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THE BIOCHEMISTRY OF MEMORY CONSOLIDATION: A MODEL SYSTEM FOR THE PHILOSOPHY OF MIND

ABSTRACT. This paper argues that the biochemistry of memory consolidation provides valuable model systems for exploring the multiple realization of psychological states.

Biologists frequently use simple model systems to study complex biological phenomena and processes. Gregor Mendel's peas, Thomas Morgan's *Drosophila*, Darwin's finches, and J. Z. Young's squid giant axon are all famous examples. Philosophers, for their part, regularly approach their problems through simple illustrative examples. In the philosophy of mind, the reduction of water to H_2O, the reduction of the temperature of a gas to the mean kinetic energy of its constituent molecules, and the multiple realizability of mousetraps and Turing machines are well-known examples. It should, therefore, be interesting to cognitive scientists to find biological model systems that complement the familiar stock of illustrative examples in the philosophy of mind. The biochemistry of memory consolidation in mice, sea slugs, and fruit flies constitute model systems potentially linking long-term changes in behavior as the result of experience to biochemical changes within nerve cells. These model systems merit philosophical attention, since they provide a rich body of empirical detail that facilitates the articulation and testing of theories of multiple realization and multiple realizability.

To substantiate the foregoing thesis, this paper will review a sample of cases. Bickle (2003), does the important work of bringing attention to the extensive biochemical literature relating to memory consolidation. He also argues that there is a unique physicochemical realization for memory consolidation. Nevertheless, there are substantive reasons to think that memory consolidation is multiply realized and multiple realizable. The biochemistry of memory consolidation also bears on Shapiro's (2000, 2004) theory of what

Synthese (2007) 155: 65–98
DOI 10.1007/s11229-005-2566-9

is involved in having distinct kinds of realizations of a given function. Where one might think that Shapiro's theory supports Bickle's contention that memory consolidation has a unique physico-chemical realization, it does not. In fact, applying Shapiro's theory to the biochemistry of memory consolidation highlights an important respect in which his theory is tangential to the prime motivation for thinking about multiple realization. On a third front, the biochemistry of memory consolidation provides an empirical basis for discussing the distinction between multiple realization and multiple realizability. More specifically, Bickle (2003), is dismissive of talk of what is nomologically or conceptually possible, hence of multiple realizability (as opposed to multiple realization). There are, however, good empirical reasons to respect a notion of multiple realizability in addition to a notion of multiple realization. Related to this is the contention in Shapiro (2004) that philosophers have yet to attend closely enough to the role of constraints on what nomologically possible realizations there are. If, however, one respects Shapiro's contention, one finds that the constraints on the realization of memory consolidation by proteins are loose enough to allow for multiple realizations. Finally, the biochemistry of memory consolidation provides empirical evidence regarding the conjecture that if cognitive processes such as memory consolidation are species-specific, it is more likely that there will be unique physico-chemical realizations of them (Cf., e.g., Kim 1972; Endicott 1993; Polger 2004). What the biochemistry shows, however, is that there is little hope of this. Even species-specific forms of memory consolidation are multiply realized. These sample applications clearly suggest that figuring out where the model systems work, where they do not, and why are fruitful questions for the philosophy of mind.

1. BICKLE'S RUTHLESS REDUCTIONISM

Probably the most important feature of Bickle's *Philosophy and Neuroscience: A Ruthlessly Reductive Account* is its emphasis on the value of the biochemistry of memory consolidation for thinking about multiple realization and multiple realizability. Here is what he thinks this biochemistry shows. He considers something like the following anti-reductionist argument:

All psychological kinds are multiply realized in physical-chemical kinds.
If all psychological kinds are multiply realized in physical-chemical kinds, then no psychological kinds are reducible to physical-chemical kinds.
==========
Therefore, no psychological kinds are reducible to physical-chemical kinds.

Call this the "multiple realization argument." According to Bickle, most reductionists will be tempted to respond to the multiple realization argument by attacking the second premise. He, however, proposes to challenge the first premise on empirical grounds. More specifically, he contends that cellular and molecular neuroscience provide reason to believe that the first premise is false. Bickle's challenge takes roughly this form:

Memory consolidation in mammals is uniquely realized by the biochemical pathway ϕ.
Memory consolidation in *Aplysia* is uniquely realized by the biochemical pathway ϕ.
Memory consolidation in *Drosophila* is uniquely realized by the biochemical pathway ϕ.
==========
Therefore, all memory consolidation in animals on earth is uniquely realized by the biochemical pathway ϕ.
Therefore, all memory consolidation in animals on earth is uniquely realized.
Therefore, (since memory consolidation in animals on earth is a psychological kind) there exists a psychological kind that is uniquely realized.
Therefore, not all psychological kinds are multiply realized in biological kinds.

The first inference is a defeasible inductive generalization, where the remaining steps of this argument are a reconstruction that connects the generalization about memory consolidation to the first premise of the multiple realization argument.

There are, of course, a number of ways one might challenge Bickle's argument, but for the purpose of showing the utility of the scientific models of memory consolidation, the most valuable approach is to work through the consequences of the biochemical fact that each of the proteins constituting the biochemical pathway ϕ consist of distinct sequences of amino acids in mammals, *Aplysia*, and *Drosophila*.[1] Bickle is simply mistaken in his claim that "The molecular mechanisms determining neuron activity and plasticity are the same in invertebrates through mammals" (Bickle 2003, p. 132). Far from providing an astonishing success story for some form of reductionism–a toehold for future reductionist advance–the situation appears to support the multiple realization and multiple realizability of memory consolidation. To make the case for this last thesis in the limited space of this paper, the numerous important

issues concerning what reductionism is and how multiple realization and multiple realizability bear on it will largely be set aside for another occasion.[2]

Very roughly speaking, memory consolidation is a process by which memories become more durable, lasting hours, days, weeks, and months, rather than merely seconds or minutes. Surely one can raise objections to this vague description and question whether or not it captures a single psychological function that is to be found in mammals, *Aplysia*, and *Drosophila*. Perhaps there is instead mammalian memory consolidation, *Aplysia* memory consolidation, and *Drosophila* memory consolidation; perhaps there are species-specific forms of memory consolidation. Perhaps forms of memory consolidation are even specific to individual organisms. At issue here is what principles, if any, are to guide the individuation of psychological functions.[3] For present purposes, it appears that this issue can be finessed. To begin with, the discussion will presuppose that there exists a single psychological function of memory consolidation that is common to all the biological taxa Bickle discusses. Once the basic problem for Bickle's account is on the table, it should be clear how to extend the problem to more fine grained individuations of psychological function. The overall course of the argument will be that, except for the most fine-grained individuations of psychological functions, there is very much the same case to be made for the multiple realization and multiple realizability of memory consolidation in distinct biochemical pathways.[4]

Turning to the biochemical side of things, there is room for clarification as to what Bickle takes to be the biochemical mechanism that is supposed to underlie all instances of memory consolidation. Bickle provides an extensive description of the experimental work that is involved, but he is less than fully explicit about what he thinks uniquely realizes memory consolidation. Bickle's most expansive account includes "adenylyl cyclase, cAMP, PKA, CREB enhancers and repressors, DNA, RNA polymerases, ubiquitin hydrolase, CCAAT enhancer binding protein, glutamate, dendritic spine cytoskeleton components, AMPA receptors, NMDA receptors, and so on" (Bickle 2003, p. 99, cf. p. 75). In a later passage, Bickle suggests a more narrow realization base, "There is a 'physical-chemical state,' the cAMP–PKA–CREB molecular pathway, that uniquely realizes memory consolidation across biological classes, from insects to gastropods to mammals" (Bickle 2003, p. 148). Maybe these are the same; maybe not. There is, however, no need to try to

exploit this ambiguity. It matters only to forestall any concerns about the target of the current critique. For present purposes, the focus will be on the protein kinase A (PKA) and cAMP response element binding (CREB) proteins. These proteins are surely implicated in whatever account one might advance for the realization base of memory consolidation. Further, they are sufficient to illustrate the problem with the kind of multiple realization being noted here. If these components of the biochemical pathway for memory consolidation are multiply realized, then the entire putative pathway is multiply realized. In other words, if there are biochemical pathways cAMP–PKA_1–CREB, cAMP–PKA_2–CREB, and cAMP–PKA_3–CREB, where $PKA_1 \neq PKA_2 \neq PKA_3$, then no matter what other elements might be added to the sequence – elements such as the ubiquitin hydrolase mentioned above – the pathway is still multiply realized.

So, how are PKA and CREB proteins involved in the biochemistry of memory consolidation across biological taxa? Bickle devotes large portions of two chapters in his book to a synopsis of the biochemical literature on this and related matters. He also provides ample references to the literature.[5] For present purposes, however, a simplified account should suffice. Neurons are active when an organism performs some learning task such as navigating through a maze or becoming conditioned to some stimulus. This nerve cell activity creates cyclic adenosine monophosphate (cAMP) molecules within the cells. These cAMP molecules then bind to PKA molecules found in the cytosol. When cAMP binds to the regulatory subunits of PKA, the regulatory subunits change shape and release the catalytic subunits. When concentrations of the free catalytic subunits of PKA reach sufficiently high concentrations, the subunits migrate in significant numbers into the cell nucleus where they ultimately lead to the phosphorylation of two types of molecules: CREB enhancers (CREB-1) and CREB repressors (CREB-2). The CREB enhancers initiate transcription of DNA, where the CREB repressors shut down transcription. The proteins produced following DNA transcription are transported to the neuronal synapses where they make enduring changes to the synapse, enduring changes that are hypothesized to constitute memory consolidation.

Bickle does not say what he means by the realization relation. Nor does he offer a theory of when two realizations constitute distinct kinds of realizations. Nevertheless, the following conjecture is reasonable. Bickle believes that the realization relation at issue in the

biochemistry case is a species of non-causal determination relation, wherein the process of memory consolidation is determined by the combined actions of a collection of cAMP molecules, a collection of PKA molecules, a collection of CREB-1 molecules, and a collection of CREB-2 molecules (among other components). The psychological natural kind of memory consolidation is, thus, related to collections of individuals from numerous physico-chemical natural kinds. One might well consider the way in which various theories of realization relations handle the biochemistry of memory consolidation, but that is the subject of another paper. For the space of the present paper, the working hypothesis is that this is the sort of realization relation Bickle has in mind.

A reasonable place to begin to critique Bickle's view is with the amino acid sequences in the various proteins. This is what biochemists refer to as the primary structure of a protein, a kind of structure where there are some salient chemical natural kinds. Chemical kinds at this level might be individuated by saying that molecules that differ in the number or configuration of their constituent atoms constitute distinct chemical kinds. This chemical taxonomy has the virtue of working for many cases. Pentane and 2-methylbutane are recognized as distinct molecules, since they contain the same atoms but in distinct bonding relations. Propane and butane are distinct chemical kinds in virtue of containing distinct numbers of atoms. Butane contains a carbon atom and two hydrogen atoms not contained by propane. The last example has a clear extension to the biochemistry of proteins. Two proteins that have identical amino acid sequences, save for the fact that one has an aspartic acid side chain ($–CH_2–CO_2^-$) where the other has a glutamic acid side chain ($–CH_2–CH_2–CO_2^-$) will constitute distinct chemical kinds in a perfectly intelligible, legitimate, and familiar sense recognizable to biochemists.[6]

It is a well-known biochemical fact that the amino acid sequences of proteins generally differ across diverse biological taxa. Were PKA, CREB-1, and CREB-2 not found to have distinct amino acid sequences in different taxa, this would be a surprising exception to the biochemical rule. Yet, when questioned about the significance of such differences, Bickle simply demurs on empirical grounds (Cf., Bickle 2003, p. 157, fn. 37). Fair enough. A review of the relevant experimental literature makes it abundantly clear that PKA and the CREB proteins in distinct species have distinct sequences of amino acids.

Consider, first, the multiple forms of PKA. Regarding the regulatory (R) subunit of PKA, Bergold et al. (1992), report that

> cAMP-binding domains of the Aplysia [R] subunit have 79% amino acid identity with murine [mouse] RIα, 76% with RIβ, and 75% with the Drosophila R subunit.
>
> The aligned R proteins are dissimilar in the region of amino acid residues 57–86, with only 16% identity of the Aplysia R subunit with murine RIα and 13% with the *Drosophila* subunit. This region in Aplysia is greatly enriched (50%) in proline, glutamate, serine, and threonine (PEST) residues. Other RI subunits have a corresponding domain close to their amino terminal: for example, murine RIα, with 39% PEST residues, and *Drosophila*, with 37%. (Bergold et al. 1992, p. 388).

In other words, in just the regions of R that bind cAMP, there is about a 20–25% discrepancy in the amino acid sequence across *Aplysia, Drosophila*, and mouse. In the region corresponding to residues 57–86 of the *Aplysia*, the divergence is even greater. Based on different biochemical techniques, Kalderon and Rubin (1988), report similar results, namely, that "The [*Drosophila*] translation product is clearly more similar to the mammalian type I (71% amino acid identity) than type II (32% amino acid identity) regulatory subunit sequence" (p. 1540). As for the catalytic subunits of PKA, Beushausen et al. (1988), report that

> The Aplysia, mouse, cow, and *Drosophila* sequences are almost identical in length and easily aligned. The Aplysia sequence contains 1 more residue (Gly 65) than the mammalian polypeptides, while the *Drosophila* sequence has an insertion of 2 residues at the N-terminus (Thr-Ser-Asn replaces Ala 7). The overall amino acid identity is 83%–85% with the mammalian catalytic subunits and 83% with the *Drosophila* subunit. Between residues 183–288, the sequence differs from the mammalian sequence at only 1 position, and from the Drosophila sequence at only 4 positions.

So, while there is greater similarity in the amino acid sequences in the catalytic subunits of PKA than in the regulatory subunits, there is still a divergence in amino acid sequences in both.

Next consider CREB-1, the DNA transcription enhancers. Relying on work reported in Bartsch et al. (1998), Bickle writes, "One of these products, the CREB1a polypeptide isoform [in *Aplysia*], displayed 95% amino acid sequence homology to mammalian CREB proteins, meaning that 19 out of every 20 amino acids in the protein sequences were identical across divergent species" (Bickle 2003, p. 144).[7] But, of course, the fact that there is 95% identity between the *Aplysia* and mammalian CREB forms means that there is a 5% divergence in amino acid sequence.

Regarding CREB-2, the DNA transcription repressors, Yin et al. (1994), report that

> We cloned a *Drosophila* CREB gene, *dCREB2*, to facilitate genetic manipulation of cAMP-responsive transcription in flies. This gene produces several isoforms that share overall structural homology and nearly complete amino acid identity in the basic leucine zipper with mammalian CREBs. The dCREB2-a isoform is a PKA-responsive transcriptional activator, whereas the dCREB2-b product blocks PKA-responsive transcription by dCREB2-a in culture. ... The numerous similarities in sequence and function between dCREB2 and mammalian CREBs suggest that cAMP-responsive transcription is evolutionarily conserved" (Yin et al. 1994, p. 49).[8]

Again, while one can be impressed with the degree of commonality among the set of CREB-2 proteins, one must also note that there remain divergences in amino acid sequence. The CREB-2 proteins have different forms in the diverse taxa in which they have been studied.

For the sake of subsequent discussion, it should be noted that differences in amino acid sequences are causally relevant to the process of memory consolidation.[9] Amino acids differ among themselves in size, charge, and polarity. These properties influence the chain's interactions with other components of a biochemical pathway. Changes to the amino acid sequence of the regulatory subunit of PKA, for example, can change the way in which it binds cAMP and releases the PKA catalytic subunits. Changes to the amino acid sequence of the catalytic subunit of PKA can influence the rate at which it adds a phosphate group to other molecules in the biochemical pathway. Differences in the amino acid sequence of a chain, thus, matter to the process of memory consolidation, where differences in, say, the light absorption of a chain do not. Each of many different amino acid sequences constitutes a chemically and physically distinct component making a distinct causal contribution to what is for now supposed to be a single psychological function of memory consolidation.

One line of response to the observation that there are distinct amino acid sequences in mammalia, *Aplysia*, and *Drosophila* is to maintain that there nevertheless exists some common physico-chemical property. That is, the idea would be to find a unique physico-chemical property that is shared by the cAMP–PKA–CREB pathway in mammals, the cAMP–PKA–CREB pathway in *Aplysia*, and the cAMP–PKA–CREB pathway in *Drosophila*. This kind of response follows up on an observation made by Jaegwon Kim, who writes,

> [T]he fact that two brains are physico-chemically different does not entail that the two brains cannot be in the "same physico-chemical state." ... To argue that the human brain and the canine brain cannot be in the same brain state because of their different physico-chemical structure is like arguing that there can be no microphysical state underlying temperature because all kinds of objects with extremely diverse microphysical compositions can have the same temperature; or that water-solubility cannot have a microstructural "correlate" because both salt and sugar which differ a great deal from each other in atomic composition are soluble in water. If the human brain and the reptilian brain can be in the same "temperature state," why can they not be in the same "brain state," where this state is characterized in physico-chemical terms? (Kim 1972, pp. 189–190).

Applying this point to the present case, Kim is surely correct that one cannot simply move from the fact that there are distinct amino acid sequences in the mammalian, *Aplysia*, and *Drosophila* pathway to the conclusion that there is no common physico-chemical property. Yet, it is surely one of the virtues of these model systems that biochemists know enough about the relevant biochemistry to make a credible case that there is no such property. One can survey some possible candidates showing how they fail to provide a unique physico-chemical realization for memory consolidation. The first possibility is an appeal to the concept of homology, the second an appeal to functional groups, and the third an appeal to the higher-order structure of proteins.

1.1. *The Homology Response*

The biochemists working with PKA, CREB-1, and CREB-2 frequently refer to the proteins in Mammalia, *Aplysia*, and *Drosophila* as homologs. Yet, a common conception of homologous structures is that they are identical structures that have different functions. Thus, the bones in the forelimb of a bat and of a human are structurally the same, even though they have evolved to have different functions. The forelimb of the bat has the function of enabling flight, while the forelimb of a human has the function of facilitating manipulation. So, there is implicit in this biochemical literature a notion of the sameness of structure that grounds Bickle's talk of a common biochemical pathway. Bechtel and Mundale (1999), may well have something like this argument in mind when they write,

> One might think, at first glance, that the ability to make comparisons across species actually depends upon multiple realizability. In fact, it is the very *similarity*

(or more precisely, *homology*) of brain structures which permits us to generalize across certain species. So in this latter respect, in the context of neuroscientific research, they are not multiply realized (Bechtel and Mundale 1999, pp. 177–178).

This argument appears to differ from the preceding homology argument insofar as Bechtel and Mundale claim that it is brain structures that are not multiply realized, rather than cognitive or psychological functions that are not multiply realized. Further, their argument that homologies constitute a basis for structural similarity must be simpler than the argument given above insofar as their argument does not invoke any conception of what a homology is. Still, one can see the affinities between the argument given here and the argument given by Bechtel and Mundale.

To begin with, it should be noted that, to put matters generously, the definition of homology suggested here does not enjoy universal acceptance. A rival notion of homology is based on a notion of *similar* structures. Thus, in the glossary of their evolution textbook, Edward Dodson and Peter Dodson give the following definition: "*Homology*: In a series of related organisms, similarity of structures because of descent from common ancestors, without regard to function" (Dodson and Dodson, 1985, p. 565). In the glossary to Strickberger's textbook, there is the following:

A common use of this term is to characterize the similarity of biological features in different species or groups because of their descent from a common ancestor. Since similarities can sometimes be quantified, especially for amino acid sequences in protein or base sequences in nucleic acids, homology has also been defined as the *extent* to which two species share an ancestral character (i.e. homology = degree of ancestral similarity), and the value obtained can then be used to help establish phylogenetic relationships between species. ... Among other definitions are those that consider homology strictly qualitative – for example, two structures in different species are or are not homologous (similar) – and omit any quantitative considerations as to the degree of homology. (Strickberger 1996, p. 602).

In both accounts, homology involves similarity of structure rather than identity of structure. This permits a rational reconstruction of the biochemist's use of "homolog" and "homology" without having to admit that there is such a thing as *the* physico-chemical cAMP–PKA–CREB molecular pathway. There are, instead, many similar molecular pathways; there are many molecular pathways that realize what is, for the moment, assumed to be the single psychological process of memory consolidation. So, while the concept of homology allows for there being a common physico-chemical structure to

the diverse cAMP–PKA–CREB pathways, the concept in conjunction with the hypothesis that the pathways are in fact homologous, does not guarantee that there is one. Nor does it begin to specify what such a common structure would be. So, Bickle still needs an account of the unique physico-chemical structure that is common to the diverse cAMP–PKA–CREB pathways.

1.2. *The Amino Acids in Functional Groups Provide a Unique Realization*[10]

The starting point for this response is a finding which Bickle draws from Bartsch et al. (1998), namely, that "the key phosphorylation site in the *Aplysia* protein's phosphorylation (P) box, the site where freed PKA catalytic subunits induce their effects, is completely conserved between *Aplysia* CREB1a and mammalian CREB. *Every* amino acid is identical across the P box sequences" (Bickle 2003, p. 144). In other words, while it is true that the amino acid sequences for whole proteins are multiply realized, there are restricted regions of the proteins – the functional groups where proteins interact with their substrates – where the amino acid sequences do not vary. This provides an opening one might try to exploit, namely, one might argue that it is the functional groups of the proteins that are in fact uniquely realized. So, what the biochemistry of memory consolidation *really* shows is that memory consolidation is uniquely realized in a particular collection of functional groups.

The principal problem with this response is that it is simply not true that all the functional groups in the cAMP–PKA–CREB pathways are, in fact, uniquely realized. What holds for proteins holds for fragments of proteins. One would expect this failure of unique realization given only an understanding of the general nature of proteins, but this is experimentally confirmed in some of the functional groups of the cAMP–PKA–CREB pathways. The CREB proteins have two primary functional groups, a basic region-leucine zipper (bZIP) and an activation or phosphorylation domain. These functional groups consist of distinct amino acid sequences. Usui et al. (1993), report divergences between the *Drosophila* dCREB2 and three mammalian CREBs. Bartsch et al. (1995), report that "Ap[lysia]CREB1 has 42% homology with the mouse CREB1 over the whole length of the protein, while the basic region-leucine zipper (bZIP) and the phosphorylation domain (P box), characteristic of CREB1, are 96% and 90% identical, respectively." (Bartsch et al.,

1995, p. 979.) Even the two most functionally important regions of the protein differ by a small degree. So, the appeal to functional groups, rather than entire proteins, merely reduces the number of amino acids giving rise to multiple realization.

1.3. *The Appeal to Higher-Order Biochemical Structure*

The central observation of the foregoing arguments has been that the amino acid sequences in the PKA, CREB-1, and CREB-2 proteins vary across mammalia, *Aplysia*, and *Drosophila*. In other words, the PKA, CREB-1, and CREB-2 proteins vary in their primary structure. Yet, biochemists also recognize secondary, tertiary, and quaternary structure having to do with the way amino acid chains fold and cluster. One might suppose that the higher-order structures of the proteins in the cAMP–PKA–CREB pathways constitute the unique realization base for memory consolidation in terrestrial organisms.[11] Although this is an instance of Kim's point about distinct physico-chemical kinds being able to share a physico-chemical property, one might also observe that the model for this sort of move is the idea that the temperature of a gas is uniquely realized in the mean kinetic energy of the constituent molecules of the gas. Each particular ensemble of molecules and their velocities that yield the same mean kinetic energy might in some sense constitute a distinct realization of the gas temperature, but there is nonetheless a higher order natural kind that unifies the ensembles and constitutes a unique realization of the temperature of a gas.

There are two kinds of response to this appeal to higher-order structure. One is a simple conceptual argument; the other is an empirical argument based on extrapolations from differences in the primary structure of amino acids to likely differences in secondary, tertiary, and quaternary structure. The conceptual argument is based on the transitivity of the realization relation.[12] Suppose that B has distinct realizations C_1, C_2, and C_3. B is then multiply realized. Now suppose that the realization relation is transitive so that, if A is realized by B and B is realized by C, then A is realized by C. If A is realized by B, then A has distinct realizations C_1, C_2, and C_3. Thus, A is also multiply realized. To review this in terms of our biochemical case, it could be that memory consolidation (A) is uniquely realized in some set of higher-order protein structures (B). But, if these higher-order structures are themselves multiply realized in distinct amino acid sequences (C_1, C_2, and C_3), then memory

consolidation is still multiply realized. So, given the distinct primary structures involved in memory consolidation, even if there were a unique higher-order physico-chemical realization of memory consolidation, there is still a case for the multiple realization of memory consolidation.

Turn now to the empirical argument. The central point of this argument is that there are likely to be chemical and physical differences in the secondary, tertiary, and quaternary structure of the PKAs and CREBs in mammalia, *Aplysia*, and *Drosophila*. Such differences are causally relevant to the way in which PKAs, CREB-1s, and CREB-2s bring about memory consolidation.[13] Differences in secondary, tertiary, and quaternary structure will influence such things as how PKA tetramers dissociate into their regulatory and catalytic subunits and how the catalytic subunits bring about the phosphorylation of other biochemical substrates. Thus, the different secondary, tertiary, and quaternary structures of the distinct PKA, CREB-1, and CREB-2 molecules will still constitute distinct realizations of memory consolidation. The differences are only likely since Bickle does not provide a specific hypothesis about just exactly what higher-order structures might constitute the realization base for memory consolidation. So, it is likely that the most higher-order protein structure can do for Bickle is to provide another realization base for memory consolidation; it is unlikely to provide for a single physico-chemical realization base for memory consolidation. To flesh out these claims, the discussion will work through the types of higher-order structure in ascending order.

Biochemists recognize two types of secondary protein structure, α-helices and β-sheets. (see Figure 1) In an α-helix, hydrogen bonds in the polypeptide backbone cause single continuous strands of amino acids to twist up into helices with their side chains projecting outward radially. In β-sheets, hydrogen bonds link multiple segments of amino acid sequences into sheets with the side chains projecting either above or below the surface of the sheet. One can get a sense of how secondary structures figure into proteins by inspecting a ribbon diagram of the catalytic subunit of PKA shown in Figure 2. This molecule contains a number of α-helices and a few β-sheets held together by stretches of additional amino acids.

Consider one of the α-helices in the lower right hand corner of Figure 2. Ordinary and scientific language surely allow some sense to saying that the catalytic subunits of the PKAs in mammalia, *Aplysia*, and *Drosophila* are the same. Nevertheless, this alone

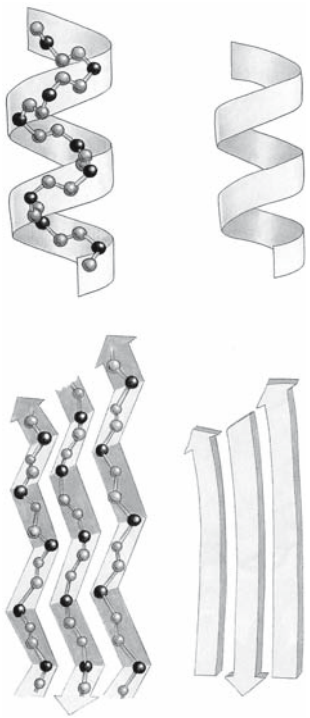

Figure 1. Based on Alberts et al. (2002), p. 137.

Figure 2. From http://www.nih.go.jp/mirror/Kinases/pkr/3D/xray/2cpk/2cpkwalk.html.

does not reveal any physical or chemical property common to these subunits that might constitute part of a realization base for memory consolidation. One cannot move from the claim that these α-helices are the same to either the claim that these α-helices are *chemically* the same or the claim that they are *physically* the same. In fact, the α-helices clearly do differ in chemical and physical properties. Since mammals, *Aplysia*, and *Drosophila* will have different amino acids in this helix, the helix will differ physically and chemically from species to species. An insertion or deletion of an amino acid in an α-helix will change its length and mass and perhaps its shape and charge distribution. A substitution of one or more amino acids for another will likely change the mass, shape, and charge. These types of alterations do not exhaust the types of changes to be found in chains of amino acids, but these alterations are likely to be found throughout almost any significant segment of a protein. This provides good grounds for supposing that there will be chemical and physical differences among α-helices in distinct species. Further, what applies to this particular α-helix applies to others and what applies to α-helices applies to β-sheets as well.

Secondary structures have another feature that is potentially relevant to finding a common physical and chemical basis for memory consolidation. In these structures, it is the polypeptide backbone, the series of NH–CH–CO units, that is responsible for the helical and sheet forms. Hydrogen bonds between peptide units four apart from each other on a single chain give rise to the helix; hydrogen bonds between the strands of peptide units in separate segments of a single chain give rise to the sheet. In α-helices and β-sheets, the amino acid side chains simply get out of the way of the hydrogen bonding of components of the polypeptide backbone. Thus, one might suppose that it is cores of the α-helices and β-sheets (the polypeptide chains stripped of their amino acid sides groups, as it were) that constitutes the physico-chemical realization base for memory consolidation.

One problem with this contention, however, is that it omits the essential role played by the strands of amino acids that connect the α-helices and β-sheets into proteins. Secondary structures floating freely in cells will not have the physical and chemical properties they need to bring about memory consolidation. Further, this move does not really make all homologous secondary structures physically or chemically the same. For one thing, such divergences include insertions and deletions of amino acids. This means that

the length, volume, and mass of a given α-helix core and the area, volume, and mass of a given β-sheet core will differ from taxon to taxon. For another thing, even limiting one's attention to the cores of α-helices and β-sheets ignores the way in which helices and sheets interact with other components of the molecule. Helices and sheets bend in ways that are conditioned primarily by the interactions of their side chains with the side chains of other parts of the protein. The effects of such interactions are illustrated in the subtle differences in the bends of the secondary structures in Figure 2. Such bends change the physical and chemical properties of the α-helices and β-sheets. In the case of the PKA catalytic subunit, these bends will change the molecule's ability to bind cAMP and to release the PKA regulatory subunit. The binding can be more or less tight and the release can be more or less rapid. Binding affinities and reactions rates are not only chemical properties of the molecules, they are arguably the most critical chemical properties. They are the *raison d'etre* of these proteins. Further, what holds for the PKA catalytic subunit, holds in clearly extensible ways for the PKA regulatory subunit, the CREB proteins, and indeed all proteins.

With tertiary structure, the principal problem is again the likely diversity in structure.[14] The tertiary structure of a protein is the overall three-dimensional conformation of a single polypeptide chain. Figure 3 illustrates how changes in primary structure affects tertiary

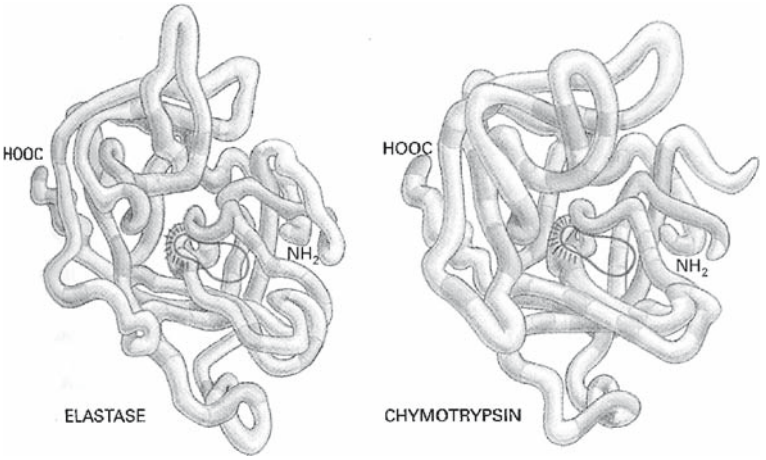

Figure 3. From Alberts et al. (2002), p. 143.

structure. The darker regions on the two molecules correspond to regions of identical amino acid sequence between a molecule of elastase and a molecule of chymotrypsin. Although the overall shapes are similar, there are nonetheless physical differences. Further, these physical differences will make a difference to the chemical properties of the molecules. They will change the binding of the protein's substrates and the rates at which chemical reactions involving the molecules take place. Granted, the differences one finds between elastase and chymotrypsin will be greater than the differences one will likely find between mammalian, *Aplysia*, and *Drosophila* PKA catalytic subunits, PKA regulatory subunits, CREB enhancers and CREB inhibitors. Still, the same point applies, namely, that there are likely divergences in tertiary structure, divergences that are likely candidates for distinct realizations.

Finally, there is the hypothesis that the quaternary structure of proteins provides the unique physico-chemical property underlying memory consolidation. To begin with, it is less clear what one means by quaternary structure than it is what one means by primary, secondary, and tertiary structure. One might mean by "quaternary structure" the existence or number of separate polypeptide chains in a single protein. Alternatively, one might mean the interactions and organization of the separate polypeptide chains in a single protein. Consider the first interpretation. The only protein in the cAMP–PKA–CREB pathways that has quaternary structure is PKA. It is a tetramer with two catalytic and two regulatory subunits. To say that memory consolidation is uniquely realized in the quaternary structure of PKA conflicts with the hypothesis that it is the entire cAMP–PKA–CREB pathway (and indeed the entire chemical process including the insertion of new proteins into the synaptic membranes) that is responsible for memory consolidation.[15] Then there is the second interpretation of "quaternary structure." On this understanding, it appears that quaternary structure suffers from the same problem with the consequences of differences in primary structure as do secondary and tertiary structure. That is, differences in primary structure give rise to more or less subtle differences in quaternary structure, which in turn give rise to physical and chemical differences in such things as the binding constants and reaction rates of the proteins.

To this point in the section, the principal aim of the argument has been to show that shifting attention away from primary structure toward secondary, tertiary, and quaternary structure does

not avoid multiple realization. PKAs, CREB-1s and CREB-2s differ in primary structure and in all likelihood secondary, tertiary, and quaternary structure. Differences in primary structure propagate upwards, so to speak. There is, therefore, nothing to be gained in this shift of attention. Now, however, there is also a cost to be considered. We have a theory of chemical natural kinds that enables us to classify the primary structures of amino acids into distinct natural kinds. This is the theory that molecules differing in the number or configuration of their constituent atoms constitute distinct chemical kinds. Secondary and tertiary structures do not have a comparable theory of kinds to ground their individuation.[16] When, for example, is one α-helix (β-sheet) of the same physical or chemical kind as another? Are they the same when they have the same curvature? What are the natural kinds of curvatures? Curvature can vary continuously with the environment of the α-helix (β-sheet), so how do these break up into natural kinds? When, for example, do two tertiary structures have the same 3-D conformation? What are the natural kinds of conformations, when conformations can vary continuously with environment? In short, anyone proposing to have higher-order structures constitute a realization base for memory consolidation must set aside a theory of chemical natural kinds that works for familiar cases and undertake the burden of developing a viable theory of these higher-order natural kinds.[17] This is part of the cost of appealing to higher-order structures as constituting the realizers of memory consolidation.

Bickle's project is to find a unique physico-chemical property that realizes memory consolidation. It is not enough that ordinary language, or even ordinary scientific language, says that two structures are the same. Even if one can say that two structures are the same, it does not follow that they are physically or chemically the same. If all that unifies the distinct amino acid sequences realizing memory consolidation is evolutionary homology or some functional commonality of the proteins, then this does not provide a unique physico-chemical realization for memory consolidation.

1.4. *Distinct Proteins Structures are only Trivially Different Realizations of Memory Consolidation*

In response to much of the foregoing, one might contend that protein structures are only trivially different ways of realizing memory consolidation.[18] The structural differences that have been alluded to

do not really make a difference. After all, there are amino acid substitutions that do not substantially change the physical or chemical properties of the proteins of which they are a part. Such substitutions are variations that must, in fact, make relatively small changes to the overall chemical and physical properties of the molecules, else the organism that contains them would die.

Two observations are pertinent here. First, there is good reason for there to be many distinct amino acid sequences that are very similar in physical and chemical structure. Such variability allows for a pool of genotypic and phenotypic variation upon which natural selection can act. Variations that confer essentially the same physical and chemical properties to a molecule can be preserved in a population and recombined each generation through sexual reproduction. One might say that evolution by natural selection is a diachronic theory, but what is important here is that this diachronic theory places a synchronic requirement or constraint on the physics and chemistry of life. That constraint appears to be that there must be many physically and chemically similar items realizing life forms. It is surely no accident that the two most important types of molecules in the living world, proteins and DNA, are both chain structures in which there can be multiple variations with very similar overall chemical and physical properties. Here is a case where having small physical and chemical differences is theoretically important.

The second thing to observe depends on the theory of chemical kinds according to which molecules differ in virtue of either their constituent atoms or the way in which those constituent atoms are arranged. This theory of chemical kinds provides a principled way to distinguish among realizations: each distinct amino acid sequence is a distinct chemical molecule that constitutes a distinct component of a realization of memory consolidation. Thus, each distinct chemical variant of PKA constitutes a distinct component in the realization of memory consolidation and each distinct chemical variant of the CREB enhancers constitutes a distinct component in the realization of memory consolidation. To say that distinct but similar molecules constitute the same component of a realization of memory consolidation constitutes an abandonment of this principle. Perhaps this is tolerable. Alternatively, there may be some way to make a principled grouping of the similar PKAs, CREB-1s, and CREB-2s into individual components a single realization. The point of this observation, and the previous one, is simply to challenge any easy supposition that chemically similar molecules

constitute a single realization component. Perhaps these observations do not make for an insuperable challenge, but they do make for a challenge.

2. ARE DISTINCT AMINO ACID SEQUENCES REALLY DISTINCT KINDS OF REALIZATIONS OF MEMORY CONSOLIDATION?

The discussion to this point has assumed that distinct amino acid sequences constitute distinct realizations of memory consolidation. Shapiro, however, urges suspicion of assumptions about what constitute distinct kinds of realizations. In fact, he thinks philosophers should reject the assumption that distinct amino acid sequences constitute distinct kinds of realizations of memory consolidation.[19] Here is an opportunity to explore, first, one option for trying to save Bickle's view that memory consolidation is uniquely realized and, second, Shapiro's theory of distinct kinds of realizations.[20]

Shapiro notes that "as far as I know, no philosopher has ever tried to complete the sentence, 'N and M are distinct realizations of T when and only when_____'" (Shapiro 2000, p. 636). So, he offers a completion. The core of Shapiro's account is that a function T is realized by distinct bases M and N if, and only if, M and N differ in ways that are causally relevant to their execution of function T.[21] This proposal delivers plausible results in Shapiro's favorite parade case where he suggests that a waiter's corkscrew and a double-lever corkscrew constitute distinct realizations of the function of being a corkscrew, since they bring about cork removal by distinct mechanisms (see Figure 4). Further, the proposal is plausible when Shapiro contends that a red waiter's corkscrew and a green waiter's corkscrew do not constitute distinct kinds of realizations of a corkscrew, since the color of the corkscrew is causally irrelevant to the way in which the cork is removed. The proposal does, however, run contrary to tradition and common intuitions insofar as it is committed to asserting that an aluminum waiter's corkscrew and a steel waiter's corkscrew do not count as distinct kinds of realizations of corkscrew or waiter's corkscrew. According to Shapiro, aluminum and steel do not count as distinct realizations, since they contribute the same causal power, rigidity he supposes, to the corkscrews they constitute. If Shapiro's theory is applied to the case of memory consolidation, one might say that the distinct amino acid sequences do not constitute distinct functional analyses of memory consolidation;

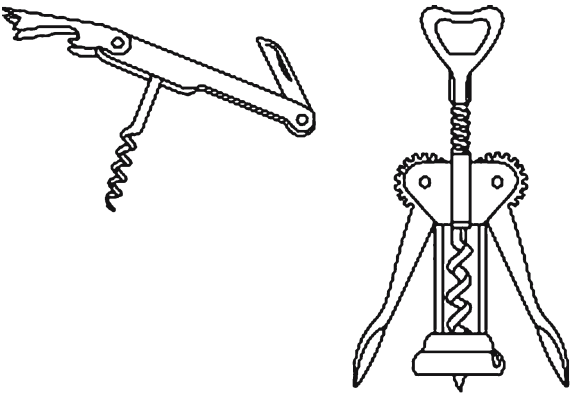

Figure 4. From Shapiro (2004), p. 2.

they contribute the same causal powers to the process of memory consolidation, hence that they do not constitute distinct kinds of realizations.

Gillett (2003), emphasizes an important kind of challenge to the application of Shapiro's account. Suppose that both aluminum and steel contribute rigidity to the corkscrews they realize. Nonetheless, aluminum and steel have different atomic/molecular structures in virtue of which they are rigid. The atoms in the aluminum corkscrew bond to each other in one way that makes for rigidity; the atoms in the steel corkscrew bond to each other in another way that makes for rigidity. Shapiro handles this worry by contending that one must attend to the functions being analyzed.[22] He contends that, while aluminum and steel might constitute distinct realizations of *rigidity*, this does not show that aluminum and steel constitute distinct realizations of *corkscrew*.[23] Shapiro, thus, appears to be committed to the principle that if F_I is uniquely decomposed into subfunctions F_A, F_B, and F_C, where F_A, F_B, and F_C, are each multiply realized in distinct materials, F_I does not count as being multiply realized.

This last principle runs afoul of the transitivity of realization argument that was covered in the discussion of the potential to find higher-order structures that might realize memory consolidation. In addition, this principle suggests counterintuitive results. Here are two problematic types of cases. First, a carburetor is typically assumed to be multiply realized and multiply realizable. It, however, can be functionally analyzed as a tube with a throttle plate

and a narrowing that contains an opening for a fuel jet. If this is the unique functional analysis of a carburetor, then it screens off all other analyses. Thus, Shapiro's theory will be committed to the view that carburetors are uniquely realized. Second, consider the case of a Turing machine program for computing the successor function, $S(x) = x + 1$, over the natural numbers using a unary representation system.[24] Maybe some notions of multiple realizability do not apply to computer programs, but Shapiro's does.[25] One might think this program is multiply realizable, if not multiply realized. One realization would be the program, $\{S_0\ 1\ R\ S_0,\ S_0\ 0\ 1\ S_1\}$, where another would be the program $\{S_0\ 1\ L\ S_0,\ S_0\ 0\ 1\ S_1\}$. The first program adds a "1" to the right end of the input string, where the second program adds a "1" to the left end. In so far as there is a functional property "being a Turing machines for computing successor by scrolling to the end of an input string and adding a single '1" and in so far as this property screens off the two Turing machine programs, Shapiro appears to be committed to the counterintuitive result that the successor function is not multiply realizable in the distinct Turing machine programs. These are quick and dirty objections, but they do merit attention.

Consider now the application of Shapiro's theory to the multiple realization of memory consolidation. There appear to be two ways to apply Shapiro's theory to this case: either there is no functional analysis between memory consolidation and primary amino acid sequence or there is. In neither case, however, does one end up with the conclusion that memory consolidation has a unique physical or chemical basis. Take the first way to apply Shapiro's theory, namely, assume that there is no underlying functional analysis of memory consolidation. Shapiro admits that rigidity is multiply realized in aluminum and steel in the corkscrew case. So, he allows that differences in material composition can sometimes give rise to differences in realization.[26] In particular, if there is no underlying functional analysis of memory consolidation, it would seem that Shapiro's view is that memory consolidation will be multiply realized in distinct amino acid sequences. So, just as Shapiro's theory allows that the atomic and molecular structure of aluminum and steel can constitute two ways of giving rise to rigidity, so his theory appears to allow that the atomic and molecular structure of mammalian PKAs, *Aplysia* PKAs, and *Drosophila* PKAs can constitute distinct ways of giving rise to memory consolidation. So, on

this application of Shapiro's theory, there is no unique physical or chemical realization of memory consolidation.

Now take the second application. Suppose that one maintains that memory consolidation is a high-level function that can be analyzed into lower-level functions that will screen off the primary structure of amino acids. Perhaps this would go by way of hypothesizing that each protein in the cAMP–PKA–CREB pathway is functionally characterized in the same way for all biological taxa. So, one might say that the function of PKA in all organisms is to bind excess cAMP and release PKA catalytic subunits in the presence of this excess cAMP. The function of CREB enhancer proteins in all organisms is to be phosphorylated and to initiate DNA transcription. The function of CREB repressor proteins in all organisms is to be phosphorylated and to inhibit DNA transcription.[27] Next, one might maintain that the specific amino acid sequences constitute distinct realizations of the particular functionally characterized proteins, even though they do not constitute distinct realizations of memory consolidation. The lower-level functionally characterized proteins screen off the distinct amino acid sequences from the higher-level psychological function of memory consolidation.

Yet, even this second way of applying Shapiro's theory of multiple realizations does not establish the view that there is a unique physical or chemical kind underlying memory consolidation. Memory consolidation is realized in distinct amino acid sequences.[28] Memory consolidation is not however *multiply* realized in distinct amino acid sequences. Memory consolidation is, therefore, uniquely realized in the distinct amino acid sequences. These are conclusions Shapiro's theory can deliver. Still, it is not the case that there is a unique physical and chemical kind realizing memory consolidation. The distinct amino acid sequences are still physically and chemically distinct. The fact that one lumps distinct amino acid sequences together as the one kind of realization does not force one to lump them together as one physical or chemical kind of realization. Clearly, it does not follow from Shapiro's theory that a taxonomy of kinds of realization will map exactly onto a taxonomy of physical or chemical kinds. So, on this application of the theory, it still does not turn out that there is a unique physical or chemical realization of memory consolidation.

This last application invites closer attention to Shapiro's theory proper and one consideration that diminishes his theory's bearing on the traditional multiple realization and functionalism issues in

the philosophy of mind. As is well known, when Putnam and Fodor were presenting the multiple realizability arguments, they were concerned to refute type–type identity theories that sought a single neurological, or physical, or chemical type for each psychological type. Their claim about multiple realizability was that for each psychological type, there are many possible neurological, physical, or chemical types that realize it. For each putative psychological natural kind, there are many possible neurological, physical, or chemical types. Shapiro's theory of realization makes no reference to lower level types or natural kinds, hence does not capture this element of the original conception. What this suggests is that, while Shapiro's approach to multiple realization encourages looking at old issues in new ways, his new perspective has lost touch with an important theoretical motivation for attending to multiple realizability. While the biochemistry of multiple realization was not essential to arriving at the conclusion, it does provide a clear means of fleshing it out.

3. MULTIPLE REALIZABILITY

The discussion to this point has been about the multiple realization of memory consolidation, rather than the more familiar issue of its multiple realizability. This has simply been a matter of following Bickle.[29] At least part of the motivation for the shift has been to bring scientific results to bear on what Putnam described as his speculative empirical hypothesis that psychological states are multiply realizable. Here again one can see the value of current models of the biochemistry of memory consolidation. It provides a useful corrective to Bickle's hasty dismissal of multiple realizability as unscientific intuition mongering. Further, it facilitates investigation of Shapiro's suggestion that physical constraints may, in unexpected ways, prevent the multiple realization of psychological states and processes. Where Shapiro indicates how this could happen for some biological structures and processes, the biochemistry of memory consolidation provides some relatively well understood model systems of some plausibly cognitive processes.

In *Philosophy and Neuroscience*, Bickle is frequently dismissive of "traditional" issues in the philosophy of mind (cf., e.g., Bickle 2003, p. 1, p. 32). A case in point is his handling of a *modus ponens* multiple realizability argument that goes something like this:

All psychological kinds are multiply realizable in physical-chemical kinds.
If all psychological kinds are multiply realizable in physical-chemical kinds, then no psychological kinds are reducible to physical-chemical kinds.

Therefore, no psychological kinds are reducible to physical-chemical kinds.

The difference between the multiple realization argument that he thinks is worthy of attention and the multiple realizability argument that he treats with contempt is the reliance on a modality in the multiple realizability argument. Consider what Bickle has to say about multiple realizability,

> This broader sense of multiple realiz*ability* and philosophers' 'possible world' fantasies do not concern me. I don't know whether identity holds across 'all possible worlds,' or even across 'all physically possible worlds.' I don't know the 'conceptual' or 'nomological limits' of our psychological concepts. But I take comfort in the fact that you don't either, regardless of the strength of your intuitions... . I steer clear of pragmatically fruitless questions. I'll worry about brainless yet pained or belief-entertaining aliens and robots as soon as one crosses my path. My concern is with existing earthly creatures. If the scope of my concern is too narrow for your philosophical sentiments, so be it (Bickle 2003, pp. 133–134).

In short, Bickle's reason for dismissing the multiple realizability argument is that he takes the relevant modality to constitute mere philosophical intuition mongering, cut adrift from scientific grounding. Further, he evidently believes that one need not care about the possibility of P, say, a brainless yet pained organism, unless one has an actual instance of P. Yet, both of these considerations is insufficient grounds for dismissing multiple realizability arguments. The biochemistry of memory consolidation helps show this.

To begin with, the challenge here is not to get Bickle to care about modality or to persuade him to worry about uninstantiated possibilities. It is, instead, to understand scientific theorizing and, more specifically, the philosophical consequences of current theories of the cellular and molecular processes underlying the psychological process, or processes, of memory consolidation. To this end, one should note that science regularly countenances certain things as possible and certain other things as impossible. It is possible, for example, to increase the mutation rate in a human population by increasing the amount of U^{238} in the environment. It is possible for certain influenza viruses to survive for over a day on a telephone receiver under certain conditions. Science knows about possibilities like this without necessarily exposing a human population to the given amount of U^{238} or by placing a sample of an influenza

virus on a telephone receiver under those conditions. Rather, science can discover laws that govern how things happen in the world, then make defeasible inferences about what possibilities exist.

Even more damaging to Bickle's position is the fact that biochemists talk about possible protein structures that are not necessarily actualized.

> Since each of the 20 amino acids is chemically distinct and each, in principle, occur at any position in a protein chain, there are $20 \times 20 \times 20 \times 20 = 160,000$ different possible polypeptide chains four amino acids long or 20^n different possible polypeptide chains n amino acids long (Alberts et al. 2002, p. 141).

More interestingly, the possibilities are not mere introductory textbook fare, they are the subject of theoretical investigation by biochemists. Biochemists interested in the structure of proteins are engaged in efforts to use computer programs to predict protein structure from amino acid sequence. To do this, they assume that there are on the order of 1000–2000 types of folds that amino acid sequences can assume. They try to find folds for new amino acid sequences that are similar to folds of known amino acid sequences. In other words, they are trying to find the possible structures of new amino acid sequences. What makes this enterprise feasible is that biochemists know about the properties of amino acid sequences and the principles that govern their interactions. Biochemists know that amino acid number, sequence, size, charge, and polarity are among the most important factors shaping overall protein conformation. In general, the more similar two proteins are in the number, sequence, size, and chemical properties of their constituent amino acids, the more similar the two proteins will probably be in higher-order structure and functionality. Thus, two proteins that differ only at one point, say, in substituting one amino acid of a given size, polarity, and charge for another amino acid of similar size, polarity, and charge will be more likely to have similar higher-order structures and functionality than two proteins that have more significant differences in amino acids. This means that, assuming identity of psychological process realized, one can expect multiple realizability of the process in as many distinct amino acid sequences as there are sequences that do not much affect the functionality of the protein. Thus, what biochemistry says about the laws governing amino acid sequences enables one to make defeasible predictions about what possibilities there are in the world. So, contrary to Bickle's suggestion, the conclusion that the biochemistry underlying

memory consolidation is multiply realizable need not be motivated by crude intuition mongering or science fiction fantasy.

One of the central ideas in Shapiro (2004), is that philosophers may have overestimated the plausibility of multiple realization and multiple realizability because they have not taken proper account of the way in which physical constraints can impose limitations on what nomologically possible realizations there can be to psychological processes. One illustration of the potentially surprising role of constraints comes with a review of the biology of eyes. Where a philosopher might suppose that there are any number of nomologically possible ways in which to construct an eye, it turns out that the physics of light has limited the evolution of eyes to something on the order of eight different designs.

What makes the molecular biology of memory consolidation interesting to this issue is, first, the fact that molecular biologists have a reasonably good working knowledge of the constraints that are involved in the construction of proteins and, second, that one can now determine in a general way that these constraints are loose enough to allow for the multiple realizability of memory consolidation. The principal constraints that determine the overall conformation of proteins come from hydrogen bonding among elements of the polypeptide backbone, through hydrogen bonding of the amino acid side chains, the opportunities for formation of disulfide bonds among certain amino acids, and the size, polarity, and charge of the amino acid side groups. These are the sorts of facts alluded to above. It is working knowledge of these sorts of properties of amino acids and the principles governing them that enables structural biochemists to generate computer programs that can make at least rough predictions of the functional groups and overall conformation of individual amino acid sequences. Further, from what is known about the multiple realization and multiple realizability of memory consolidation in distinct amino acid sequences, one can see that these constraints are not so severe as to preclude multiple realization.

4. MORE NARROW REDUCTIVE STRATEGIES

The early stages of this paper temporarily assumed for the sake of argument that memory consolidation is the same psychological kind in mammalia, *Aplysia*, and *Drosophila*. On this assumption, there

is reason to believe that memory consolidation is multiply realized in distinct sequences of amino acids. What happens, however, on the assumption that memory consolidation is one kind of psychological process in mammals, another kind in *Aplysia*, and another in *Drosophila*? Endicott (1993), Kim (1972), and Polger (2004), for example, discuss the possibility of discovering such species-specific reductions. Perhaps under this supposition, it would turn out that in each species there is a unique realization of a psychological kind.

In truth, the move to species-specific psychological processes changes little vis a vis the multiple realization of memory consolidation in distinct amino acid sequences. Even in the absence of some particular journal article documenting the range of amino acid sequences in *Aplysia*, or *Drosophila*, or mammalia, what biochemists know about the genetics of these organisms at least predicts that the relevant proteins in each taxon will be multiply realized in distinct amino acid sequences. Naturally occurring populations of organisms contain a pool of genetic variability. Further, mutation introduces new variability in every generation. Species differ in the amount of genetic variation they carry and in their mutation rates, but each species has some degree of genetic variation in essentially every gene. Insofar as a species contains a genetic mutation that changes the amino acid sequence for one of the proteins in the species's cAMP–PKA–CREB pathway, there will be multiple realizations of the cAMP–PKA–CREB pathway in that species.

Further, the move to species-specific forms of memory consolidation does little to address its multiple realizability. It could turn out that, say, *Aplysia* happens to have a unique set of cAMP–PKA–CREB proteins, each of which is uniquely realized in but one sequence of amino acids. Nonetheless, one can invoke facts about the way the charge, size, and sequence of individual amino acids interact to make defeasible inferences about what protein sequences will preserve protein functionality. This provides for a scientifically respectable multiple realizability argument against a species-level form of memory consolidation that does not trade in mere intuitions.

Incidentally, the problem with the proposal to look for species-specific memory consolidation mechanisms can easily be modified to handle a proposal to think of memory consolidation as a natural psychological function unique to each individual. That is, even on the supposition that each individual organism is an instance of a specific natural kind of psychological process of memory

consolidation, it will turn out that this process is multiply realizable, even if not multiply realized. Somatic mutations acquired during the course of an individual organism's lifetime might give rise to cell lines that have cAMP–PKA–CREB proteins with one amino acid sequence, while other cell lines have cAMP–PKA–CREB proteins with another amino acid sequence. Thus, memory consolidation would be multiply realized in two distinct types of cAMP–PKA–CREB pathways within the same organism.

5. CONCLUSION

This paper has been a sales pitch for the value of the mammalian, *Aplysia*, and *Drosophila* model systems of memory consolidation for philosophical discussions of the multiple realization of cognitive functions. The value of this biochemistry is not to be gauged so much by the fact that it constitutes a break from thought experiments, or intuition mongering, nor by the fact that it is hard to see how this information can fail to be relevant to philosophical theorizing about the mind.[30] Rather, it is that, at this point in time, the molecular biochemistry of memory consolidation illuminates certain philosophical theories with some relatively well-understood scientific facts. This biochemistry bears on multiple realization, the nature of the realization relation, the applicability of a particular theory of realization to particular cases, multiple realizability, the possible role of constraints in theorizing about multiple realizability, and the plausibility of species-specific and individual-specific multiple realization of a cognitive process. That is, the proof of the value of these scientific model systems for the philosophy of mind lies in its actual application to specific issues.

As a final point, it should be noted that the nature of life as we know it suggest that the multiple realization and multiple realizability of memory consolidation is just the tip of the philosophical iceberg. All known life forms are constituted to a significant degree by amino acid chains, so that molecular biochemistry will also have to be taken into consideration in an examination of the multiple realization and multiple realizability of other psychological states and processes. This means that even qualitative states are likely to be multiply realized in the biochemistry of the brain.

ACKNOWLEDGMENT

Thanks go to Fred Adams, Marica Bernstein, Carl Gillett, Sandy Goldberg, Brad Monton, and Larry Shapiro for comments on an earlier draft of this paper. Thanks also go to Marica Bernstein for guidance to resources in the relevant biochemistry. Thanks to the philosophy departments at the University of Cincinnati and the University of Kentucky for the opportunity to present some of the ideas in this paper. Thanks to Jackie Sullivan for comments on a shorter version of this paper presented at the 2005 Society for Philosophy and Psychology. Special thanks go to John Bickle for the invitation to speak at the University of Cincinnati, for comments on a shorter version of this paper presented at the 2004 Central States Philosophical Association Meetings, and for comments on another portion of this paper delivered at the 2005 Southern Society for Philosophy and Psychology. These exchanges have been a model of constructive philosophical discussion. Alas, after all this, John still does not think that memory consolidation is multiply realized. A final thanks to two careful reviewers for *Synthese* for providing any number of helpful comments and suggestions.

NOTES

[1] One alternative critical line is based on the fact that in *Aplysia* the relevant neurons are serotonergic, where in mammals the relevant neurons are glutaminergic. Another line would focus on the "downstream effects" of the biochemical processes considered here. (This point was raised by Jackie Sullivan in her commentary on a shorter version of this paper.) Still another line might draw attention to the hypothesis that there appear to be two distinct types of LTP in the mammalian cases. Still another line might challenge the interpretation of the experimental evidence that is supposed to link the biochemical process ϕ with memory consolidation. (These last two possibilities were raised by the anonymous reviewers for *Synthese*.) While each of these lines (among still others) is worthy of attention, none of these is as significant as the line to be pursued here, namely, that memory consolidation is multiply realized in distinct amino acid sequences. The consequences of there being distinct amino acid sequences is more significant since amino acids are ubiquitous in terrestrial life forms, suggesting that all psychological properties might be multiply realized.

[2] Type-type reductionism will make a brief appearance in the discussion of the motivation for Shapiro's theory of multiple realization and in a review of the prospects for species-specific reductions of psychological processes.

[3] Shapiro (2004), for example, raises this issue.

[4] Bickle, in personal communication, reports that he assumes only for the sake of argument that the memory consolidation is a single cognitive function in mammals, *Aplysia*, and *Drosophila*. If a broad psychological kind of memory consolidation is uniquely realized, then so are the species-specific versions.

[5] See, for example, Bartsch et al. (1995, 1998), Davis and Squire (1984), Izquierdo and Medina (1997), Soderling and Derkach (2000), and Yin et al. (1994, 1995).

[6] For present purposes, there is no need to suppose that molecules individuated in terms of the number and configuration of their constituent atoms exhaust the chemical kinds. For example, ketones, aldehydes, and carboxylic acids constitute legitimate chemical kinds individuated, not by the entirety of a molecule's structure, but by a portion of the molecule.

[7] What Bickle says here is potentially misleading. Although he does not cite a page from Bartsch et al. (1995), the relevant passage appears to be the following. "CREB1a is 95% homologous to mammalian CREB and CREM proteins *in its C-terminal DNA binding and dimerization domain (bZIP) and its phosphorylation domain (P box)*" (p. 212, emphasis added). So, more precisely, it is not the entire proteins that share 95% of their amino acids, but just two functional subregions that do. This reconciles the conclusion from Bartsch et al. (1998), with another conclusion in Bartsch et al. (1995), namely, that "Ap[lysia]CREB1 has 42% homology with the mouse CREB1 over the whole length of the protein" (p. 979).

Incidentally, Bernstein (2005), complains about the validity of the notion of "x% homology" used by Bartsch, and others. For present purposes, this notion can go by the wayside. It is not needed to run any arguments in this paper. The centerpiece of this paper is the undisputed fact that there are diverse sequences of amino acids in mammalia, *Aplysia*, and *Drosophila*. How much these sequences diverge and whether or not there is a viable notion of "x% homology" is an independent issue.

[8] Cf. Yin et al. (1995), Figure 4B, p. 5126 for a detailed comparison of the amino acid sequence of the bZIP domains of *Drosophila* dCREB2 and mammalian CREB, CREM, and ATF-1.

[9] This, of course, assumes that there is non-basic causation above the level of something like quantum mechanics.

[10] Robert Richardson (personal communication) mentioned kind of response.

[11] In discussion of these issues, Bickle has been exploring this line of response.

[12] Carl Gillett gave this argument in personal communication.

[13] This assumes that there are no problems with non-basic causation or lower levels of protein structure excluding the causal efficacy of higher levels of protein structure.

[14] Bickle suggests that 3-D conformation, charge distribution, and protein domains will in some way provide for a unique realization of memory consolidation. Of course, insofar as 3-D conformation is multiply realized, so will be the combination of 3-D conformation, charge distribution, and protein domains. So, the problems with tertiary structure described here carry over to the details of Bickle's proposal.

[15] As an incidental methodological point, one must be careful to use physical or chemical properties, rather than functional properties or descriptions, to characterize quaternary, tertiary, and secondary structure. PKAs illustrates the point,

since their subunits are generally labeled functionally. The PKA catalytic subunits are those that function to catalyze the phosphorylation of various substrates. The PKA regulatory subunits are those that function to regulate the action of the catalytic subunits. The point is not that all higher-order structures are functionally characterized; they are not. Hemoglobin is another tetramer, but its subunits are characterized structurally and simply labeled α-globin and β-globin.

[16] Perhaps quaternary structures could divided into natural kinds as dimers, trimers, and tetramers, but this is hardly an adequate basis for realizing memory consolidation.

[17] As an aside, notice that to say that there are higher-order natural kinds of proteins that realize memory consolidation is an empirical question. Still, it is not one that biochemists are likely to answer in scientific journals, such as *Cell* or *Journal of Neurophysiology*. It is an empirical question that will require some philosophical attention to issues of interest to philosophers, namely, the development of a theory of natural kinds adequate to higher-order protein structures.

[18] Shapiro (2004), p. 48, p. 53, makes comments that suggest that he would adopt this view.

[19] Shapiro (personal communication).

[20] This section covers only the possible multiple realization of memory consolidation in distinct amino acid sequences. Insofar, however, as one thinks that it is something other than the primary structure of amino acids that constitutes the realization base of memory consolidation, one will have to address Shapiro's question about whether this realization base is really one or many. In the absence of any appealing alternative to the hypothesis that the primary structure of amino acids constitutes the realization base for memory consolidation and in the interests of simplicity, these alternatives will be set aside for now.

[21] The "non-core" portion of Shapiro's theory is the idea that there can be realizations that are so similar they are only trivially different (Cf., Shapiro, (2004), p. 48, p. 53). Since this idea was addressed in the last section, it will not be reviewed in this one.

[22] Cf., Shapiro (2000), pp. 644–645, Shapiro (2004), pp. 56–57.

[23] Shapiro is committed to the claim that aluminum and steel are not *distinct* realizations of corkscrew. It is not clear, however, whether he further maintains that aluminum and steel are not realizations of corkscrew at all. In other words, Shapiro is committed to the view that rigidity screens off aluminum and steel as *multiple* realizations of corkscrews, but he is not clearly committed to the view that rigidity screens off aluminum and steel as realizations of corskcrews. This might be put another way. Is rigidity a "multiplicity filter" or a "realization filter"? In what follows, the assumption will be that Shapiro maintains that lower level functional analyses only screen off multiple realizations, rather than all realizations. This is assumed in order to allow Shapiro to maintain that, ultimately, all higher-level properties are realized in basic physics. In addressing these issues, Shapiro must evidently consider the transitivity of realization argument given above.

[24] In this system, let the number zero be represented by a "1" in a single tape square, the number one be represented by a single "1" in adjacent tape squares, the number two represented by a single "1" in three adjacent tape squares, and so forth.

[25] Cf., Shapiro (2000).
[26] Cf., Shapiro (2000), p. 644.
[27] These analyses are simplifications of the relevant biochemical pathway, but this changes nothing of philosophical significance.
[28] But, cf. footnote 22 above.
[29] But, Bechtel and Mundale (1999), and Shapiro (2004), also make the shift from multiple realizability of psychological properties to the multiple realization of psychological properties in terrestrial animals.
[30] Cf., Bickle (2003), p. 1.

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