Behavioral and Social Research Program
National Institute on Aging
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Social Neuroscience of Aging Exploratory Workshop

Background Materials and Statements from February 2007 Workshop Participants

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Lis Nielsen, Ph.D.
Psychological Development and Integrative Science
Telephone: 301-402-4156
Email: nielsenli@nia.nih.gov

Jennifer Harris, Ph.D
Genetics Consultant to BSR
Telephone: 301-496-3138
Email: HarrisJe@mail.nih.gov

Anneliese Hahn, M.S.
Research Program Analyst
Telephone: 301-402-4447
Email: hahnan@nia.nih.gov

Background Statement for Workshop on Social Neuroscience of Aging

Lis Nielsen, BSR
Jennifer Harris, Genetics consultant to BSR

The Behavioral and Social Research Program (BSR) at the National Institute on Aging (NIA) will hold an exploratory workshop on the Social Neuroscience of Aging on February 7-8, 2007, in Washington, D.C. The goal of this workshop is to stimulate new research on the social neuroscience of aging, examining the neurobiological basis of social behaviors of relevance to aging, with particular emphasis on the mechanisms and pathways linking social behaviors and social environments to the physical health, functionality, and psychological well-being of middle-aged and older adults.

The emerging discipline of social neuroscience directly addresses relations between genetic and neurobiological systems and aspects of emotional function, social behavior, and the socio-cultural environment. This includes research addressing how social network size, social context, social demands, and relationship quality impact neurobiological function, as well as studies of the neurobiological and genetic underpinnings of emotional regulation and understanding, attitudes and stereotypes, affiliation and bonding, moral behavior, communication, trust, and social exchange.

Recent application of neuroscience tools to the study of topics in developmental, social, and personality psychology is yielding insights into the biological underpinnings of a variety of social phenomena. These include emotion regulation in social contexts (Coan, Schaefer & Davidson, in press; Butler, Wilhelm & Gross, 2006); attitudes and stereotype formation (Wheeler & Fiske, 2005); and the impact of social factors on physical and mental health (Hawkley et al., 2006; Cacioppo et al., 2006) and on the neurobiological mechanisms underlying reciprocity, trust, and empathy (de Quervain et al., 2004; Kosfeld et al., 2005; Jackson, Meltzoff, & Decety, 2006; Singer, 2006). Research in social neuroscience has also significantly advanced our knowledge of the neural representation of the self and related constructs (Heatherton, Macrae, & Kelley, 2004), the neural underpinnings of theory of mind (Gallagher & Frith, 2003), and the brain and information processing mechanisms underlying emotional influences on social interaction, social judgment, and social exchange (Ito, Thompson, & Cacioppo, 2004; Greene et al., 2001; Eisenberger, Lieberman, & Williams, 2003; Sanfey et al., 2003; King-Casas et al., 2005).

The rapidly growing research area of social neuroscience has spawned two new journals, special issues in major neuroscience publications and a host of well-attended symposia on social neuroscience at large international research conferences. With a few notable exceptions (e.g., McDade, Hawkely, & Cacioppo, 2006; Levy et al., 2000; Hawkley, Masi, Berry, & Cacioppo, 2006; Epel et al., 2004; Sturm et al., 2006), relatively little attention has been paid to these phenomena in the context of midlife and older age. However, recent work in social and personality psychology of aging is revealing how trajectories of social and emotional function differ from that of cognitive function over the lifespan, with the majority of evidence suggesting that that socioemotional abilities, including interpersonal problem solving, and the ability to

experience emotion and process emotionally salient information in both social and nonsocial contexts is largely preserved in older age. Moreover, the changes in socioemotional abilities and social motives that have been documented in older age are likely to influence, in turn, the structure of the social network and choices of social partners, and have been proposed to prime the use of strategies favoring the regulation of emotional states and maintenance of close relationships over other instrumental or interpersonal goals (Carstensen, 2006; Carstensen, Isaacowitz, & Charles, 1999). How the differing strengths of socioemotional, cognitive and physical capacities at different life stages, in combination with life course changes in social motives and goals, impact physical health and psychological well-being at different life stages is as yet unknown. Researchers are only beginning to explore the neurobiological correlates of these changes (e.g., Mather et al., 2004). Furthermore, how neurobiological changes in older adults such as decreases in brain matter and reductions in neurotransmitter function on the one hand, and neurogenesis and neuroplasticity on the other, influence or are influenced by age-related changes in social and motivational factors is virtually unexplored.

Application of the social neuroscience approach to these aging issues holds the potential for bringing a richer developmental focus to this research area. Thus the recent NIA-commissioned National Research Council Report from the Committee on Aging Frontiers in Social Psychology, Personality, and Adult Developmental Psychology, entitled When I'm 64, (Carstensen & Hartel, 2006), highlighted advancing social neuroscience research on aging as a critical next step for the behavioral and social sciences (http://www.nap.edu/catalog/11474.html). BSR is also interested in advancing genetic studies of social behaviors and aging under the broad umbrella of social neuroscience. The recent Institute of Medicine report entitled Genes, Behavior, and the Social Environment (Hernandez & Blazer, 2006) (http://www.nap.edu/catalog/11693.html), emphasizes that "the influence of social, behavioral, and genetic factors on health involves dimensions of both time (critical stages in the life course and the effects of cumulative exposure) and the context or culture within which variables operate to influence health outcomes" (p. 5), a theme which has influenced our planning and goals for this meeting.

Of particular relevance to aging, there is a need to understand: (1) how social behaviors and social motives and their neurobiological underpinnings develop and change over the lifespan; (2) how changes in social networks at different life phases (marriage, parenting, caregiving, widowhood, retirement, reductions in network size due to functional limitations or death of network members) influence neurobiological systems for social and emotional function; and (3) how these developmental changes in social context and social behaviors impact physical health and psychological well-being at different stages of life. In addition, individual differences in these relations can shed light on risk and resilience profiles or on protective factors in the social environment, including how social factors modify genetic expression over the life course.

In our view, important contributions to the social neuroscience of aging are likely to emerge from research that (1) takes a lifespan approach to the study of neurobiological underpinnings of social behavior; (2) refines our ability to measure and identify phenotypes and endophenotypes of social behaviors of relevance to aging; (3) advances methods for measurement of social environments of relevance to aging outcomes; (4) explores the influence of social and cultural context on social behaviors of older adults; (5) and provides bridges to potential interventions and translational research to improve the health and well-being of older adults.

We are convening this exploratory workshop to advance discussion on these themes among experts in aging research, social neuroscience, and genetics, with the goal of stimulating new lines of investigation. The summary report from this workshop, as well as prepared statements by participants, will be made publicly available on the NIA website, and serve as part of our outreach to the scientific community, as we seek to encourage cutting edge research in this emerging area.

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Charge to Participants in the Social Neuroscience of Aging Workshop

In preparation for the NIA Exploratory Workshop on the **Social Neuroscience of Aging**, participants were asked to prepare a short (2-4 pages) statement outlining their views on how cutting edge research in the social neuroscience of aging can be most fruitfully advanced. These statements are intended to set the foundations for dialogue, at the workshop, on research and resource needs for achieving this goal.

As described in the following background document, it is assumed that multilevel, interdisciplinary research exploring the neurobiological and genetic mechanisms liking social behaviors and social environments to aging-relevant outcomes is a critical programmatic goal for BSR. Participants were asked to offer creative, well-informed input on where the emerging research opportunities lie within their own and related fields.

Participants were asked to consider the following questions when preparing their statements:

1. What do you perceive to be the one or two pivotal findings from your own work or work in your field, that have advanced our understanding of the neurobiological or genetic underpinnings of social behaviors? Where do you see this line of research developing from here? How can it shed light on lifespan developmental issues or issues specific to aging?

2. How can we better specify the neurobiological and genetic mechanisms and pathways linking social behaviors and environments to aging-relevant outcomes? What are the conceptual and methodological advances required?

3. What are the current pitfalls and obstacles to progress? Where are there gaps in our current knowledge that would be logical next steps to try to approach?

John T. Cacioppo, University of Chicago

1) What do you perceive to be the one or two pivotal findings from your own work or work in your field that have advanced our understanding of the neurobiological or genetic underpinnings of social behaviors? Where do you see this line of research developing from here? How can it shed light on lifespan developmental issues or issues specific to aging?

Epidemiological research indicates that social isolation is related to an increased risk of infectious, cardiovascular, and neoplastic diseases. People's perceptions of objective circumstances are often more powerful determinants of their mental and physical health than the objective circumstances per se, and this appears to be the case for social isolation, as well (Cacioppo et al., 2002a, 2002b; Cacioppo, Hughes et al., 2006; Hawkley et al., 2006). Perceived social isolation, or loneliness, is a debilitating psychological state that adversely affects the quality of life every day for a large segment of the population (Davis and Smith, 1998). However, loneliness is not just a consequence of social isolation; it is a stable, heritable trait (Boomsma Willemsen, Dolan, Hawkley, and Cacioppo, 2005; Boomsma, Cacioppo, Slagboom, and Posthuma, 2006) distinguishable from other personality factors such as extraversion, neuroticism, hostility, and negative affectivity that affects the way lonely people perceive and interact with others (Cacioppo, Hawkley, Ernst et al., 2006).

Lonely individuals are not simply unhappy—they have heightened sensitivity to threats and attacks. Defensive behaviors such as preventative rejection of others may help fend off treachery, rejections or attacks. It is this ingrained, egocentric and self-protective focus on threats that drives their anxiety and caustic interactions and allows them to minimize the short-term damage of negative interactions but at the cost of potentially self-defeating hostility, fault-finding and blaming (Cacioppo and Hawkley, 2005; Rotenberg, 1994). Consistent with this model, we have found two very different patterns of neural activity to underlie how lonely and nonlonely individuals think about other people (Cacioppo, Norris, Decety, Monteleone, and Nusbaum, 2007). One set of brain regions, often associated with reward systems (i.e., ventral striatum), is down-regulated in lonely people when viewing pleasant pictures involving people in contrast to equally pleasant and arousing pictures of scenes and objects. Another set of brain regions, associated with visual attention and theory of mind, varies in response to unpleasant social (in contrast to matched nonsocial) pictures, indicating that lonely individuals are more attentive to social cues but think about this information in a more egocentric fashion than nonlonely individuals.

To identify biological mechanisms of the higher risk in lonely older adults for infectious, cardiovascular, and neoplastic diseases, we analyzed genome-wide transcriptional profiles in leukocytes from individuals who chronically experienced high vs. low levels of loneliness in their daily lives (Cole, Hawkley, Arevalo, Sung, Rose, and Cacioppo, 2007). High-lonely older adults over-expressed genes involved in immune activation, transcriptional control, and cell proliferation, and under-expressed genes supporting mature B lymphocyte function and Type I interferon response. Despite showing elevations in circulating cortisol, high-lonely individuals showed a paradoxical under-expression of genes bearing glucocorticoid response elements and a corresponding over-expression of genes bearing binding motifs for the proinflammatory transcription factor NF-κB. The present findings are consistent with animal models of stress-

induced glucocorticoid resistance via receptor desensitization, and suggest that social isolation may influence the risk of inflammatory disease in the human social ecology by blocking the leukocyte transcriptional response to GR-mediated anti-inflammatory signaling.

Together, this research indicates that aging influences fundamental molecular and cellular processes, neural and hormonal responses, local and central regulatory mechanisms, rudimentary perceptual and sensorimotor functions, attentional and memorial processes, feeling and reasoning, social interactions and relationships, social expectations and norms, population demographics and institutional demands, and much more. Disciplinary scientific analyses have advanced our understanding of important variables that play a role in aging phenomena. When many such variables are at work to produce a given outcome, however, the focus on single variables yield a biased understanding. When the variables at work in aging also derive from multiple levels of organization (e.g., overeating because blood sugar is low, behavioral habit, social facilitation, or culture prescription), then multidisciplinary approaches that draw upon the expertise, theories and measures from multiple levels of organization may be necessary to explain the phenomenon and to develop effective preventions or treatments. This is particularly the case when variables interact to produce the outcome (e.g., particular genetic dispositions triggered by certain environmental conditions; behavioral influences of a hormonal response being contingent on a social context). Comprehensive theories of such aging phenomena benefit from the multidisciplinary approach of social neuroscience.

2) How can we better specify the neurobiological and genetic mechanisms and pathways linking social behaviors and environments to aging-relevant outcomes? What are the conceptual and methodological advances required?

Recent scientific and technological advances have dramatically altered the data available to study complex behaviors and healthy aging. Estimates among biologists a decade ago were that 100,000 genes were needed for the cellular processes that are responsible for human behavior and aging, but humans have only a quarter that number of genes (Pennisi, 2005). This finding has fostered a recognition that a gene may have multiple small effects (pleiotropy), that many genes may act in additive and configural fashions to produce small effects both on specific abilities and on general abilities, and that genetic expression can be altered by the social as well as the physical environment in which humans live and work. The advent of single-nucleotide polymorphisms (SNP) microarrays permits genome-wide association studies that would have been considered impossible less than a decade ago, and microarrays are on the horizon with all functional DNA polymorphisms in the genome (Butcher, Kennedy, and Plomin, 2006).

In addition to the global analysis of genes (genomics), technologies now exist for large-scale analyses of gene transcripts (transcriptomics), proteins (proteomics), and metabolites (metabolomics) in cells, tissues, and organisms. Among the important advances in quantitative analyses of these data are multivariate genetic analysis, which goes beyond analyzing the variance of each phenotype considered separately to analyze the covariance between them (Butcher et al., 2006). The number of SNPs and the number of various combinations of SNPs can be very large, however, and the complexity of the mapping problem is magnified by the presence of non-isomorphic intervening steps which, for instance, contribute to variation of

phenotypic expression as a function of the physical or social context. Bioinformatics tools such as TELiS, which can be used to examine similarities in signaling pathways (transcription factor binding motifs) by genes that are found to differ between groups of interest, may be used to construct an intermediate level of organization, thereby improving the mapping of genotypes to phenotypes.

Developments in tissue and blood assays, ambulatory recording devices, non-contact recording instruments, and powerful and mobile computing devices have also burst onto the scene this past decade. These technologies make it possible to measure a variety of biological parameters in naturalistic as well as laboratory settings and in population-based health research. One such development is the use of drops of whole blood collected on filter paper from a simple finger prick to collect and analyze biological samples that previously required venipuncture (e.g., McDade et al., 2000). McDade, Williams, and Snodgrass (2006) identify more than 100 analyses that can now be measured in dried blood spot samples, approximately half of which have particular relevance to population-level health research (e.g., cortisol, CD4+ lymphocytes, C-reactive protein, glycosilated hemoglobin, IgE, Epstein Barr Virus, TNFα). With the inclusion of these measures in population-based health research, the weak associations that one would predict to exist between multiple determined variables (e.g., stress and C-reactive protein or blood pressure) and the potential influences of moderator variables (e.g., age, ethnicity, socioeconomic status) can be tested. These potential moderator variables may operate through differential reactivity (e.g., certain ethnicities or age-cohorts may show salt sensitivity) or differential exposure (e.g., certain ethnicities or age-cohorts may consume more salt in their diets). Distinguishing between these processes is crucial to moving from the description of associations to the delineation of causal mechanisms.

Spatially multidimensional electromagnetic, hemodynamic, and optical imaging devices coupled with temporally precise electrophysiological methodologies now make it possible to track changes in brain activity with spatial and temporal resolution resulting in data structures containing millions of elements (Herrington, Sutton, and Miller, in press). Although not yet appropriate for inclusion in population-based health research, these techniques make it possible to test specific hypotheses about the CNS mechanisms underlying a variety of psychological processes, and the transduction of these psychological factors into peripheral biological activities and healthy aging. These laboratory techniques are already being used to test a subset of respondents in population-based studies, and ambulatory versions of electroencephalography are currently being developed.

The use of functional brain imaging in studies of the aging mind, the addition of genetic data to studies of life circumstances and aging trajectories, the expansion of genetic data to include genome-wide transcriptional profiles, and the inclusion of biomarkers in population surveys hold great promise, but it is important to ensure that the theories and expertise from these various scientific fields are represented in a deep and meaningful way. An fMRI study that shows an area of the brain is more active during a memory-task advances knowledge only to the extent that the behavioral and neurobiological perspectives represent cutting-edge understandings. Moreover, humans are inherently social creatures. One of the major functions of the human brain is to enable skilled social interactions and stable and satisfying social relationships. Delineating the neural mechanisms underlying satisfying social interactions and adaptive social behaviors is one of the major challenges of the neurosciences in the 21st century.

Moreover, recent "epidemics" such as obesity and cardiovascular disease cannot be fully explained in terms of genes alone because major shifts in the human genome require much longer periods of time to unfold. These new health challenges require consideration of environmental exposures (e.g., the deployment of soda machines and fast food options in public schools) and individual differences in response to exposures (e.g., individual consumption patterns, salt sensitivity). Importantly, cultural, economic, political, social, psychological, behavioral, and environmental assessments are becoming more detailed, multidimensional, reliable, sensitive, and temporally rich. Early measures of social and behavioral predispositions were once characterized by general indices with poor reliabilities and validity. Although self-report measures often are viewed with suspicion because respondents may not be willing or able to respond accurately, the proper application of psychometric procedures to scale construction and validation and the inclusion of validating behavioral metrics have produced self-report measures with reliability and validity coefficients that rival or exceed the psychometrics of many physiological assessments (e.g., Burleson et al., 2003).

3) What are the current pitfalls and obstacles to progress? Where are the gaps in our current knowledge that would be logical next steps to try and approach?

There are a variety of obstacles to progress, but the single largest at this time is the paucity of funding for strong research proposals. This makes it difficult for junior investigators to obtain funding, for all investigators to maintain programs of research, and for the field to reach a critical mass. A second obstacle in this area, in particular, is that traditional recipients of NIA funding are the individuals most likely to be tapped by CSR for participation on study panels, and these investigators have shown little interest in expanding the breadth of proposals and increasing the competition for the limited grant dollars that are available for aging research. Third, experimental studies in social neuroscience and aging tend also to be cross-sectional. Longitudinal studies are sorely needed in the field. Experimental longitudinal studies are also badly needed, although in most instances the descriptive longitudinal database is not sufficient to justify the expense of an experimental longitudinal study.

Finally, with the development of the complex datasets outlined above, we need an infrastructure that would not only make these datasets publicly available but reasonable to relate to one another. The simplest method of mapping (or translational tables) across levels of data is the correlative approach. A strength of a correlative approach is often in identifying associations that might be replicable and worthy of further study, not in post hoc hypothesis testing. The development and adoption of false discovery rate methods represented a shift from the approach of minimizing Type I error rates because the cost of near-zero false discovery rates was a high false negative rate. Specifically, research on complex outcomes (e.g., health outcomes, social behavior) indicates that the ratio of the number of missed small discoveries to false discoveries can be substantially greater than one, and we have come to understand that the cost of missing important but small associations (Type II errors) is often greater than the cost of a false "discovery" (Type I error), as when small associations carry large economic ramification once scaled to the level of the population. An important goal of scientific theory is to describe the causal interrelationships among factors, thereby explicating the mechanism responsible for the phenomenon of interest. *Moving from the specification of associations to mechanisms is an important objective for future research using biological measures in social science surveys*. The

correlative approach may generate variables (e.g., genes, neurophysiological circuits, demographic or lifestyle factors) or contextual moderators that are candidates for a causal mechanism. When such associations realized in a theoretical fashion, their discoveries are often best considered as representing hypothesis generation, however. Moreover, the correlative approach may not indicate the nature of the specificity of the association across levels of representation. Therefore, attention needs to be paid to going beyond thinking of associations to thinking about the interfaces between levels of representation. For instance, the nature of the mappings between elements at different levels of representation determines the limits of interpretation one can draw about an association. Moreover, doing so reinforces the intellectual transition from specifying correlates to specifying and testing mechanisms.

Andreas Meyer-Lindenberg, National Institute of Mental Health

Genetic Dissection of the Human Social Brain and Aging -

Implications for the Social Neuroscience and Aging

Review of Own Work

Well-being and survival in primates, including humans, depends critically on social interactions (*1*), and disturbed social behavior is a key component of diseases such as autism, schizophrenia, and anxiety disorders (*2*). Social cognitive neuroscience, a new research field, has started to delineate neural systems for social information processing (*2, 3*); however, little is known about specific neurobiological factors shaping the human social brain. Since many aspects of social function are highly heritable (*4*), we have adopted a genetic approach to identify molecular and systems-level mechanisms of social cognition in humans.

Perhaps the most striking genetic variant of human social behavior is Williams syndrome (WS), caused by hemizygous microdeletion of ~25 genes on chromosome 7 (*5*). People with WS are socially fearless, eagerly interacting even with complete strangers, and show high empathy (*6*). This remarkable hypersociability is coupled with increased non-social anxiety (*7*), suggesting dysregulation of the amygdala, and a critical hub for fear signaling which monitors environmental danger (*8*). We studied the neural basis of genetic hypersociability with functional neuroimaging (*9*) during viewing of socially relevant (angry and fearful faces) and socially less relevant fearful pictures (dangerous scenes not showing humans). Mirroring the behavior profile, amygdala activation in participants with WS, relative to matched normal controls, was reduced for threatening faces, but increased for threatening scenes. This indicated a dissociable neural substrate for social and non-social fear, in agreement with recent findings in nonhuman primates (*10*). What circuit mediated this abnormal amygdala activation? We found altered activation in WS in a network of three prefrontal brain areas: dorsolateral, cingulate, and orbitofrontal cortex. Two of these, orbitofrontal and cingulate cortices, were functionally linked to amygdala in healthy controls, as predicted by normal neuroanatomy (*11*). In WS, orbitofrontal cortex, which we had previously shown to be structurally abnormal (*12*), did not show activation or functional linkage, suggesting orbitofrontal pathology as the proximate cause of hypersociability. More generally, these results identify multiple layers of amygdala control during social processing under genetic influence in humans. These circuits, identified through the rare, but pronounced genetic effects on the social brain in WS, now provided a basis to study common genetic variants affecting aspects of complex social behavior in healthy humans, where each individual gene contribution is expected to be small. Using multimodal structural functional neuroimaging methods in large genotyped groups of healthy volunteers (*13, 14*), we aimed to identify brain systems mediating these subtle genetic effects in order to link cellular and molecular neurobiology to the behavioral level, and to further dissociate systems-level mechanisms based on their underlying genetic architecture (*15*).

One such variant is a functional 5'-promoter polymorphism of the serotonin transporter (5-HTTLPR) gene. Human carriers of the short allele form have increased anxiety-related personality traits (*16*) and elevated risk for depression but only when exposed to environmental adversity (*13*). A previous study found increased amygdala reactivity in carriers of the risk allele (*17*), providing a neural correlate for elevated anxiety but leaving open the question on how this dysregulated amygdala response arises. We set out to map neural circuits that might be responsible (*18*). Analysis of structural neuroimages showed reduced volume in short allele carriers in the cingulate, one of the two key regulatory areas highlighted in our WS study (*9*). Functional imaging confirmed that the cingulate was tightly coupled to amygdala as a feedback circuit implicated in the extinction of negative affect (*19*). Communication within this circuit was strongly modulated by genotype: coupling of amygdala activity with subgenual cingulate was selectively reduced in short allele carriers. Although previous attempts to link neural activation to personality had failed (*17*), we found that the cingulate-amygdala linkage predicted almost 30 percent of variance in temperamental anxiety. These results suggest that psychiatric risk associated with 5-HTTLPR is mediated by reduced connectivity in a circuit for fear extinction and provide a plausible neural mechanism for the striking gene by environment interaction observed epidemiologically (*13*), since fearful associations arising in the context of adversity may persist if extinction is compromised.

Another common genetic variant associated with complex behavior is found in *MAO-A*, encoding a key enzyme for the catabolism of serotonin during neurodevelopment. Several lines of evidence link this gene to trait impulsivity and violence in humans and animals (*20*), and a low activity variant (*MAOA-L)* predicted violent offenses in males who were maltreated as children (*14*). Investigating neural systems associated with this variation (*21*), we found, very similarly to 5-HTTLPR, an impact on structure and function of amygdala and cingulate cortex, indicating a shared mechanism of emotional regulation under serotonergic control. However, *MAO-A* also affected structure and activation of caudal regions of the cingulate associated with cognitive control, as well as orbitofrontal cortex, possibly reflecting broader metabolic effects of MAO-A (*22*) and suggesting that propensity for violence may require breakdown of several neural social regulatory processes.

If the delineated circuits are critical for human sociality, they should respond to molecules mediating prosocial behaviors. In non-human mammals, the neuropeptide oxytocin, dubbed the "love hormone," is a key effector of attachment and social recognition (*3*). Oxytocin effects in humans were recently demonstrated by a behavioral study showing selectively increased trust after hormone administration (*23*). Since this suggested once again involvement of the amygdala, which is linked to trust (*24*)—presumably because of its role in danger monitoring—and highly expresses oxytocin receptors (*25*), we studied amygdala circuitry after double-blind crossover intranasal application of placebo or oxytocin (*26*). Oxytocin potently reduced amygdala activation and decreased coupling to brainstem regions implicated in autonomic and behavioral manifestations of fear, indicating a neural mechanism for the effects of oxytocin in social cognition in human brain and providing a potential therapeutic approach to social anxiety currently being tested in social phobia and autism, where amygdala hyperactivation in the context of gaze fixation has been reported (*27*). Based on these results, we are currently

examining neural effects of genetic variants, previously associated with autism (*28, 29*), in the receptors for oxytocin and its sister neuropeptide vasopressin, to further characterize prosocial neural mechanisms and continue our genetic dissection of the human social brain.

Implications for the Social Neuroscience of Aging

A relevant finding from our own research in social neuroscience, summarized above, is the delineation of neural mechanisms underlying gene by environment (GxE) interactions relevant to social behavior (*19, 21*), highlighting circuits for prefrontal regulation of limbic structures by prefrontal cortex. Similar findings have been reported by other groups (*30, 31*). Importantly, Canli, Lesch and coworkers have recently shown directly that 5-HTTLPR genotype effects in these circuits are modulated by history of environmental stressors (*32*). Although all of these studies are cross-sectional and have largely been performed in young adults, we believe, echoing the contention of Caspi and Moffitt, that investigation of these mechanisms has clear implications across the lifespan trajectory (*33*). Further research requires longitudinal studies that are designed to ascertain G and E factors comprehensively and in our view should include characterization of neural mechanisms implicated by genetic variation as impacted by environmental stressors. I expect that these studies will benefit from newly emerging candidates from whole genome association studies that go beyond the current, comparatively narrow list of genes investigated for social behavior. An illuminating example of how such research for a complex trait combining whole genome association in pooled samples with neuroimaging could proceed is given by the recent identification of the KIBRA gene involved in long-term memory and hippocampal function (*34*). Given the genetic complexity underlying social behavior and associated psychiatric conditions, study sizes for these longitudinal studies are expected to be large and funding initiatives such as the Genes and Environment Initiative as well as data sharing by consortia (as for example for the Framingham study) will be relevant for success. In addition to these large-scale, but necessary, studies, further cross-sectional work in imaging genetics and social cognitive neuroscience in aged populations should establish the transferability of previously obtained results as well as investigate age-specific or at least predominant stressors, such as loss. Given that the major mechanisms uncovered so far concern prefrontal regulation, and prefrontal cortex is an important site for neural change in aging, specific attention should be paid to this region and its connectivity. Interestingly, a recent study has suggested the medial prefrontal regulatory activity may in fact be improved in the aged (*35*), suggesting a potential asset that should be investigated further for genetic concomitants. An important further perspective that needs to be explored more is in the domain of neural mechanisms linked to genetic risk for neural aging, in analogy to research on ApoE4 and risk for cognitive decline (*36*), in the social domain. For example, preliminary data from our group (Pezawas, Meyer-Lindenberg, Mattay and Weinberger, unpublished) strongly suggest age-dependent effects of 5-HTTLPR on key structures for memory and social cognition. Conversely, as neurons decay and experience accumulates over a lifetime, neural mechanisms of plasticity, which are extensively studied in the young, may be differently challenged and important in the aged, and neural mechanisms linked to variants in genes such as BDNF (*37, 38*) and other neurotrophins may be important modulators of this process (*39*). Finally, an important perspective will be epistatic interactions in neural circuits relevant for social cognition, predicted to be a key phenomenon in complex genetics (*40*) and recently observed in neural circuits linking amygdala to cingulate (*39*).

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C. Sue Carter, University of Illinois at Chicago

Sociality, Neuropeptides and Health

Impediments and obstacles to progress and missing information

1. **Lack of understanding of protective systems**. It is critical to identify the physiological, and especially the neural, substrates through which sociality impacts on various systems, such as the hypothalamic-pituitary-adrenal (HPA) axis and immune system. Although the processes responsible for disease are widely studied, those underlying wellness and longevity remain poorly identified. In this context, we need a better understanding of the natural systems necessary for protection and healing.

2. **Individual differences.** Largely missing from our current understanding of these systems is an understanding of individual differences, which are the result of genetic and epigenetic influences. Some components of known protective systems, such as the receptors for neuropeptides, including vasopressin and oxytocin, as well as the better-known components of the HPA axis, such as glucocorticoid receptors, are logical targets for this work. Many other systems remain to be identified. Epigenetic changes are important since they can be influenced by experience, and epigenetic processes, depending on mechanisms such as gene methylation or silencing, also may be reversible.

3. **Methodological weaknesses.** Appropriate methods for measuring social and neural processes systems in humans are needed. Not all measures are of equal value, and the usefulness of "biomarkers" needs further evaluation. Current methods often lack sensitivity and specificity. Many behavioral studies rely on self-report. Contemporary tools, such as neural imaging, do not have the necessary sensitivity to resolve tissue specific changes, and generally do not elucidate neural circuits (but see Kirsch, et al., 2005). Methods for measuring brain chemistry are invasive and can change the processes that they are measuring. Noninvasive methods, such as sensitive methods for measuring hormones in saliva, offer promise (Carter, et al., 2007).

4. **Medications and drug interactions.** Feedback systems are critical for health, and can be blocked or damaged by pharmacological manipulations. It is critical to understand the effects of medications, such as those used to manipulate blood pressure or cholesterol, on the basic biological systems involved in emotion and social behavior. In addition, many people, especially the elderly, take multiple drugs. However, drug interactions are rarely studied and poorly understood.

Background and some pivotal findings in social neuroscience.

Social behaviors and social bonds rely on neural substrates that are shared with other forms of emotion and also with the maintenance of good health. Health and wellness require more than the simple absence of illness. Active neurobiological systems are responsible for human health and longevity. Also critical to human health are reciprocal social bonds and attachments. There is considerable evidence for the health benefits of perceived social support. Studies of the neurobiological basis of social behavior also help us understand the deeper biological substrates

responsible for the health benefits of sociality. The same physiological processes that regulate social bonding also may reduce reactivity to various stressors and concurrently facilitate health. These may be of particular importance as protective or vulnerability factors in aging.

Knowledge of the evolution of social behaviors helps us understand their proximate causes.

It has recently been argued that among the major driving processes in species evolution, in addition to mutation and natural selection, is "natural cooperation" (Nowak, 2006). The power of cooperation is particularly apparent in highly social rodents, and in turn these models have been useful for describing the physiological mechanisms through which social behavior modulates health and protects against the "stress of life."

The emotional core of the mammalian nervous system evolved long before modern cognition and depends heavily on archaic brainstem structures (Porges, 2007). However, because the brain stem is conserved, it is possible to use animal models in the analysis of the neurobiological basis of social behavior and its benefits, especially in the context of stressful experiences. Studies of socially monogamous versus nonmonogamous species have provided new insights into the genetic and neuroendocrine basis of social behavior. Prairie voles are small rodents that share with humans the traits of social monogamy (Carter, et al., 1995). Prairie voles have the capacity to form social bonds and develop extended families. Neural systems underlying relationships and emotions are based on ancient biological substrates, including brainstem-based processes that also regulate the autonomic, and especially the parasympathetic, nervous system (Porges, 2007). Recently we have found that prairie voles also have a human-like autonomic nervous system, with high levels of parasympathetic activity (Grippo, et al., 2007), which may allow this species to be used as a model for understanding the social and neuroendocrine control of parasympathetic function.

Studies of social bonding in prairie voles have been especially helpful to our understanding of the behavioral, neuroendocrine and autonomic effects of two sexually dimorphic brain hormones: oxytocin and vasopressin (reviewed Carter, 1998; 2003; 2007).
Oxytocin and vasopressin are neuropeptides with crucial roles in defining what it means to be a mammal (Carter and Altemus, 1997). The presence of mammary glands is the taxonomic defining feature of Mammalia. Oxytocin probably played a pivotal role in the evolution of mammals including humans, by permitting the birth process, protecting the infant (Tyzio, et al., 2006), and also by facilitating lactation, thus allowing postnatal cortical-intellectual development in young dependent on their mother as a source of both food and care-giving.

Oxytocin and vasopressin are synthesized in and are particularly abundant in the hypothalamus, but may reach distant receptors including those in the cortex and lower brain stem areas responsible for autonomic functions, thus helping to orchestrate behavioral and emotional responses. Oxytocin also sits at the center of a neuroendocrine network that coordinates social behaviors and concurrent response to various stressors, generally acting to reduce reactivity to stressors. Oxytocin tends to decrease fear and anxiety, and increase tolerance for stressful stimuli (Kirsch, et al., 2005). Oxytocin may even protect the vulnerable mammalian nervous system from regressing into the primitive states of lower brainstem dominance (such as the "reptile-like" freezing pattern with an associated shutdown of higher neural processes), that mammals–with a

need for high levels of oxygen–are designed to avoid (Porges, 2007). At the same time, oxytocin may encourage various forms of sociality and even "trust" (Kosfeld, et al., 2005). Oxytocin and vasopressin have the capacity to move through the brain by diffusion (rather than acting only across a synapse), and thus can have pervasive effects on the central nervous system (Landgraf and Neumann, 2004). Oxytocin is unique in having only one receptor and in using the same receptor for many functions, thus allowing coordinated effects on behavior and physiology. However, the oxytocin and vasopressin molecules also affect each other's receptors, often – but not always - with effects that are in opposite directions

Vasopressin also plays a role in social behaviors and has adaptive functions in the face of behavioral and physiological stressors. Vasopressin is structurally similar to oxytocin and probably evolved from a common ancestral molecule; however, the hypothalamic synthesis of vasopressin is androgen-dependent, and this molecular may be of particular importance in males (DeVries and Villalba, 1997; Carter, 2007). Vasopressin, acting centrally (in areas including the extended amygdala and lateral septum), may elevate vigilance and defensiveness, possibly serving in some cases as an antagonist to the effects of oxytocin. Working together, these ancient molecules may allow sexual-dimorphic responses to emotionally contradictory tasks, such as forming social bonds, and at the same time permit rapid behavioral and autonomic reactions in the face of threats.

Prairie voles are highly sensitive to their social environment and may offer a model for understanding the causes and consequences of social experiences. For example, prolonged isolation is associated with increases in CRF, corticosterone, vasopressin and in some cases increases in oxytocin (Rusico, et al., 2007; Grippo, et al., in review), which in this context again may be protective. Isolation also may produce reductions in neurogenesis (Ruscio, et al., in review), as well as increases in sympathetic arousal as measured by heart rate and decreases in parasympathetic activity, especially in the face of stressors (Grippo, et al., unpublished). Social experiences, including those associated with pair bonding and parental behavior, can in some cases have opposite effects including reductions in "stress" hormones, increases in "trust" (Kosfeld, et al., 2005) and increases in cellular proliferation. It is of interest to note that prairie voles have an exceptionally long lifespan – perhaps 2-3 times longer than most laboratory rodents.

Epigenetics holds a second clue to the origins of species and gender differences in sociality.

A deep understanding of behaviors, such as those that characterize mammalian sociality and reproduction requires awareness of experiential factors that lead to the development of the adult nervous system (Weaver, et al., 2004). Of particular interest is the fact that males and females may respond differently to stressors, especially during early development. Aging also affects females and males differently, and it is possible that neuropeptides such as vasopressin and oxytocin are responsible in part for sex differences in aging, especially with reference to gender differences in the protective effects of social support.

Sex differences are thought to be due to interactions between genetics and the hormonal and experiential history of the individual. It was originally believed that most sex differences were due to the presence of male sex hormones, including testosterone in males and the absence of

this hormone in females. As we have now come to expect, research in monogamous mammals did NOT follow the pattern predicted from research in nonmonogamous species, such as rats. Male versus female prairie voles responded in very different ways to both early social experiences and exposure to hormones (reviewed Carter, 2003; 2007). Males seem especially vulnerable to negative effects of early experiences, possibly explaining the increased sensitivity of males to various developmental disorders (Teicher, et al., 2003), and perhaps contributing to the eventual sex difference in longevity. However, depression–which is a major issue in aging–is roughly twice as common in women. It is likely that there is an important role for oxytocin and vasopressin in depression as well as anxiety, and the mechanisms for this need to be understood. These and other sex differences in the brain suggest a new understanding of age-related differences between males and females.

Particularly intriguing is the fact that stressful experiences and specific "stress" hormones seem to have very different effects on males and females (DeVries, et al., 1996). When male prairie voles were exposed to a brief stressor (such as three minutes of swimming) they quickly formed new pair bonds, but when females were treated in the same manner they seem unable to form a pair bond, and in some cases even avoided a familiar mate. Interestingly, stressed females, though unwilling to form pair bonds with males, did pair with other females. Male and female prairie voles form pair bonds under different conditions and different endocrine mechanisms permit or facilitate pair bonding in males and females. Social psychologists have used these findings to argue that sex differences in the reaction to stressful experience in humans may share mechanisms with those found in prairie voles (Taylor, et al., 2000; 2006).

Social bonds are powerful medicine … but why? Definitions of pair bonds in humans and other animals use apparently similar emotional and social behaviors: positive social behaviors, social selectivity rather than promiscuity, mate guarding or "jealousy,"and stress or anxiety in the absence of the loved one. However, the object of a social bond is not always a member of the opposite sex. It can be a child, pet, or even an inanimate object. Ideally social interactions are reciprocal, but this is not always the case. However, it is the feeling, emotions and desires–the internal (emotional-visceral) state of the individual that underlies the effects of social experiences. Social support and trust appear to rely on a concoction of naturally occurring chemicals with broad actions including effects on the autonomic nervous system and immune system.

Most neurobiological research on social behavior was begun in the context of reproduction. However, the advantages of social living extend well beyond reproduction to the very roots of longevity and survival. Humans, like other social species need social bonds. Traditional societies typically were centered on groups and often on extended families (Hrdy, 2005). Social bonds were virtually guaranteed by prolonged proximity. Mobility and modern economics quickly changed cultures, but human physiology is not so readily changed. By examining the physiology of social bonding, we may gain insight into another observation that has emerged from modern medical research. Isolation has powerful effects. A growing body of evidence suggests that individuals with a perceived sense of social support are more likely to avoid or survive illness and have longer lives than otherwise similar people who live alone or who experience a sense of loneliness (Uchino, et al., 1996; Singer and Ryff, 2001; Cacioppo, et al., 2006).

Modern medicine has sophisticated tools for discerning what makes us sick. But health is not solely the absence of illness. We remain exceptionally ignorant regarding the source of the good health that most humans enjoy for much of their lives. We do know that separation or grief can have devastating consequences for emotional and physical health. Knowledge of the scientific basis of sociality and social bonds allows a glimpse into mechanisms through which social relationships help to protect the human body.

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Shelley E. Taylor, University of California, Los Angeles

Social Support Needs of Older Adults

Our research explores the social support needs of older adults and addresses the mechanisms that underlie responses to these needs, especially gaps in social support. Because social support is a consistently strong predictor of morbidity and mortality, understanding its dimensions and biological underpinnings in older populations is of paramount importance. We adopt a research model that integrates the sociodemographic, genetic, neural, endocrine and psychological levels of analysis (see Figure 1).

Gender Differences in Social Support Needs and Mechanisms

Our work has identified somewhat different social support needs for older men and women. Whereas older men derive their social support heavily from their spouses and thus, are especially vulnerable to bereavement, women derive their social support from a broader array of sources, including children, friends, relatives, and spouse, and thus, are especially vulnerable to stressors that may isolate them from their social networks, such as disability or geographic relocation (Gurung, Taylor, and Seeman, 2003). In addition, older women (but not men) report that their spouses are a major source of their social support problems (criticism, cold behavior) (Gurung et al., 2003). Social support is an especially important resource for managing stress, and so its dimensions can inform the problems facing aging and elderly adults.

We have proposed that women's social support seeking is characterized by a "tend-and-befriend" style of responding to stress, which is oxytocin-based and that links social support needs and responses to the caregiving/attachment system. Biological mechanisms underlying men's social support needs are not yet known, although fight-or-flight appears to better characterize men's responses to stress than women's (i.e., men are more likely to respond to stress through withdrawal, substance abuse, or aggression, whereas women are more likely to respond to stress by seeking social support).

A growing animal and human literature on affiliative behavior suggests that an oxytocin-based mechanism may, in fact, be implicated in older women's responses to social support gaps and their reactions to concomitant stressors. In a laboratory study, we found that oxytocin levels were elevated in older women who reported gaps in their social support networks, including loss of mother or pet, reduced contact with friends and difficulties with spouse (Taylor, Gonzaga, Klein, Hu, Greendale, and Seeman, 2006). Two independent laboratories have now replicated these findings. Based in part on this evidence, we suggest that elevations in oxytocin may signal gaps in social support and act as an impetus to seek out support from other sources (see Figure 2). In addition, evidence from our lab suggests that this mechanism is not operative among men. We also found that women with elevated oxytocin levels have elevated cortisol responses to laboratory stressors (the Trier Social Stress Task) (Taylor et al., 2006).

Cultural Differences in Social Support Use

The population of older adults in the U.S. is not only growing rapidly, but rapidly developing a significantly different demographic composition from previous generations, with larger numbers of African-Americans, Asians, and Hispanics. We have examined cultural differences in support seeking behavior and consistently found that Asians/Asian-Americans are less likely to seek out and are actually stressed by the receipt of social support, especially emotional support, relative to European Americans (e.g., Taylor, Sherman, Kim, Jarcho, Takagi, and Dunagan, 2004). In a recent laboratory investigation, we found that Asians/Asian Americans responded to a manipulation of explicit social support with increased distress and higher cortisol responses to stress, whereas European Americans' distress and cortisol levels were lower when they were exposed to an explicit social support manipulation (Taylor, Welch, Kim, and Sherman, in press). Findings such as these underscore a need for multicultural investigations.

Toward the Future

Social conditions, such as divorce, bereavement, and geographic mobility, mean that many older adults will have social support gaps that need to be addressed. We believe that focused multiethnic studies with older adults that examine the constellation of sociodemographic, psychological, social, and biological pathways that influence social support needs and effects will provide valuable information for addressing these issues. Many of the conceptual and methodological advances needed to enlighten these issues have already been made. What has been lacking are studies that integrate across these multiple levels of analysis.

Gaps in our current knowledge include some of the following issues. First, at the sociodemographic level, we need more information about the trajectories of aging and trajectories of social support within diverse ethnic groups. This information will be relevant not only for accurate projections of health care needs, but also for planning culturally sensitive interventions. Important research questions remain unresolved. For example, does the Hispanic paradox (i.e., the relatively good health and low mortality of Hispanics, despite their frequently disadvantaged status) hold up in older adults, and if so why? Do Asians/Asian-Americans experience health risks due to their unwillingness to seek and use social support? How does acculturation affect these patterns? These are examples of the kind of questions that could be answered by a better understanding of the psychosocial needs of older adults in different cultural groups.

At the lifespan level, what are the genetic and early environmental antecedents of the ability to attract and effectively use social support? Our work has implicated the serotonin transporter gene (Taylor, Way, Welch, Hilmert, Lehman, and Eisenberger, 2006) and early family environment (Taylor, Eisenberger, Saxbe, Lehman, and Lieberman, 2006) in these processes. Although this work is still at early stages, our current findings suggest that ethnic differences in allelic variation in 5-HTTLPR (e.g., Asians are disproportionately s/s) may underlie some of the cultural differences we have seen in our social support research. (Among other implications, findings such as these suggest that genetic and neural investigations need to incorporate macro-level variables such as ethnicity).

Other critical questions include assessing whether social support trajectories established early in life affect social support and health into old age, as appears to be likely. In what form are social support benefits from early life "stored" and by what pathways does early social support continue to influence health in old age? How do these pathways lead to or interact with health-related vulnerabilities, such as metabolic syndrome (Lehman, Taylor, Kiefe, and Seeman, 2005) and elevated C-reactive protein (Taylor, Lehman, Kiefe, and Seeman, 2006) to affect specific health outcomes?

Research on the biological mechanisms associated with social support seeking and health consequences of social support continues to be needed. Close cooperation between animal and human researchers who examine caregiving/attachment/ social support systems will foster the development of non-invasive human counterparts that elucidate mechanisms that may be comparable to those seen in animal models. For example, experimental research manipulating oxytocin levels has been hampered until recently by restrictions on experimental manipulations with humans, although this particular technical problem now appears to be solved. But many questions regarding underlying mechanisms remain. For example, why is elevated plasma oxytocin associated with greater autonomic and cortisol responses to stress, whereas exogenously administered oxytocin is associated with lower stress responses, relative to control conditions? In what ways are dopamine pathways implicated in the mental and physical health effects of social support? These are examples of issues that cooperation between animal and human researchers may elucidate.

Conclusion

Our overarching recommendation is for multiethnic studies of older men and women's social support needs that integrate the sociodemographic, psychological, genetic, neural, and endocrine levels of analysis.

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Note: This list includes only our own work on these issues.

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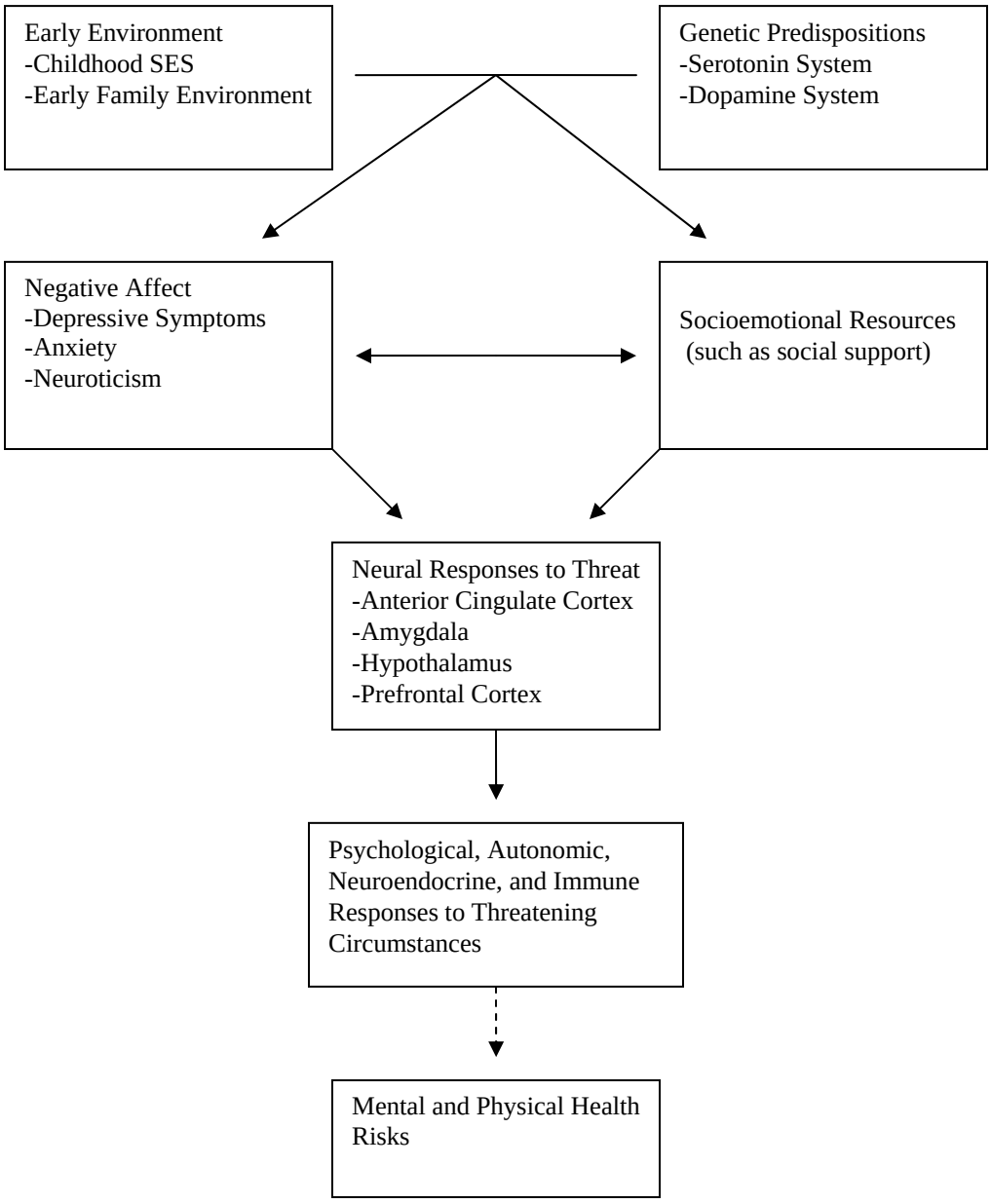

Figure 1. Origins and Effects of Socioemotional Resources.

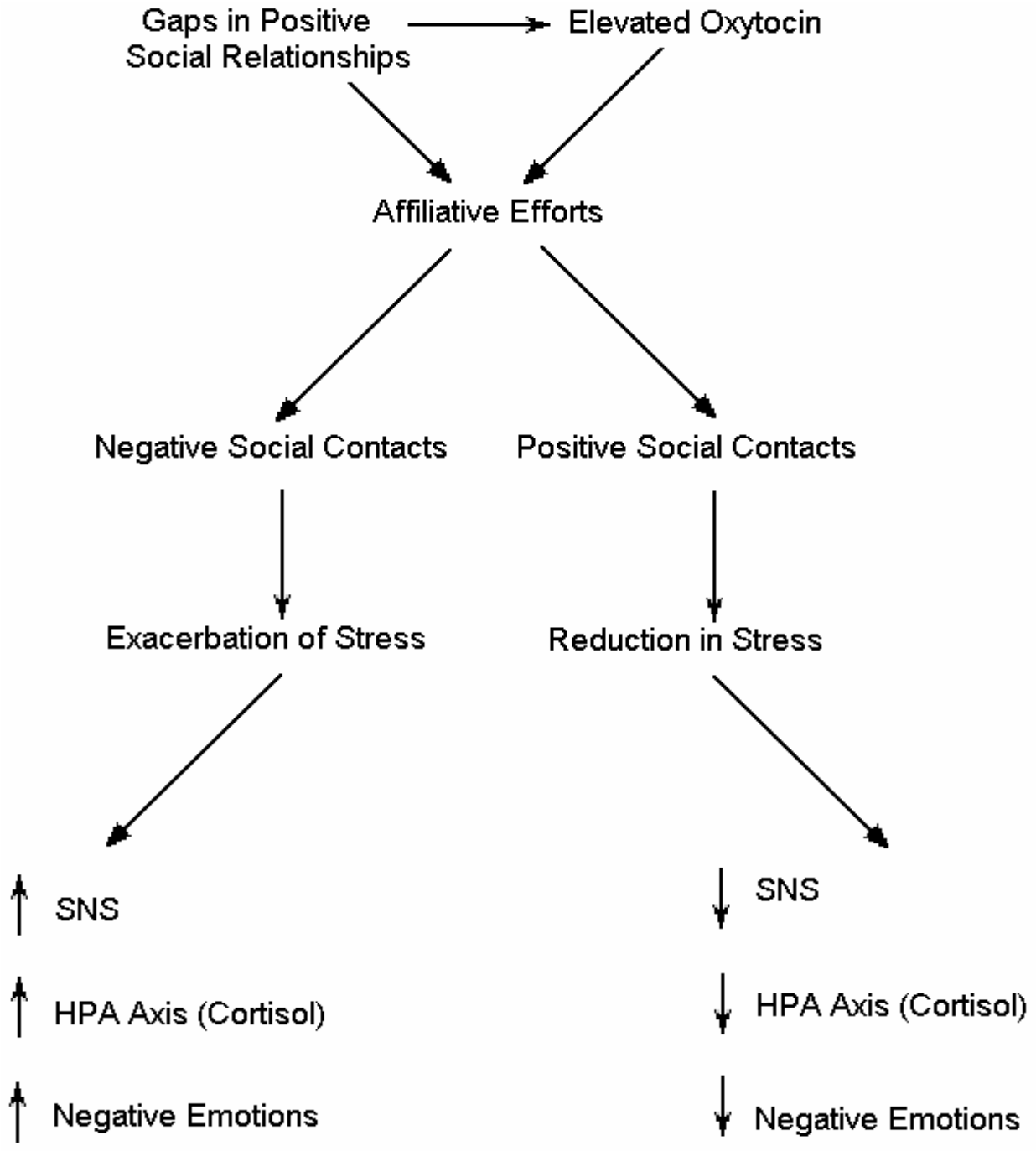

Figure 2. A Model of Affiliative Responses to Stress.

Ralph Adolphs, California Institute of Technology

1) What do you perceive to be the one or two pivotal findings from your own work or work in your field that have advanced our understanding of the neurobiological or genetic underpinnings of social behaviors? Where do you see this line of research developing from here? How can it shed light on lifespan developmental issues or issues specific to aging?

I suppose the role of the prefrontal cortex in social behavior, emotion, regulation, and decision-making. The relevance to aging would be the possibly disproportionate atrophy and consequent dysfunction of the prefrontal cortex in aging, with consequences especially for decision-making, perhaps especially financial decision-making and the implications that has for independent living.

An important question that, to my knowledge, has not received that much attention is how future planning and "mental time travel" into the future change over the lifespan. Memory changes have been looked at a lot, but healthy functioning may depend more on the ability to project oneself into the future, and to plan and prepare for future events, than on the ability to reminisce about the past. One could argue that memory for the past is really only useful insofar as it is incorporated into planning for the future. There has been a recent spate of paper on prospection, future "mental time travel", including fMRI studies (e.g., review by Buckner and Carroll, TICS 2006). It would seem that this domain is ripe for investigating in aging.

2) How can we better specify the neurobiological and genetic mechanisms and pathways linking social behaviors and environments to aging-relevant outcomes? What are the conceptual and methodological advances required?

Conceptually, we need a better inventory of what the social behaviors and processes are. We also need better characterization of the social environment, which is variable, complex, and to some extent created by the subject. We also need more sophisticated accounts of how genes and environment interact in generating dysfunctional behavior. The recent paper by Canli et al. (PNAS, Oct. 2006) is a good example of the kinds of studies needed. We also need to maintain a focus on individual differences.

Methodologically, there are several challenges:

--validating animal models of human aging. Given the usually large differences in total lifespan, this is a challenge.

--translating laboratory tasks/stimuli to the real world. Aside from the general challenge of ecological validity, this may be particularly relevant to aging since it is often more difficult to test subjects in the lab and to eliminate possible confounds due to the artificial nature of stimuli and task demands. Tasks are sometimes taken from, and piloted on, younger people (e.g., students), and the extension to applicability in older people may not work.

--imaging connectivity. Both structural and functional connectivity are likely to be changing in important ways across the lifespan, and the technology is there to investigate these in some detail now.

3) What are the current pitfalls and obstacles to progress? Where are the gaps in our current knowledge that would be logical next steps to try to approach?

It would seem to me that one pitfall or difficulty is in distinguishing healthy aging from disease associated with aging. Are neurological and psychological changes seen in older people due to normal aging, or preludes to, or manifestations already of, some specific pathological process? To the extent that features seen in healthy aging are distinct from those seen in known pathologies, this seems surmountable; to the extent that they overlap, it may be very difficult to distinguish them.

James R. Carey, University of California, Davis

Social Neuroscience of Aging: Biodemographic Perspectives

INTRODUCTION

The purpose of this report[1] is to outline what I consider to be promising new areas of biodemographic research on the *social neuroscience of aging*. As with most areas of science, biodemography and social neuroscience of aging are impelled by technical and conceptual advances and a guiding vision. Without the former the road ahead is blocked and without the latter there is no road ahead[2].

BACKGROUND

Biodemography is unique in two respects[3]. *First*, it is one of a small number of subdisciplines arising from the social sciences that has embraced biology (e.g. evolutionary psychology; neuroeconomics). However, unlike the others which focus more narrowly on biological sub-areas (neurology) or concepts (evolution), biodemography has no explicit biological boundaries making it not only a more all-encompassing interdisciplinary concept, but also one that has deeper biological roots. *Second*, the hierarchical organizations that are inherent to both biology (cell, organ, individual) and demography (individual, cohort, population) form a chain in which the *individual* serves as the link between the lower mechanistic levels and the higher functional levels. Biodemography is thus ideally suited to complement, engage and inform research on human aging through theory building using mathematical and statistical modeling, hypothesis testing using experimental methods, and coherence-seeking using genetics and evolutionary concepts. In short, biodemography serves as both a looking glass through which researchers in the social and biological sciences can see each other's worlds, and a Rosetta stone for inter-disciplinary communication and cooperation. Research in the biological-demographic hybrid-zone has been neglected due partly to the conservatism that is inherent to science, and partly to differences between the two paradigms (and thus in the questions asked).

Broadly speaking, biodemographers are well positioned to engage in neuroscience of aging-related research because no other groups of researchers focus on the individual in the same way or to the same degree. This is important because the individual is the quintessence of biological relevance since all discoveries at lower levels of biological organization (neurological; genetics) must ultimately be tested and understood at this level. Although there multiple points of engagement, behavioral studies related to aging in social species will likely be one of the key

[1] Report for Social Neuroscience of Aging exploratory workshop, February 7-8, 2007, Washington, D.C. Adapted from an earlier 'Opinion Report' on the future of Biodemography solicited by Behavioral and Social Research (BSR) Program, National Institute on Aging in response to recommendation from National Advisory Council on Aging (NACA), BRS Report, May 2004.

[2] Concept from: Woese CR. (2004) A new biology for a new century. *Microbiology and molecular biology reviews* 68: 173-186.

[3] Overview chapter contained in: Carey JR, Vaupel JW (2005) Biodemography; pp 625-658 in Poston D, Micklin M (eds): *Handbook of Population*. New York, Kluwer Academic/Plenum Publishers.

concepts for interdisciplinary research including life course behavioral 'microanalysis' which, in turn can be linked to neurological and behavioral genetic mechanisms as well as behavioral determinants of mortality in social contexts.

RESEARCH OPPORTUNITIES

Biodemography of Sociality

The *biodemography of sociality* is concerned with ecological, behavioral and evolutionary determinants of cooperative behavior including the biological and social value of cooperation and caregiving and theories based on genetic (i.e., inclusive fitness/selfish gene), mutual cooperation (i.e., reciprocal altruism) and group selection (e.g., unrelated individuals help in defense of group) arguments. Example research topics include:

1. Behavioral genetics of sociality. It is now possible to manipulate social environment and study effects on gene expression, protein synthesis, and hormone titres. For example, honey bees can be artificially inseminated bred for specific life history components, have a completed genome sequence and soon will have a complete microarray of all genes.
2. Linkage of non-human and human models of sociality. The genetic, molecular, cellular, neurological and organismal processes in non-human social animals that underlie demographic patterns can be mapped out and manipulated, and resulting changes can be monitored as inter-individual dynamics and as demographic trajectories at the level of societies. Like humans, social insects have clearly defined "occupations" that can be studied in the context of their effects on sociality and life span[4] (e.g., complex social behavior linked to reproductive status which, in turn, is linked to foraging behavior and ultimately to differential mortality and aging).
3. Brain aging in social insects. Physiological aging in the brain of honey bee workers is better explained by social role than chronological age. Age-dependent learning deficits are a function of social role, not of chronological age per se (cognitive performance declined with age in foragers, but not in same-aged nurse bees, ms in preparation). Learning performance of bees can improve when they revert from foraging to nursing. Does the link between social task performance and neuronal damage stem from (1) social effects on individual activity level, so bees and their brains "wear out" at different rates according to different social task; or (2) the physiological process of senescence is controlled by social signals, so bees have a regulatory physiology of neuronal aging that responds to the social environment itself. In many animals, including humans, both activity level (inactiveness, exercise, harsh physical labor) and physiological or social factors (such as stress or loneliness), can affect the process of aging. However, the honey bee is the only genetic model organism in which similar factors appear to be more important for rates of senescence than age itself.

Biodemography of Behavior and Behavioral Genetics

Because demography is deeply imbedded in the fields of evolution, ecology and behavior, a framework for biodemographic research emerges from each area by considering the

[4] Amdam GV et al (2006) Complex social behaviour derived from maternal reproductive traits. Nature *439:*76-78.

demographic components. Thus *evolutionary biodemography* is concerned with the demographic changes that occur in organisms over time and with how these evolved forms are better adapted for coping with the demands of their environment; *behavioral biodemography* is concerned with how ecological and evolutionary processes explain the occurrence and adaptive significance of behavior patterns and the use of behavioral processes to predict demographic patterns, and *evolutionary biodemography of development* is concerned with questions related to how genotype and phenotype interact over generational and gestational time spans. The concept is important to biodemography because it is fundamental to an understanding of a number of human diseases (Alzheimer's disease; multiple sclerosis; diabetes; CVD; Down's syndrome) and involves embryonic development, the differentiation of adult cell types, regeneration, and aging. Example research topics include:

1. Biodemography of behavior. Relevant questions include: Can old individuals learn to find hiding places that they can get to even though they lack the motor abilities of younger flies? How is observable behavior influenced by interaction of gene expression and conditions prevailing as individuals mature? Existing paradigm of ethology needs to incorporate concepts of *degenerative behavior*, *behavioral gerontology* and the *behavioral ecology of the life course*[5]. Virtually nothing is known about the co-evolution of longevity and sociality including the evolution of social behavior.
2. Aging in evolutionarily relevant (wild) environments. Neurological and behavioral studies involving individuals in their natural habitat are important, not only because they are situated in an evolutionarily relevant environment, but because of the neurological and behavioral effects of *environmental enrichment*—exposure to a combination of complex inanimate and social stimulation factors. Unlike individuals maintained in an impoverished laboratory environment, exposure to the wild (enriched) environment may have profound and robust effects on the brain and the behavior of individuals[6].
3. Neuroscience, genetics and family structure. It is estimated that three-quarters of cognitive abilities are attributable to genetics and family environment. Thus, human capital may be determined by inheritable factors and family size. Genetic testing for susceptibility for cancer and other common conditions results in a new phase in health and illness—the pre-symptomatic phase. The use of genetics to test behavioral hypotheses about the adaptive advantage of the organization of lion prides shed new light on kin selection concepts[7].
4. Behavioral ecology of aging in social species. The elderly often exhibit behaviors fundamental to behavioral ecology including[8]: (1) Altruism—selfless behavior performed for the benefit of others such as caregiving, allomothering, group defense and nest care; (2) dominance and leadership—to dominate is to possess priority of access to the necessities of life and reproduction. Understanding the governance of animal societies by dominance hierarchies and how this changes with age provides the fundamental basis for studying the

[5] Including integration of concepts in neuroeconomics, evolutionary psychology, and behavioral genetics.
[6] vanPraag, H., Kempermann, G., and Gage, F.H. (2000) Neural consequences of environmental enrichment. *Nature Reviews Neuroscience*, **1**, 191-198..
[7] O'Brien SJ et al. (2005) Big cat genomics. *Annual Review of Genomics and Human Genetics* 6: 407-429.
[8] Carey, J.R. and Gruenfelder, C.A. (1997). Population biology of the elderly. In *Biodemography of Longevity* (eds K. Wachter and C. Finch), pp. 127-160. National Academy Press, Washington, DC.

behavioral dynamics of social groups; (3) learning and culture—learning is any change of behavior of individuals due to experience and can include self-teaching, imitation, and one-on-one and group exchanges of information. Little is known about the age dynamics and learning in culture in non-human species.

CONCLUSION

Biodemography combines the encapsulatable problems of basic biology (cell, gene, and neuron)[9] with the focus on *parts* and on *mechanisms* with the holistic problems of evolution and the individual with the focus on the *whole* and on *functions.* It is becoming a force for unifying biology and demography, a platform for interdisciplinary research (including neuroscience), a concept for bringing together scholars from different professional cultures, and a theme for inter-institutional support. Biodemography adds value to its respective "parent" disciplines by suggesting new insights and useful perspectives to old problems as well as by generating new ones relevant to both fields. The emerging fields of biodemography and the social neuroscience of aging have the potential to be both complementary and mutually informing because both are concerned with aging and both span the natural and social sciences.

[9] Sapp, J. (2003) Genesis: The Evolution of Biology. Oxford University Press, Oxford

Todd Heatherton, Dartmouth College

Social Neuroscience of Aging

Social neuroscience merges evolutionary theory, experimental social cognition, and neuroscience to elucidate the neural mechanisms that support social behavior. From this perspective, just as there are dedicated brain mechanisms for breathing, walking, and talking, the brain has evolved specialized mechanisms for processing information about the social world, including the ability to know ourselves, to know how others respond to us, and to regulate our actions in order to co-exist with other members of society. The problems that are studied by social neuroscience have been of central interest to psychologists for decades, but the methods and theories that are used reflect recent discoveries in neuroscience. Although in its infancy, there has been rapid progress in identifying the neural basis of many social behaviors. Here I consider how such an approach might be useful for understanding social aspects of aging.

The approach I have taken to understanding the social brain is to use functional neuroimaging. These methods provide researchers with the capacity to study the working brain in action, thus providing a new window for examining previously intractable mental states, such as the experience of self (Macrae, Heatherton, and Kelley, 2004). Indeed, imaging research has identified a number of brain regions that appear to subserve highly specialized social capacities, such as recognition of faces and emotional expressions, theory of mind, social emotions such as empathy, judging trustworthiness and attractiveness, cooperation, and so forth. The gist of these studies is that "people" are given privileged status by the brain as it processes information in the environment (see Mitchell, Heatherton, and Macrae, 2002). Of course, imaging data are only useful to the extent that they are considered in concert with theory, behavioral evidence, and extant knowledge of functional neuroanatomy. In terms of aging, therefore, we can make certain predictions regarding how social cognition changes as people grow older based on the accumulated evidence of anatomical and behavioral changes that are documented in the aging literature.

The theoretical underpinnings of my research program is based on the idea that humans have evolved a fundamental need to belong, which encourages behavior that prevents people from being evicted from their social groups (Bowlby, 1969; Baumeister and Leary, 1995). Humans are social beings who live in groups. According to this perspective, the need for interpersonal attachments is a fundamental motive that has evolved for adaptive purposes. Over the course of human evolution, those who lived with others were more likely to survive and pass along their genes. Adults who were capable of developing long-term committed relationships were more likely to reproduce, and also more likely to have their offspring survive to reproduce. Baumeister and Leary (1995) argued that the need to belong is a basic motive that activates behavior and influences cognition and emotion, and that it leads to ill effects when not satisfied. Indeed, even today not belonging to a group increases a person's risk for a number of adverse consequences, such as illnesses and premature death (see Cacioppo et al., 2006). Interestingly, aging can be considered a relatively recent adaptive problem, in that only recently have people achieved life spans into the 70s, 80s, and beyond. An open question, therefore, is whether social mechanisms that have evolved over time are preserved in aging. Put another way, one might argue that the adaptive challenges associated with group living may differ substantially for older adults, and

that the mechanisms that guide social behavior reflect solutions that evolved for solving challenges that are less relevant to young humans (e.g., mate competition).

Given the fundamental need to belong, my research program examines a social cognition system that monitors for signs of social inclusion/exclusion and alters behavior to forestall rejection (Heatherton and Krendl, in press). Such a system requires four components, each of which is likely to have a discrete neural signature. First, people need self-awareness—to be aware of their behavior so as to gauge it against societal or group norms. Second, people need to understand how others are reacting to their behavior so as to predict how others will respond to them. In other words they need "theory of mind" or the capacity to attribute mental states to others. This implies the need for a third mechanism, which detects threat, especially in complex social situations. Finally, there needs to be a mechanism for resolving discrepancies between self-knowledge and social expectations or norms, thereby motivating behavior to resolve any conflict that exists. It is possible that all of these component processes are affected by human aging. Here I briefly note the relevant neural regions associated with each area, as well as a few ideas about how they might be impacted by aging.

Self-awareness– A series of imaging studies conducted over the past 10 years have indicated that the medial region of the prefrontal cortex (MPFC) plays a vital role in self-awareness (Craik et al., 1999; Heatherton et al., 2006; Johnson et al., 2002; Kelley et al., 2002; Macrae et al., 2004; Moran et al., 2006; Schmitz et al., 2004; Ochsner et al., 2004). This region is more active, for example, when people report on their personality traits, make self-relevant judgments about pictures, or retrieve autobiographical memories of past events. Interestingly, the MPFC has also been identified as part of a “default network,” which also includes the posterior cingulate gyrus and precuneus. This network is most active when the brain is at rest (i.e., not engaged in an overt cognitive task) and deactivates during any cognitive task that directs attention away from self. An abundance of PET and fMRI data suggests that the default network plays a dominant role in self-awareness. Recent studies have shown a reduction in the default network, including MPFC, in early Alzheimer’s disease (Grecius et al., 2004; Wang et al., 2006) and there is an abundance of evidence that the frontal lobes are particularly vulnerable to aging (e.g., Craik and Grady, 2002). Accordingly, understanding the nature of changes in self-awareness during aging, and its attendant neural correlates, appears to be an important approach, especially given recent work on changes in autobiographical memory changes in aging.

Theory of Mind– In addition to recognizing our own mental states, living harmoniously in social groups requires that we are able to accurately interpret the emotional and mental states of others (Heatherton and Krendl, in press). The ability to infer the mental states of others is commonly referred to as mentalizing, or having the capacity for theory of mind (ToM). The rapidly emerging neuroimaging literature on ToM has consistently implicated MPFC as a central component of the neural systems that support mentalizing (Amodio and Frith, 2006; Gallagher and Frith, 2003; Macrae et al., 2004). Interestingly, neuroimaging research has demonstrated that the ability to mentalize relies heavily on similar neural networks engaged in processing self-relevant information, notably MPFC. However, this region of MPFC tends to be more dorsal in ToM studies than in self-references studies, where the activity tends to be more ventral. Although activity in other brain regions has been observed during ToM tasks—notably the superior temporal sulcus (STS), the temporo-parietal junction (TPJ), and less often the

amygdala—dorsal MPFC appears to play a central role in the ability to make mental state attributions about other people. The literature on aging is somewhat controversial with regard to changes in ToM capacity with aging. Although the first paper on this topic found that older adults were comparable to younger adults (Happe et al., 1998), subsequent studies have documented age-related declines in ToM (Maylor et al., 2002; Sullivan and Ruffman, 2004). Other research indicates that they may be age-related differences in interpersonal judgment. Research by Fredda Blanchard-Field's group (see Blanchard-Fields and Horhota, 2006) has shown that older adults make less use of situational information when making interpersonal judgments (unless they are highly motivated). According to some researchers, maintaining social ties and connections may be an important component of healthy aging. Hence, understanding the impact of aging on ToM may have important practical applications.

Detection of Threat– According to my working model, people need to be vigilant for negative social information that indicates the possibility of imminent social exclusion. One candidate brain region is the amygdala, which plays a special role in responding to threatening stimuli (Blanchard and Blanchard, 1972; Feldman Barrett and Wager, 2006; LeDoux, 1996). Affective processing in the amygdala is a hard-wired circuit that has developed over the course of evolution to protect animals from danger. For example, much data support the notion that the amygdala is robustly activated in response to primary biologically relevant stimuli (e.g., faces, odors, tastes, etc.), even when these stimuli remain below the subjects' level of reported awareness (e.g., Morris et al., 1998; Whalen et al., 1998). Researchers have documented considerable evidence that the amygdala plays an important role in understanding facial expressions of emotion, and that damage to the amygdala can interfere with using emotional information in person perception. Interestingly, some evidence suggests that there are age-related declines in decoding emotional expressions (Malatesta et al., 1987). Moreover, according to Carstensen's socioemotional selectivity theory, older adults show a positivity bias and selective attention away from negative stimuli (e.g., Mather and Carstensen, 2003). Indeed, other researchers have documented differential processing of facial cues as a function of age (Keightley et al., 2006) and it appears that older and younger adults recruit different brain regions when processing emotional faces, with older adults showing less amygdala activity (i.e., Gunning-Dixon et al., 2003). More recently, however, Mather and Knight (2006) found that older adults were not impaired in the automatic processing of angry expressions. Thus, many questions remain regarding the motives and abilities of older adults to process social cues. One practical implication for this line of research involves trustworthiness judgments. Older adults are susceptible to scam artists, perhaps in part because they are too trusting. This may be due in part to faulty person perception.

Self-Regulation– When people act in ways that threaten their group inclusion, they should be motivated to alter their behavior to repair social relationships. Self-regulation allows people to alter our behavior, to make plans, choose from alternatives, focus attention on pursuit of goals, inhibit competing thoughts, and regulate social behavior (Baumeister, Heatherton, and Tice, 1994). Neuroscience research indicates that various regions of prefrontal cortex are responsible for the human capacity for self-regulation (Banfield et al., 2004). Age-related changes in the frontal lobes might change self-regulatory capacity. That is, considerable evidence indicates that older adults have difficulty with some executive functions, such as inhibiting irrelevant or distracting information so that they have difficulty attending to relevant stimuli. At the same

time, some evidence indicates that older adults are better than younger adults at some aspects of self-regulation (see the chapter on self-regulation in the NRC report "When I'm 64"). For instance, young people seem better at initiating change but older adults appear to be better able to maintain changes that they make. In the social domain, recent research by von Hippel and colleagues has found that older adults are more likely to say socially inappropriate things, which von Hippel attributes to reduced inhibitory capacity (see von Hippel and Dunlop, 2005). Thus, there are many aspects of self-regulation that may be relevant to understand from an aging perspective.

Using imaging to study social cognition may be able to provide new insights into the effects of the aging brain on social behavior, providing both practical information and basic scientific information regarding the social brain.

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Robert W. Levenson, University of California, Berkeley

1) What do you perceive to be the one or two pivotal findings from your own work or work in your field that have advanced our understanding of the neurobiological or genetic underpinnings of social behaviors? Where do you see this line of research developing from here? How can it shed light on lifespan developmental issues or issues specific to aging?

From my own work, two findings seem particularly relevant (Levenson and Ruef, 1992; Werner, Roberts, Miller, and Levenson, under review). In the earlier study, we found that accurate reading of the emotions of a stranger was associated with a physiological state in which the autonomic responses of the rater mirrored those of the person being rated. This finding suggested that one way we come to know what others are feeling is by having miniature versions of those feelings ourselves, a form of emotional "mimicry" that enables us to "read" our own emotions to know what another person is feeling. Over time, we came to understand that this was only one way that emotions of others can be recognized. There is likely to be a second route, a colder "cognitive" pathway where we recognize emotions in another person based on processing the available cues and comparing them to our own storehouse of knowledge about emotions. One offshoot of this line of work is the possibility that, as we age, we may differentially improve or deteriorate in our abilities to read the emotions of others via one or the other route.

In the more recent study studying patients with frontotemporal lobar degeneration and age-matched controls, we found that the ability to recognize negative emotions being experienced by film characters declined with neural loss in frontal and temporal brain regions. This neural loss, however, was not associated with decrements in emotional reactions to films. This underscores the likelihood that different aspects of emotion are subserved by different neural substrates. In this case, "having" emotions was not affected by neural loss in these particular brain regions; however, "recognizing" emotions was. Given the significant incidence of dementing disorders in late life and the different patterns of neural loss associated with the different dementias, this provides an important opportunity to study the neural substrates of emotion and to understand areas of loss and preservation of emotional functioning in dementia.

2) How can we better specify the neurobiological and genetic mechanisms and pathways linking social behaviors and environments to aging-relevant outcomes? What are the conceptual and methodological advances required?

3) What are the current pitfalls and obstacles to progress? Where are the gaps in our current knowledge that would be logical next steps to try to approach?

For both of these questions, I believe the major obstacles are going to be on the behavioral side of the equation rather than the biological side. We need to have ecologically valid and precise ways of studying, classifying, and quantifying social behavior under laboratory conditions if we are ever going to be able to link these social behaviors to particular genes and neural circuits. Unfortunately, in our rush to improve measurement on the biological side (e.g., recent advances

in neuroimaging and molecular genetics); it is tempting to short change our measurement of social behavior. Arguably the most fundamental social behaviors to understand are attachment, which creates bonds between co-specifics, and dominance, which organizes social groups. Social behaviors of these types are not likely to be interchangeable with social cognitions and social judgments. Most paradigms in social neuroscience involve processing social and emotional information rather than engaging in social behaviors. The fMRI magnet is not a hospitable environment for studying social interaction (but for an important first step see Coan, Schaefer, and Davidson, in press).

Similarly, if we are going to search for links between social behaviors and polymorphisms in putatively socially relevant genes (e.g., those that influence oxytocin, vasopressin, etc.), we will be severely hampered if we are only studying social judgments or studying social behaviors that are crudely measured. Studying neurological patients does not place the same kinds of constraints on the range of social behaviors that can be studied as do neuroimaging studies. However, patient studies have less precision in mapping the brain areas associated with this social behavior.

Finally, because of the expense and time involved in neuroimaging, studies in social neuroscience often lack important control conditions necessary to determine the specificity of findings (e.g., is it any emotion or just a particular emotion?). This is a blueprint for lack of replicability and for findings that later must be reinterpreted in more parsimonious ways.

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Janice Kiecolt-Glaser, Ohio State University College of Medicine

1) **What do you perceive to be the one or two pivotal findings from your own work or work in your field that have advanced our understanding of the neurobiological or genetic underpinnings of social behaviors? Where do you see this line of research developing from here? How can it shed light on lifespan developmental issues or issues specific to aging?**

The extent to which the immune system is governed by the nervous and endocrine systems has become increasingly evident. The recognition of this interdependence has altered views about basic immunological functions. For example, heightened proinflammatory cytokines are a well-documented correlate of syndromal depressive disorders. However, even relatively modest levels of anxiety and depressive symptoms can elevate proinflammatory cytokine production. Moreover, both physical and psychological stressors can directly provoke transient increases in proinflammatory cytokines. Furthermore, stress and depression also contribute to greater risk for infection, prolonged infectious episodes, and delayed wound healing, all processes that indirectly fuel sustained proinflammatory cytokine production. Compounding the risks, poor sleep, one very commonplace consequence of stress and depression, enhances inflammation.

In addition to these three pathways, evidence from animal and human studies show that stress and depression can permanently alter the responsiveness of the immune system; stressors can effectively prime the inflammatory response, promoting larger cytokine increases in response to subsequent stressors and/or minor infectious challenges. Thus, it is not surprising that chronic stressors have been linked to sustained overproduction of a key proinflammatory cytokine, IL-6, which is associated with a spectrum of age-related diseases.

Importantly, these relationships are bi-directional; unquestionably, cytokines have substantial effects on the central nervous system (CNS), including production and enhancement of negative moods, and physical symptoms including lethargy and fatigue. Indeed, there is evidence that the immune system has a role in the behavioral features of both depressive and anxiety disorders.

Furthermore, older adults show greater immunological impairments associated with stress or depression than younger adults. Indeed, chronic stressors may accelerate the aging of the immune response and enhance overproduction of proinflammatory cytokines, as illustrated by work from caregivers.

In terms of how this line of research develops from here, there are crossovers with several other key areas. One very provocative and promising area is nutritional neuroscience, which suggests novel intervention opportunities.

Based on the central role that inflammation appears to play in so many age-related diseases, we have recently become interested in dietary influences on inflammation. Newer work from our lab is focusing on how findings from nutritional neuroscience can better inform our understanding of behavior-immune relationships. Omega-6 (*n*-6, primarily from refined vegetable oils such as corn, sunflower, and safflower) increases the production of proinflammatory cytokines, while the omega-3 (*n*-3) polyunsaturated fatty acids (PUFAs) found in fish, fish oil, walnuts, wheat germ

and flax seed can curb n-6 activities; higher *n*-6:*n*-3 ratios promote proinflammatory cytokine production. Importantly, high *n*-6:*n*-3 ratios also predict greater increases in cytokines during stressful periods, as well as higher levels of depressive symptoms, e.g., a number of studies have shown that depressed patients have lower average plasma levels of *n*-3 PUFAs than nondepressed controls; similarly, there are significant relationships within these populations between severity of depressive symptoms and both lower plasma levels of *n*-3 PUFAs and higher *n*-6:*n*-3 ratios.

A recent study from our lab addressed how interactions between PUFA levels and depressive symptoms were related to proinflammatory cytokine synthesis in older adults. We found that depressive symptoms and *n*-6:*n*-3 ratios worked together to enhance proinflammatory cytokines beyond the contribution provided by either variable alone, with substantial variance explained by their interaction: 13 percent for IL-6 and 31 percent for TNF-α, whereas full models accounted for 18 percent and 40 percent, respectively. Although predicted cytokine levels were fairly consistent across *n*-6:*n*-3 ratios with low depressive symptoms, higher *n*-6:*n*-3 ratios were associated with progressively elevated TNF-α and IL-6 levels as depressive symptoms increased. These data suggest that diets with high *n*-6:*n*-3 PUFA ratios may enhance risk for both depression and inflammatory diseases, particularly when individuals already have elevated levels of depressive symptoms. More broadly, the findings highlight the ways in which diet may enhance or inhibit depression-related inflammation among older adults. These behavior-dietary-immune interactions have important implications for both mental and physical health.

2) **How can we better specify the neurobiological and genetic mechanisms and pathways linking social behaviors and environments to aging-relevant outcomes? What are the conceptual and methodological advances required?**

Epigenetic modifications reflect changes in gene function without alterations in the DNA sequence. The findings from Caspi et al. provide one of the best-known behavioral examples, relating stressful life events to the onset of major depression. Despite the fact that the occurrence of stressful life events has been repeatedly associated with the onset of major depression, the effects are not consistent; while it is true that many individuals become depressed following major events, many other individuals appear to be relatively protected. Accordingly, it has been argued that some of the variability in individual vulnerability to depression following stressful events may be related, at least in part, to genetic factors, particularly serotonin genes. In support of this hypothesis, Caspi et al. found that 33 percent of individuals who had one or two copies of the short allele of the 5-HTT promoter polymorphism became depressed following stressful life events, compared to 17 percent of those with two copies of the long allele; in fact, among the latter, risk for depressive symptoms remained relatively flat despite the number of stressful life events, while those with one or two short alleles showed a dose-response relationship, with increasing levels of depressive symptoms as the number of life events increased. Epigenetic factors are clearly important in understanding how the social environment influences those who do and do not succumb to a disease for which they have clear genetic risks, and behavior, broadly defined, is central to these questions.

3) What are the current pitfalls and obstacles to progress? Where are there gaps in our current knowledge that would be logical next steps to try to approach?

Using the case of key serotonin genes as an example, the majority of studies have found no significant associations between self-reported affect and personality dimensions and 5-HTT polymorphisms, raising serious questions regarding the validity of these findings. Furthermore, most studies demonstrating a positive association between 5-HTTLPR and affect have involved very large sample sizes. For genetic studies where a key trait or facet is controlled by multiple genes (which appears to be the majority of the work thus far), the size of the sample needed to show significant effects may be a key barrier.

Indeed, reading the literature on genetic influences on cytokine production shows similar discrepancies. For example, the health relevance of cytokine/CRP polymorphisms is still a matter of considerable debate in the literature; for instance, though most studies of the IL-6 G174C polymorphism indicate that the 174G allele is associated with increased IL-6 levels and is a risk factor for various diseases, two studies take the opposite position and state that it is the 174C allele that is associated with high levels, and three studies indicate that the C allele is the disease risk factor. Furthermore, there might be both an age and sex effect on these associations, although there is even some contradiction as to the specifics in these studies. As for TNF-α, there are also many pathologies involving TNF-α that do not associate with the 308 polymorphism (e.g., rheumatoid arthritis), and at least one study that states that this polymorphism does not affect levels.

It is reasonable to speculate that some of the "noise" in the cytokine polymorphism literature may be related to unmeasured behavioral variables. Just as the data from Caspi showed a gene by life event interaction, measurement of behavioral variables relevant to stress/depression and related constructs may help with a better understanding of the discrepancies in the cytokine polymorphism literature–and thus eventually to a better understanding of how cytokines may contribute to affect regulation.

Susan T. Fiske, Princeton University

Pivotal Findings from the Fiske Lab: The Dog Didn't Bark

My current research focuses on social cognition, motivation, and affect, especially as applied to prejudice. Topics include (a) category-based versus individuating social responses, especially affect; (b) the culturally universal dimensions of social group categories; (c) ambivalent prejudice, especially sexism; (d) core social motivations—belonging, understanding, controlling, self-enhancing, and trusting—and their relevance for social adaptation; (e) social neuroscience of social cognition. My work on stereotypes of older adults has documented specific patterns of beliefs, prejudiced emotions, and discrimination that distinctly characterize this group.

Neuroscience of Social Perception. Developmental neuroscientists have for several years studied theory of mind, namely how and when people think about the contents of other people's minds (e.g., Saxe, Carey, & Kanwisher, 2004). Social psychologists have studied a more specific but related problem, namely the attribution of personality traits (Fiske, 2004, Chapter 3). People need to predict what other people will do, and the other person's perceived disposition is the preferred mode of prediction. People less often use, for example, shared social norms to explain another person's behavior. Social psychology's last half-century of research on attribution theory offers precise, validated paradigms for testing how people think about other people's minds. With graduate student Lasana Harris and Assistant Professor Alexander Todorov, I have neuroimaging data using one classic attribution paradigm to show ***the unique priority given to inferring chronic, idiosyncratic dispositions (unique attitudes, individual personality, idiosyncratic intent), compared to other kinds of mental contents, in the medial prefrontal cortex*** (Harris, Todorov, & Fiske, 2006). Work on social cognition, cross-cutting with social, cognitive, and affective neuroscience offers topics applicable to aging.

As an example of related aging research, the theory of mind work focuses on development at the beginning of the lifespan, when children first realize that other people have thoughts, feelings, and intentions that differ from their own. One neural mechanism may be the development of control systems that inhibit one's own mental experience, in order to focus on the other person's inferred mental experience (Lieberman, 2007). Older adults are impaired on some types of social reasoning tasks, as a function of declining domain-general resources (McKinnon & Moscovitch, 2006), especially the executive selection processes (German & Hehman, 2005). And older adults may have less ability to identify negative facial expressions and theory of mind from faces (Phillips, MacLean, & Allen, 2002). All this suggests fruitful avenues for examining social perception processes in older adults and for research in the methodological complexities in comparing neural responses of older and younger adults (Hartel & Buckner, 2006).

Neuroscience of Prejudice. Given current immigration patterns and global interdependence, people of all ages and states of health are increasingly likely to encounter people from unfamiliar groups. Social psychology has decades of evidence documenting the spontaneous and unconscious ways that people react to outgroups (i.e., those not their own). For example, I have

shown that people rapidly categorize other people by age, gender, and ethnicity, activating stereotypes, emotional prejudices, and discriminatory tendencies (Fiske, 1998). Certain social goals (e.g., being on the same team) and certain social values (e.g., egalitarianism) override these default category-based reactions (Fiske, 2002).

Neuroimaging data provide a unique window into the spontaneous activation of relevant neural systems, as well as their malleability by social context. Recent research indicates amygdala activation to social outgroups, under superficial conditions of category-based responding, especially for implicitly biased participants (Hart et al., 2000; Phelps et al., 2000). Fiske has shown that ***this amygdala response to outgroups evaporates for more socially involved types of processing*** (Wheeler & Fiske, 2005).

Of particular interest is our identifying four distinct types of outgroups, those that elicit: disgust, envy, pity, and admiration (Fiske et al., 2002). These emotions follow from universal dimensions of social perception, namely perceived warmth (positive intent) and perceived competence (ability to enact it; Fiske, Cuddy, & Glick, in press). Older adults all over the world fall into the pity cluster, who are seen as incompetent but harmless (nice, sincere, warm) (Cuddy et al., in press). Other outgroups elicit might be viewed as hostile and incompetent (poor people all over the world) or as exploitative but competent (rich people all over the world). The constellations result in different types of behavior toward these groups, including active and passive harm (attack vs. neglect), active and passive facilitation (helping vs. going along). Older adults, for example, receive a terrible combination of active help but passive neglect (Cuddy, Fiske, & Glick, in press).

Our ongoing neuroscience work demonstrates particular neural signatures of emotional responses to these distinct kinds of outgroups. For example, we have consistently found that poor people, specifically ***homeless people and drug addicts, elicit both behavioral indicators of disgust and neural correlates such as amygdala and insula activation (respectively implicated in vigilance and disgust). These same groups emphatically do not activate the medial prefrontal cortex regions that otherwise invariably activate in social cognition*** (Harris & Fiske, 2006). This last finding is interesting in part because of the absence (or nonsignificantly activated) mpfc, much like the Sherlock Holmes observation that the dog did not bark, providing an important clue to the mystery. We have discovered that these anomalous patterns revert to more typical social cognition patterns ***depending on social context***, for example, inferring the target person's food preferences (Harris & Fiske, in press).

Expertise in prejudice and stigma and in affective neuroscience, as well as regulatory systems can produce research with relevance to healthy aging. As an example of possible aging research in this mold, we could examine the specific neural correlates of prejudice against older adults, which combines both sympathy-pity responses (Fiske et al., 2002) and avoidance of one's own future decline and death (Greenberg, Schimel, & Mertens, 2002). Social neuroscience is beginning to track systems of responses for people more similar and dissimilar to self; activation in different parts of the medial prefrontal cortex vary as a function of similarity to self (Mitchell, Banaji, & Macrae, 2005); Similarity between self and other features centrally in behavioral studies of social cognition (Fiske & Taylor, in press). Along with relevant results from social neuroscience, this illustrates just one type of lead to pursue in ageism and distancing self from

older people. This kind of research on intergroup perception can combine information from surveys, social experiments, and neuroscience; this topic directly addresses the NRC priority on the social psychology of age stigma.

The four NIA/NRC-recommended areas of social psychology (Carstensen & Hartel, 2006) closely fit four social neuroscience themes that emerge in our work:

- Social engagement and cognition relates to potential lines of work in **social perception** examining neural and behavioral correlates of face and trait perception, related to both ages of targets and ages of perceivers, with effects on social interaction
- Stereotypes of self and others relates to the potential **prejudice** research examining ageism and age-related self-perception, again combining behavioral and neural data
- Motivation and behavior change relates to the **potential interventions** to undermine prejudice in older adults that affect well-being among older adults' social networks
- Social-emotional factors in decision-making relates to potential work **contrasting cognitive ("rational") and emotional judgments** about other people across the lifespan

Linda Waite, University of Chicago

1. One of the pivotal findings from the work of the research team conducing NSHAP (National Social Life, Health, and Aging Project) has been the feasibility of collecting detailed biological and physiological measures from large, nationally-representative samples of older adults using survey interviewers with no medical training. The NSHAP field period began in July 2005 and ended in March 2006, with 3005 completed interviews and a response rate of 75.5%.

The NSHAP interview included the collection of 13 biomeasures: (1) a core group of biomeasures including weight, waist circumference, height, blood pressure, smell, saliva collection, taste, and for female respondents, a self-administered vaginal swab; and (2) a set of modularized biomeasures including mobility, distance vision, touch, HIV testing via oral fluid collection, and blood spots.

Biomeasures were completed during the latter half of the interview when most respondents had built a positive rapport with their field interviewer, were engaged in the interview, and recognized the importance of the data being collected.[10] As a result, NSHAP achieved high cooperation rates on the biomeasures, with most measures producing cooperation rates higher than 90% (see Table 1).

Table 1. NSHAP Biomeasure Cooperation Rates*

Measure	Eligible Respondents	Cooperation Rate
Weight	2,927	98.4%
Height	2,930	98.6%
Waist circumference	2,916	97.2%
Blood pressure	2,935	98.4%
Smell	2,942	98.3%
Taste	2,809	95.8%
Saliva	2,721	90.8%
Vaginal swabs	1,028	67.6%
Get up and go	1,377	93.6%
Distance vision	1,441	96.0%
Touch	1,474	98.4%
Orasure	865	89.2%
Blood spots	2,105	85.0%

* Person-level weights are adjusted for non-response by age and urbanicity.

An additional indicator of the success of biomeasure collection in Wave I is the quality of samples collected and delivered to laboratories for analysis. Our laboratory subcontracting partners, Magee Women's Health Corporation, Northwestern University's Laboratory for Human Biology Research, Salimetrics Corporation, and the University of Chicago's Institute of Mind and Biology, provided ongoing feedback throughout the Wave I data collection period on the quality of the specimens received, including how they were collected, stored, and shipped, as well as if the results of the analyses fell within expected ranges. All four of the laboratories that processed NSHAP specimens reported receiving high-quality samples that were similar to other studies in both the quality and usability of specimens.

Data from self-administered vaginal swabs provide the first population-based estimates of Human Papillomavirus (HPV) and Bacterial Vaginosis (BV) prevalence among older women in the United States. Oncogenic subtypes of HPV have been linked to cervical cancer, the second

[10] Lundeen, Katie, Jessica Graber, Angela Jaszczak, Erin Wargo, and Stephen Smith. 2006. "Collecting Physical Measure Data in a Survey: Does the Interviewer Affect Cooperation Rates?" Presented at the Annual Conference of the American Association of Public Opinion Research, Montreal, Canada.

most common cause of cancer-related death for women worldwide. Preliminary results from NSHAP Wave I data indicated that about 6% of women aged 64-85 test positive for oncogenic HPV, which is similar to estimates from clinical studies of post-menopausal women. Preliminary findings suggest that HPV prevalence is not significantly different across age strata, race/ethnicity or sociodemographic groups.

Bacterial Vaginosis (BV) is associated with infections of the genital and urinary tracts, as well as an increased risk of sexual acquisition of HIV infections (Cauci et al. 2002). While BV is common among reproductive-age women, information is limited regarding BV prevalence among older women. Previous research suggests that nearly 31% of postmenopausal women have vaginal flora in the BV range and only 46.4% in the normal range (Cauci et al. 2002). NSHAP data indicate slightly lower rates of BV, with preliminary findings classifying about 21% of women aged 57-85 with BV, about 37% intermediate, and about 40% normal. Ongoing analyses of vaginal cell cytology data will enhance our understanding of the cytologic, pH and estrogen changes that impact vaginal health, including the presence or absence of vaginal flora and their effects on older women's health, sexuality, and well-being.

2. Genetic Data Collection. The collection of genetic material in sample surveys would greatly benefit the scientific community. Current public-use genetic data are derived from clinic-based samples. Consequently, adding genetic collection to high-quality surveys would provide information on genetic variation in nationally-representative samples.

Humans live in complex social groups, taking on different roles for which particular temperaments and physiological traits are well suited. As in animal populations, this individual variability results from differing environments and from stable genetic variation within the population. That is, different forms of a gene (i.e. polymorphisms) are maintained in the population because each contributes to different aspects of well-functioning social groups facing complex demands. These genetic variants are associated with different lifespan trajectories of health and fertility, often with different consequences at various points in the lifespan. For example, rat societies typically have sentinels who live alone and guard the burrow, while the rest live in highly interactive groups. Genetic variants are associated with temperaments that predispose the animal to either being a sentinel or living with the group. This genetic variation is not deterministic; it interacts with the cellular, physiological, physical and social environments in the development of complex traits. For instance, the sentinels have high fertility while young, but age more quickly and are at greater risk for cancer. The group-living animals have lower fertility while young, but experience slower, and healthier, aging trajectories.

A genome-wide screen of genetic polymorphism is the most effective method of obtaining genetic information on our diverse sample. Genetic data collected in sample surveys could become an invaluable resource for genetic case-controlled studies that focus on specific diseases late in the lifespan. The technology for obtaining complete genotyping from saliva samples has now improved dramatically, allowing for the safe and simple collection of genetic material.

The inclusion of genetic collection in surveys seems to be acceptable to respondents. During the informed consent process in Wave I of NSHAP, respondents were asked for permission to store their blood spots for future analyses, including genetic testing. About 89% of the 2105 respondents who were asked to provide blood spots agreed to have their samples stored. Of those, 58% indicated that the research team did not need to contact them prior to use of their

samples for future analyses.

3. Pitfalls and Obstacles to Progress. In my view, the biggest obstacles to progress to integrating neurological, biological and physiological approaches with those of sociology, come from the widely-held view within the field that social behavior is determined primarily or even exclusively through social mechanisms. Many sociologists take umbrage at the suggestion that, for example, women's gender role attitudes or gendered behavior may arise in part from exposure to sex hormones (see {Udry, 2001 #2808}. Nicholas Wade ({Wade, 2006 #2807}:191) points to sociology as a field, along with the social sciences generally, and the American Sociological Association examples of those who see race as entirely a social construct. Psychology is light years ahead of the other social sciences in recognizing and incorporating neurological, biological, and physiological theory, measures and methods in analyses of outcomes of interest to psychologists. I'm not sure what can be done to improve the situation, although there are rays of hope. Doug Massey's {Massey, 2002 #2809} Presidential Address to the American Sociological Association focus on the neurology of emotion and rational decision making in human societies. His call for increased interest in and understanding of the neurological substrates of human behavior has gone largely unheeded.

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Elissa Epel, University of California, San Francisco

Some Future Directions on Social Neuroscience of Aging

1) My work relevant to lifespan developmental issues

A guiding question for me has been: "What makes some people resilient to chronic stress while others are vulnerable?" Understanding individual stress vulnerability can offer clues to biological aging. It is often presumed that lifelong patterns of psychologically driven exaggerated stress responses contribute to biological aging, although that is difficult to demonstrate and decompose. At multiple levels of analysis, biological aging can be thought of as loss of resiliency or imbalance between traditional (catabolic) stress responsivity in tandem with impaired anti-stress or counter regulatory systems (typically anabolic). In terms of neuroendocrine function, aging is linked to impaired stress responsivity—such as slow cortisol recovery. At the cellular level, older cells lose their ability to respond to physical stressors. Thus, aging at the systemic and cellular level is intimately intertwined with stress responses to physical, and possibly psychological, challenges.

My recent research has focused on links between psychological "stress" -- cognitive aspects such as rumination, threat perceptions, and emotions -- and two physiological pathways toward disease, one systemic--insulin resistance syndrome (increased visceral fat, blood pressure, lipids, and insulin/glucose), and one at the cellular level cell –markers of aging of mitotic cells (telomere length, the protective caps at the end of chromosomes that shorten with age, and telomerase, the enzyme that can lengthen telomeres).

Previously, these cell based measures have not been examined in relation to psychosocial factors. We (Epel, Blackburn, and colleagues) have found that chronic stress, both measured subjectively or objectively, was related to greater cell aging (shorter telomeres, lower telomerase). Further, we and others have found that greater levels of the insulin resistance syndrome are linked to either shorter telomeres or lower telomerase (e.g., Epel, 2006; Gardner, 2005).

These findings led us to more experimental investigations of how telomerase functions acutely. If chronic stress can dampen telomerase, can we see effects of acute stress on telomerase? Using standardized laboratory stressors, we have observed that telomerase changes acutely in humans. This new finding leads to many more questions. For example, what are the psychological and biochemical mediators of telomerase reactivity? We are in the early stages of addressing these questions.

This line of research may have relevance to life trajectory. If emotional state can affect mitotic cell longevity, as these results suggest, this is a significant link in biological aging in that these are the cells needed to replenish certain tissues throughout the lifespan. Understanding how stress affects mitotic cell activity may provide insights into biological aging in general, as well as certain age related chronic diseases (CVD, diabetes, cancer).

In terms of future directions, I hope to identify these stress/cell aging links with greater specificity. What are the specific cognitive and emotional components of reactions to standardized stressors that affect telomerase activity? What neural activity and peripheral stress responses are affecting this important anti-aging enzyme? Does telomerase change in all mitotic cells during stress or just immune cells? Can we reverse cell aging through behavioral interventions? We are currently testing effect of psychological interventions (stress reduction, mindfulness meditation) on cell aging, and IRS.

2) Specifying mechanisms. What are the conceptual and methodological advances required?

Given the central role that chronic stress plays in accelerating aging, we need a better multilevel understanding of stress vulnerability and stress resistance. The problem becomes obvious when we realize that there is no agreed upon operationalization of either term. What is stress vulnerability or stress resistance, psychologically or physiologically? Many of us have answers to that, from our individual paradigms, but they probably have little "shared variance." It is imperative to identify the most common phenotypes of a maladaptive stress response—including whatever components are most important in the pathway toward aging--- affective, cognitive, genetic, and in terms of neural activity and biochemical substrates centrally and peripherally.

What types of stress are most damaging, and what does this look like in the brain? Studies linking brain chemistry and activity with peripheral biomarkers would be invaluable. However, we are limited by our inability to measure important central peptides in humans peripherally (e.g., NPY, oxytocin, opioids in the VTA) and there is a lack of ligands that would allow us to see PET scan activity.

There is a need to focus on early development to understand aging trajectories. Converging lines of research suggest that many of the 'big effects' on morbidity and mortality may turn out to be a measurable variable early in life – parental SES, birth weight, maternal depression. There is now much work showing effects of prenatal programming on health trajectories in later life. The epigenetic effects of maternal environment and mental health on the fetus are now clear. Early exposures—maternal diet/ malnutrition, stress, may influence DNA methylation and genetic expression. Low birth weight leads to catch up growth and later obesity and the insulin resistance syndrome. There is some suggestion that low birth weight may lead to early telomere shortening. Early experiences also shape trajectories. Early brain developments in terms of responses to social stimuli are clearly important. Attachment, social rejection and social threat appear to be potent elicitors of the HPA axis, and may underlie important states such as shame, and loneliness (e.g., Cacioppo, 2000; Dickerson & Kemeny, 2005).

There is a need for 'mechanistic' longitudinal studies. Given the nonlinearity of physiological processes (e.g., bidirectional relationships, webs of interconnections), cross sectional research can lead to false assumptions. With limited resources, there should be more focus on causal mechanisms. This includes longitudinal studies with experimental studies embedded. Well characterized samples could be taken advantage of. The lack of investment in samples that cannot be followed sufficiently, due to limited funds to extend research longitudinally, is an obstacle to understanding aging—which is a process not a trait.

Once we have developed more advanced conceptual models of phenotypes of "stress" –we need multilevel research examining how "stress vulnerability" leads to transmission of disease risk and conversely, how "stress resilience" may confer longevity. This might require multigenerational studies that include prenatal conditions. Large longitudinal studies that examine women and men in young adulthood, and how they pass on traits such as stress reactivity and telomere length to their progeny, and sub-studies to examine mechanisms in depth. Such studies require multi level analyses, and need to include social factors, genetic, behavioral phenotypes, neurobiology at least as well as it can be measured in humans.

To do these studies, we need to bring together excellent cell biologists with clinical researchers would forge collaborations that offer the ability to measure some key cellular aging processes and look at functioning in the context of humans, in vivo, in the social world.

3) Some gaps in our current knowledge, and emerging areas of research.

As described in #1, above, there are large gaps about how cell aging mechanisms work in vivo.

There are gaps in our knowledge about the social neuroscience of obesity. Obesity develops in a social cultural context, and is one of the most pro-aging conditions we know of. While we know that food environment is the major culprit we know very little about individual differences that predict eating behavior and less about how the social world impacts eating. New research points to the importance of individual differences in the reward center.

There are gaps in understanding how to promote the salutary social connections and environments that characterize longevity. As discussed in Dr. Nielsen's summary, there is now a plethora of evidence that social environments – from neighborhoods to families and relationships, influence health. We know the macro factors that matter. We know how to measure disease outcomes. We are beginning to identify the biomarkers that are likely involved in the early disease processes (often inflammation, oxidative stress, insulin resistance). Given this knowledge, it is now important to move toward intervention on a macro scale. Studies that do community level or policy level interventions that affect the social environment (increasing social capital, safety, community resources and involvement) should have the most widespread effects at the individual level. **Should a social neuroscience of aging program be concerned with interventions that promote the type of social connections that are important for health?** While the ideas below may be beyond the scope of BSR program, they may be important future directions for public health. These interventions may also serve as a way to examine change in presumed neurobiological mechanisms. **One gap is that we don't know how to directly promote social connection, compassion, and stronger families, in communities.** Given this gap, some emerging areas of intervention research could include:

- **Programs that promote social connection and meaningful roles in retirement.** In terms of aging, changing norms, negative stereotypes, and providing options for a prosocial retirement. Programs that utilize the elderly, providing a meaning role where they contribute to society, may improve their health. The Experience Corps is an example of a program that uses the wisdom and resources of the elderly to mentor young at risk

children, and has been shown to improve the elderly people's physical activity, strength, and cognitive function (http://www.experiencecorps.org/research/JHU_summary.html). These programs could be studied and disseminated.

- **Use social psychological principles or other interventions to change cultural norms about social connectedness.** Promote a sense of social responsibility to connect people with those with social disadvantage. As in #1, above, this should help both the person and beneficiary. An example of media promoting change is the clever ads that promote turning compassion into helping others through a strong visual-emotional appeal ("Don't almost give… Give"), by the Ad Council (delivers public service announcements), recently launched. See http://www.dontalmostgive.org/index.php?option=com_content&task=view&id=12&Itemid=27. How can these important messages be adopted and by communities? Will they reduce morbidity?
  Mindfulness meditation interventions may also increase compassion and social connection, but the mechanisms are unknown.

- **Interventions for pregnant mothers**. Based on work from prenatal programming as well as early maternal influences on child health, better prenatal self -care, including nutrition and stress management, may have the potential to change the health trajectory of future generations.

Mike Shanahan, University of North Carolina, Chapel Hill

1) What do you perceive to be the one or two pivotal findings from your own work or work in your field that have advanced our understanding of the neurobiological or genetic underpinnings of social behaviors? Where do you see this line of research developing from here? How can it shed light on lifespan developmental issues or issues specific to aging?

2) How can we better specify the neurobiological and genetic mechanisms and pathways linking social behaviors and environments to aging-relevant outcomes? What are the conceptual and methodological advances required?

3) What are the current pitfalls and obstacles to progress? Where are the gaps in our current knowledge that would be logical next steps to try to approach?

As a sociological social psychologist, I would emphasize the importance of (1) the measurement of phenotypes and social contexts; (2) heightened attention to research methodologies that are sensitive to the discovery of valid mixtures in a population; (3) and heightened attention—both conceptual and methodological---to gene-environment correlations.

My present research focuses on genes associated with dopamine receptors (e.g., DRD2 TaqI) and educational performance and attainment. The basic argument is threefold: (1) DRD2 A1+ (A1A1 and A1A2) undermines the capacity of people to perform well (and, thus, to achieve great things) in highly structured, bureaucratic settings (such as schools). (2) In such situations, however, the student's social capital (i.e., his or her relationships with other people) may compensate for this propensity for counterproductive behaviors. (3) Nevertheless, people with A1+ are not likely to have the high levels of social capital necessary to negate the effect of A1+ on continuation. Simply put, social capital can compensate for DRD2 A1+, but people with A1+ are unlikely to have sufficient social capital in the first place.

In fact, drawing on the DNA sub sample of the National Longitudinal Study of Adolescent Health (Add Health), I find strong support for all three expectations. For example, A1+ decreases the likelihood of continuing one's education beyond high school among both white and black boys (but not white or black girls). Further, both groups of boys with A1+ and with good social capital—they talk to their parents about school, their parents are highly educated, their parents are involved in school through PTA etc., and the school is of high quality--are as likely to continue to college/university as boys with A1- and equally good social capital. Finally, boys with A1+ are less likely to have such good social capital in the first place when compared with boys with A1-. In other words, DRD2 A1+ decreases the likelihood of continuation to college/university; but this effect is completely negated by high social capital; but boys with A1+ are unlikely to have such high social capital. This pattern is an example of a simultaneous gene-environment interaction and correlation.

This specific research—but I think this type of research more broadly—pose many challenges:

(1) What does "undermines the capacity of people to perform well in bureaucratic settings" mean? That is, what specific behavioral phenotypes mediate genetic activity and poor performance? This is a difficult question to answer because one must rely on many different types of studies—involving nonhuman animals and humans—and then link those studied phenotypes with specific behaviors in specific complex settings like schools. Ideally, there would be interplay between scientists conducting such research, and scientists studying people in "real-world" settings.

(2) Exactly how should social context (in this case, social capital) be measured? A great deal of research shows that social context is often multidimensional and it is how the multiple dimensions are organized that determines their meaning. For example, the same sets of variables are used to distinguish "organized" and "disorganized" neighborhoods – it is how the constituent elements are interrelated that differentiates the two types. A great deal of research also shows that social contexts have dynamic properties that are often highly salient with respect to behavior. For example, many temporal distinctions are known to be useful in the study of poverty and well-being (e.g., duration, periodicity, chronocity, etc.). Especially in aging studies, longitudinal patterns of social context—perhaps beginning *in utero*—may be of great consequence. Thus, social context is multidimensional and dynamic, and measures that fail to account for these complexities are likely to be misleading.

(3) The implications of the foregoing are that behavior and context have two levels of complexity (multidimensionality and dynamics) that must be captured by measures and methods. How to do this? More attention should be paid to methods that are well-suited to capture high levels of interaction among and between genetic, behavioral, and contextual variables. My own research is presently drawing upon combinatorics, which defines sets of people based on genetic and contextual variables, and then examines patterns between sets and behavioral outcomes. This family of analytic strategies is quite sensitive to high levels of interaction, and has illustrated the pitfalls of generalized linear models that assume additivity. For example, school quality can compensate for DRD2, but only if accompanied by highly educated parents who are involved in the school. Such a finding makes conceptual sense (and was replicated across white and black male samples). It was relatively easy to discover when the data were analyzed in terms of set theory, but it almost certainly would not have been discovered has a typical generalized linear framework been used. My overarching point is that we should assume high levels of interaction and dynamic properties of context and behavior and hence more attention should be paid to innovative methods.