical interpretation just offered raises the question of the role of higher level theorizing in contemporary neuroscience.[16] Surely functional neuroimaging, neural network modeling, neuropsychological assessment, and the rest of cognitive/computational neuroscience's resources and results should not be abandoned! Surely not. There remains an essential role for neuroscientific investigations and theorizing at levels above the cellular and molecular. We need these methods and careful theorizing about their results to address questions like:

- What are good experimental protocols for tracking behavioral outcomes for the psychological phenomenon we seek the cellular and molecular mechanisms of?
- Where shall we begin inserting our cellular and molecular interventions? (The possibility space in both brains and intra-neuron molecular pathways is enormous!)
- What kinds of neural activities seem to be involved? (Spiking frequency? Spiking pattern? Field potentials? Synaptic plasticity? This list only scratches the surface of possibilities, and each entry involves quite different molecular mechanisms.)

It is difficult to imagine addressing these questions exclusively at the cellular or molecular level. Yet it is also crucial to notice that these questions are *heuristic*. They are crucial questions to address *as part of the search for underlying cellular and ultimately molecular mechanisms*. Once these questions have served their heuristic function—once the appropriate higher-level tools, theoretical assumptions, and

[15] Witness the fact that "nonreductive physicalism," heir to functionalism and still probably the orthodox solution to the mind-body problem in current philosophy of mind, has developed in almost complete ignorance of neuroscience. However, there are optimistic signs that some are trying to fill this gap. Carrie Figdor has an as-yet unpublished paper that offers neuroscientific evidence for nonreductive physicalism, appealing to exactly the data (mostly from functional neuroanatomy) that Bechtel and Mundale (1999) appeal to in their arguments *against* multiple realizability. The dust is far from settled on Figdor's argument, but it is nice to see at least one nonreductive physicalist make an appeal to real neuroscience.

[16] I discuss this issue more completely in Bickle (2003), Ch. 3, Sect. 3, which includes an example of "transdisciplinary" research that combines single-cell physiology, neurocomputational modeling, and functional neuroimaging.

experimental results have identified candidate cellular or molecular mechanisms scientifically—they give way to the strategy of "intervening cellularly/molecularly and tracking behaviorally." Thus from a diachronic perspective on mind-brain science, investigation into a cognitive or behavioral phenomenon initially looks like the approach illustrated in Fig. 1, with investigations and explanations at multiple levels and the search for step-by-step linkages of features down the levels hierarchy. But when this methodology reaches candidate cellular or molecular processes in specific neurons linked in the ways revealed by neuroanatomy, investigation shifts to the approach illustrated in Fig. 8. And when these investigations succeed, a reduction of mind to molecular pathways is taken as established.

Heuristically, higher level investigations and explanations are essential to neuroscience's development. But once they have isolated the relevant neuroanatomy and the candidate cellular and molecular mechanisms, the explanatory investigation shifts to the "intervene cellularly/molecularly and track behaviorally" approach. Once these heuristic tasks are complete, there is nothing left for higher level investigations to *explain*. This is not to denigrate higher level neuroscience, but rather to locate it at the proper place recognized for it from the discipline's current cellular and molecular mainstream. Of course, many of the psychological phenomena that occupy philosophers' and cognitive scientists' attention are still in the earlier stage of investigation. This fact explains why these two disciplines recognize the levels of organization and methodology pictured in Fig. 1. But as familiarity with the scope of scientific results already gathered in cellular and molecular cognition reveals, a more "ruthlessly reductive" approach is thriving in cellular and molecular neuroscience, namely, the one pictured in Fig. 8. And neuroscience has already progressed to that stage for more cognitive phenomena than philosophers and cognitive scientists are aware.

5 Contrasts with intertheoretic reduction and mechanism

How does the reductionism espoused here compare and contrast with psychoneural reductionisms built upon theories of intertheoretic reduction drawn from the philosophy of science? Different accounts of the intertheoretic reduction relation have been employed by psychoneural reductionists.[17] But all versions attribute explanatory primacy to the reducing scientific theory vis-à-vis the reduced and reject any claim to explanatory autonomy by the reduced theory. Clearly, these features are shared by "intervene cellularly/molecularly and track behaviorally" reductionism. However, the two approaches achieve these shared features differently. Intertheoretic reductionisms achieve them by showing that the explanatory scope of the reducing theory includes at least that of the reduced. On "reduction as deduction" accounts whose lineages trace back to Ernest Nagel (1961) (like Schaffner, 1993), the deduction of the laws or generalizations of the reduced theory (or some successor to it) from those of the reducing shows this. The deductive consequences of a set of sentences can contain no additional content than the set contains. On "semantic" (model theoretic) accounts whose lineages trace back to Patrick Suppes (1956) (like Balzer, Moulines, & Sneed, 1987 or Bickle, 1998), the relation of the reducing theory's set of models *onto* the reduced theory's set (subject to a variety of additional set-theoretic constraints) shows this. On "ontological replacement" accounts (like Feyerabend, 1962),

[17] See Bickle 2003, Ch. 1, Sect. 2 and 3 for a survey with references.

the elimination of the reduced theory's entities and properties from the ontology of science characterized by the reducing theory shows this. Only the reducing theory's ontology remains intact. On successful "intervene molecularly and track behaviorally" reductions, explanations of behavior no longer appeal to features of higher levels (besides those of the functional neuroanatomy of the organism under investigation). The behavioral data is fully explained by the dynamics of interactions at the lowest level at which we can intervene directly at any given time to generate behavioral effects, along with the known anatomical connectivities throughout neural circuits leading ultimately to effects on muscle tissue attached to skeletal frames.

Beyond capturing these common features, however, the reductionism implicit in current cellular and molecular neuroscience shares little else with proposed intertheoretic psychoneural reductions. Unlike the latter, the former does not require or assume that it is possible to provide a complete account of lower level phenomena in terms of laws, generalizations, or the model-theoretic counterparts to these syntactic structures. In current cellular and molecular neuroscience, as in cell and molecular biology generally, few explanations are framed in terms of laws or generalizations. Many interactions are known to occur and have both theoretical and experimental backing; but biochemistry has not even provided molecular biology with a general (and hence generalization-governed) account of how proteins assume their tertiary configurations. Molecular biologists know a lot about how specific molecules interact within restricted contexts, but few explanatory generalizations are found in molecular biology publications. In addition, what generalizations there are do not by themselves yield extensive predictions or explanations of lower level interactions. Many factors interact (from both the molecular biological level and from chemistry and physics below, e.g., thermodynamics, electrodynamics) to produce activity within a cell's molecular pathways. Finally, real molecular neuroscience certainly does not provide what some law-based accounts of scientific theory structure require. Its explanations do not specify how molecular biological entities interact in all possible circumstances, including those to be found in all the different molecular mechanisms that nature might generate. Molecular neuroscience of the sort illustrated here seeks regularities in the activities of particular entities (e.g., the CREB α and δ isoforms) in a restricted range of circumstances (e.g., under cell-biological conditions that induce long-term social recognition memory consolidation). Challenges to psychoneural reductionism are often challenges to the plausibility of the account of theory or intertheoretic reduction on which specific reductionisms rest. Because of its contrasts with intertheoretic psychoneural reductionism, the "intervene cellularly/molecularly and track behaviorally" account drawn from recent cellular and molecular cognition does not fall victim to these challenges.[18]

However, the specificity of the entities, properties, and conditions at the lower level at work in "intervene cellularly/molecularly and tract behaviorally" psychoneural reductions raises questions about its comparisons and contrasts with the recently

[18] Robert Richardson noticed that of all the popular accounts of intertheoretic reduction from 20th century philosophy of science, my "intervene molecularly and track behaviorally" account seems closest to John Kemeny and Paul Oppenheim's (1956) account! In particular, Kemeny and Oppenheim stressed that the reducing theory need only explain the empirical data explained by the reduced and that reduction of intermediate theories was not necessary for reduction. Philosophers of science since Schaffner (1967) have dismissed Kemeny and Oppenheim's account as too weak, but perhaps in light of recent neuroscientific practice some of its basic ideas should be re-examined (except, of course, its logical empiricism-inspired account of the nature and role of theories in reduction).

revived *mechanistic* philosophy of science. At center stage in this revival is a recent analysis by Peter Machamer, Lindley Darden, and Carl Craver, drawing on earlier developments by William Bechtel, Robert Richardson, and William Wimsatt (Bechtel & Richardson 1993; Machamer, Darden, & Craver, 2000; Wimsatt 1986).The analysis is straightforward: A mechanism is "a collection of entities and activities organized in the production of regular changes from start or set-up conditions to finish or termination conditions" (Machamer et al., 2000, 3). Case studies from neuroscience figure prominently in this literature (Bechtel, 2001; Craver, 2002; Craver & Darden, 2001).[19]

This analysis of mechanism affords a tidy picture of levels within a scientific discipline (e.g., neuroscience) and of a taxonomy of interlevel experimental strategies. Craver and Darden provide a beautiful illustration of this for the continuing discovery of the neurobiological mechanisms of mammalian spatial memory (including the role of LTP) (Craver & Darden, 2001, Fig. 6.4, 118). Their figure is a specific instance of Fig. 1 above, filled in with some details from this case. Craver (2002) uses this picture to classify and distinguish a number of interlevel experimental strategies in neuroscience, including both top–down interventions with lower level measures and bottom up interventions with higher level measures. (Silva and colleagues' work discussed above would count as an instance of the latter.) Mechanists clearly recognize a role for the reductionism emphasized here (although in none of their examples from neuroscience do they discuss molecular genetic mechanisms). Yet one way in which their view differs from the reductionism espoused here is their emphasis on *multi-level* mechanisms.[20] The question is whether multi-level mechanisms are still recognized *as mechanisms* when neuroscience has successfully "intervened cellularly/molecularly and tracked behaviorally." I contend that they are not—at least not by the cellular and molecular neuroscientists doing the intervening and tracking.

Consider again the concluding quotes from Kogan et al., (2000) cited above in the last paragraph of Sect. 3. They tie molecular *mechanisms* (e.g., CREB isoforms and their role in activity-driven gene expression and protein synthesis) directly to psychological *descriptions* (e.g., long-term social recognition memory). Intervening levels between the behavioral, the neuroanatomical, and the cellular/molecular figure nowhere in their explanations. This is commonplace in cellular and molecular

[19] In his recent 2003 *Cardinal Mercier* lectures (available on line at the time of this writing at http://mechanism.ucsd.edu/~bill/), William Bechtel worries that the Machamer-Darden-Craver stress on set-up and termination conditions suggests a mistakenly restrictive focus on linear processes, leaving out a prominent class of mechanisms embedded within "larger" mechanisms that respond continuously to conditions in the latter. He proposes a replacement analysis: A mechanism is an enduring system that regularly performs some activity; it is made of component parts, each of which performs its own operation, which are then coordinated so as to accomplish the activity of the overall mechanism (*Lecture* 1). I suppose that Machamer, Darden, and Craver will accept Bechtel's alternative as a friendly amendment. Clearly they did not wish to restrict their analysis to "linear processes." In the same lectures, Bechtel provides another important case study from neuroscience, the discovery of the neural mechanisms of visual perception (*Lecture* 2). He also makes a first attempt to distinguish mechanism from intertheoretic reductionism (*Lecture* 5); his remarks served as inspiration for many of the contrasts I stressed just above between the reductionism I am developing and espousing here and intertheoretic psychoneural reductionisms. These lectures merit close study by mechanists and foes alike.

[20] There are numerous differences between mechanism and intertheoretic reductionism, especially on the demands placed upon the structure and scope of the lower-level, reducing theory. But since I have already pointed out that the reductionism espoused here also differs from intertheoretic reductionism on these same points, these challenges to reductionism by mechanists do not apply here.

cognition; examples abound. Craig Bailey, Dusan Bartsch, and Eric Kandel ask, rhetorically, "Can molecular biology provide novel insights into the mind? In this brief review we consider the possibility of *a molecular biology of cognition*" (Bailey, Bartsch, and Kandel, 1996, 13445; my emphasis). Notice the lack of any mention of intermediate levels (none is made throughout their review). Remarking on their behavioral results with transgenic mice that overexpress the regulatory subunits of cAMP-dependent protein kinase A primarily in forebrain regions, Ted Abel and his collaborators conclude that "our experiments . . . provide a framework for *a molecular understanding of the consolidation of long-term explicit memory in mice*" (Abel et al., 1997, 623; my emphasis). Descriptive terms from psychology are again tied directly to molecular mechanisms—*not* through intervening levels. Similarly, and based on their microstimulation intervention at the cellular level in primates, William Newsome and his collaborators remark that their data "establish a causal relationship between the activity of the stimulated neurons and perceptual judgments of motion direction" and "provide direct support for the linking hypothesis associating direction selectivity [in tiny, i.e., 250 *micron* clusters of similarly tuned visual neurons] with motion perception" (Salzman, Murasagi, Britten & Newsome, 1992, 2332). These are appeals directly to cellular and molecular mechanisms of psychological kinds, not appeals to the multi-level mechanisms advocated by the mechanists.

Mechanists also cannot easily take refuge in the claim that the types of cognition they are interested in are still at earlier stages of development, warranting the multi-level explanatory approach heuristically. Their favorite neuroscience examples—spatial learning and memory, visual perception—are exactly the cases where "ruthlessly reductionistic" cellular and molecular cognition has enjoyed it greatest successes to date. However, it is only fair to point out that mechanists claim to be especially concerned with *discovery* in science. If their thesis is a historical one, about the way that multi-level mechanisms have figured (heuristically) in the development of neuroscience, then obviously I have no quarrel. I acknowledge the role of multi-level investigations and explanations in earlier stages of studying a cognitive phenomenon. But it is hard to read the mechanism literature and come away believing that they are only after a historical point. There is still lots more ink to spill on this issue, but I contend that my "intervene cellularly/molecularly and track behaviorally" account of reduction better captures the practices of cellular and molecular neuroscience than does the analysis of the new mechanists.

In the end, this discussion leaves us with the classic question for psychoneural reductionists. How low can you go? Presumably, molecular biology reduces to biochemistry, biochemistry to general chemistry, and general chemistry to physics. So, reductionist, why are you not at work at the quantum level? The reductionism espoused here has an answer. We cannot (yet) intervene directly at the quantum level and track behavioral changes in well-accepted experimental protocols for cognitive phenomena. Until we can, "reducing mind to quantum events" is speculative metaphysics, not established science. In this respect the entire psycho*physical* reductionist project is at the earlier stage of development illustrated in Fig. 1, with the lower levels of organization and their affiliated sciences below molecular pathways inserted. But there is already some indication that an "intervene biophysically and track behaviorally" approach is at the doorstep. The journal *Nature* recently dedicated sixteen printed pages to two articles from Roderick MacKinnon's lab at Rockefeller University detailing the crystal structure of a voltage-dependent potassium ion (K^+) channel. (The typical *Nature* research paper rarely exceeds four printed pages, figures and all.) Among

other things, this protein functions in the passage of K^+ ions across neuron membranes to drive action potentials ("spikes") (Jiang et al., 2003a, b). These proteins contain subunits that extend out into the lipid membrane in which they are embedded and are capable of moving up and down the width of the membrane, from the extracellular to the intracellular borders. These subunits contain positively charged, hydrophobic (water repelling) arginine residues that are attracted to the extracellular side of the membrane when nearby membrane is depolarized. Their movement through the cell membrane pulls open the K^+-selective pore in the middle of the protein, enabling K^+ ions to flow in or out of the neuron through the now open channel along their concentration gradient and in response to electrostatic pressure.

The methods used in these experiments were both daunting and ingenious, especially the way that a member of this family of proteins was crystallized for x-ray crystallography and the use of a "molecular ruler" to measure the length of subunit motions within the cell membrane.[21] But the result is a step toward a *biophysical* reduction of mind. Except for heuristic and pragmatic purposes, we will no longer need to speak of membrane potentials interacting with voltage-gated receptor proteins as a mechanism. The known biochemistry and biophysics (which I have only gestured toward here) will supersede the *explanatory* need to talk that way. The next step is to "intervene biophysically" with these newly discovered mechanisms and "track behaviorally." Successful examples will constitute mind-to-biophysics reductions, leaving molecular biology as a necessary heuristic but no longer the science for uncovering explanatory mechanisms. "Ruthless" reductionism grows positively merciless.[22]

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[21] The entire study leading to these two papers, including developing all the necessary experimental techniques and controls, took 5 *years* to complete.

[22] This paper improved from excellent discussion at the workshop from which these proceedings are drawn. Huib Looren de Jong, whose commentary accompanies this essay, once again provided very useful criticism. Thanks to Max Kistler for organizing a spectacular meeting. I also thank Marica Bernstein, Carl Craver, Anthony Landreth, Robert Richardson, and Max Kistler for helpful comments on earlier drafts. Special thanks go to Alcino Silva, who helped me clarify a handful of scientific details that had been misstated in the manuscript's penultimate draft.

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