Biological Basis of Social Support

Patricia M. Whitaker-Azmitia, Ph.D.
Departments of Psychology and Psychiatry
Stony Brook University
Stony Brook, New York 11794

National Aeronautics and
Space Administration

Johnson Space Center
Houston, Texas 77058

February 2016
Since its founding, NASA has been dedicated to the advancement of aeronautics and space science. The NASA scientific and technical information (STI) program plays a key part in helping NASA maintain this important role.

The NASA STI program operates under the auspices of the Agency Chief Information Officer. It collects, organizes, provides for archiving, and disseminates NASA’s STI. The NASA STI program provides access to the NASA Aeronautics and Space Database and its public interface, the NASA Technical Report Server, thus providing one of the largest collections of aeronautical and space science STI in the world. Results are published in both non-NASA channels and by NASA in the NASA STI Report Series, which includes the following report types:

- **TECHNICAL PUBLICATION.** Reports of completed research or a major significant phase of research that present the results of NASA Programs and include extensive data or theoretical analysis. Includes compilations of significant scientific and technical data and information deemed to be of continuing reference value. NASA counterpart of peer-reviewed formal professional papers but has less stringent limitations on manuscript length and extent of graphic presentations.

- **TECHNICAL MEMORANDUM.** Scientific and technical findings that are preliminary or of specialized interest, e.g., quick release reports, working papers, and bibliographies that contain minimal annotation. Does not contain extensive analysis.

- **CONTRACTOR REPORT.** Scientific and technical findings by NASA-sponsored contractors and grantees.

- **CONFERENCE PUBLICATION.** Collected papers from scientific and technical conferences, symposia, seminars, or other meetings sponsored or co-sponsored by NASA.

- **SPECIAL PUBLICATION.** Scientific, technical, or historical information from NASA programs, projects, and missions, often concerned with subjects having substantial public interest.

- **TECHNICAL TRANSLATION.** English-language translations of foreign scientific and technical material pertinent to NASA’s mission.

Specialized services also include creating custom thesauri, building customized databases, and organizing and publishing research results.

For more information about the NASA STI program, see the following:

- Access the NASA STI program home page at [http://www.sti.nasa.gov](http://www.sti.nasa.gov)

- E-mail your question via the Internet to help@sti.nasa.gov

- Fax your question to the NASA STI Help Desk at 443-757-5803

- Phone the NASA STI Help Desk at 443-757-5802

- Write to:
  NASA Center for AeroSpace Information
  7115 Standard Drive
  Hanover, MD 21076-1320
Biological Basis of Social Support

Patricia M. Whitaker-Azmitia, Ph.D.
Departments of Psychology and Psychiatry
Stony Brook University
Stony Brook, New York 11794

National Aeronautics and
Space Administration

Johnson Space Center
Houston, Texas  77058

February 2016
# Table of Contents

Abstract ........................................................................................................................................... 1

1. Introduction and Definitions
   1.1 Social Support: Definition, Evolution, Development and Plasticity: ................................................................. 2
      1.1.1 Definition of social support .......................................................................................................................... 2
      1.1.2 Evolution of social support and importance to human well-being ................................................................. 3
      1.1.3 Development and plasticity of the social support network ........................................................................... 4
   1.2 Resilience ......................................................................................................................................................... 7
   1.3 Models Systems for the Study of Social Support ............................................................................................. 8
      1.3.1 Human environmental models .................................................................................................................... 8
      1.3.2 Human conditions ........................................................................................................................................ 11
      1.3.3 Animal models ........................................................................................................................................... 13

2. Biological Factors
   2.1 Principal Factors ................................................................................................................................................. 15
      2.1.1 Serotonin ....................................................................................................................................................... 16
      2.1.2 Oxytocin ......................................................................................................................................................... 20
      2.1.3 Brain-derived neurotrophic factor ................................................................................................................ 28
      2.1.4 Cortisol ......................................................................................................................................................... 29
   2.2 Modulating Factors ............................................................................................................................................. 32
      2.2.1 Dopamine ....................................................................................................................................................... 32
      2.2.2 Neurosteroids and steroid hormones ........................................................................................................... 34
      2.2.3 Endorphins .................................................................................................................................................... 35
      2.2.4 Neuropeptide Y ............................................................................................................................................ 36

3. Brain Regions and Networks in the Social Support System
   3.1 Cellular Components ............................................................................................................................................. 36
      3.1.1 Von economos neurons ............................................................................................................................... 36
      3.1.2 Oligodendroglia .......................................................................................................................................... 37
   3.2 Regions of Interest .............................................................................................................................................. 37
      3.2.1 Amygdala ..................................................................................................................................................... 37
      3.2.2 Prefrontal cortex ........................................................................................................................................ 38
      3.2.3 Hippocampus .............................................................................................................................................. 39
      3.2.4 Anterior cingulate cortex ............................................................................................................................ 39
3.2.5 Ventral tegmentum, ventral striatum
/nucleus accumbens ................................................................. 39

4. Summary of the Biology of Social Support System
  4.1 Summary of Principals.......................................................... 40
  4.2 Biological Factors .............................................................. 40

5. Future Directions for Research
  5.1 First Priority: Establish the Biomarkers of Social Support............ 41
    5.1.1 Animal models .................................................................. 42
    5.1.2 Human studies ................................................................... 43
  5.2 Priority Two: Experiments to Predict and Improve Outcomes......... 49
    5.2.1 Time periods of testing..................................................... 50
    5.2.2 Correlations of biomarkers with psychometric
        and physiological responses...................................................... 50
  5.3 Priority Three: Evaluating Manipulations for Maintenance
        and Repair of the Social Support Network. ............................... 51

6. Conclusions.................................................................................. 51

Literature Cited.................................................................................. 52
Abstract

The social support circuitry of the brain developed evolutionarily to not only make it easier for humans to live in close proximity, but to actually benefit from it. The beneficial effects of a healthy social support circuit are seen in improved cardiovascular, immune and emotional health. The social support circuit depends on experience-driven plasticity, that is, there are neurochemical and cellular changes which are necessary in order to respond to a changing environment. The same factors are used across the lifespan, from maternal/infant bonding, to peer bonding to pair-bonding. The principal factors involved in the experience-driven plasticity of the social support network are serotonin, oxytocin and brain-derived neurotrophic factor (which increase the integrity of the network) and cortisol (which leads to damage to the network). These factors can be measured and used to study and assess the integrity of the circuit in individuals in different environments.

To further our understanding of the biology of social support, several different model systems may prove useful in humans. Isolated and confined environments (ICEs) may provide a large number of subjects, not available in the high-fidelity environments. In human disease states, both autism and loneliness are worth studying – in particular, loneliness may model maladaptation to long-term social isolation best. In animal studies, social isolation of rodents can be very useful, in particular studies with the pair-bonded prairie vole or with rodents transitioning from parent to peer bonding.

A thorough understanding of the biology and plasticity of the social support circuit is essential in planning for the effects of separation from one’s typical social support during long-term space travel, as this circuit is ultimately responsible for many other features of human physical and mental well-being.
1. Introduction and Definitions

1.1 Social Support: Definition, Evolution, Development and Plasticity

1.1.1 Definition of social support

Social support is the belief that one is cared for and valued by others. It includes affiliation, belongingness and an expectation that others will have empathy for you and come to your assistance when needed. It is dependent on communication, both verbal and non-verbal. Social support has long been known to be a moderator of life stresses and a modulator of health outcomes (Cobb, 1976; Cohen and Wills, 1985). More succinctly, social support is defined to be the interactions in a relationship which improve coping, self-esteem, sense of belonging and competence through actual or perceived exchanges of emotional or physical resources (Gottlieb and Bergen, 2010). A range of emotional support can be considered, including empathy, caring, love and trust.

The theory of social support grew largely from the observations that those who have strong emotional bonds such as these are better able to handle stress (resilience) as well as to have better health outcomes. For example, using psychometric measures of social support scales, it has been found that increased social support buffers the impact of bereavement and loss of friends (Krause, 1986), improves birth outcomes, (Hoffman and Hatch, 1996), improves the immune system (Cohen et al, 1997) and improves responses to medication, such as antidepressants (Joseph et al, 2011). Lack of quality social relationships increases mortality from widely varying causes, including cancer and cardiovascular disease (House et al, 1988; Holt-Lunstad et al, 2010). Marriage (the central social support for most adults) either with intrinsic support or conflict has specific physiological effects which mediate these effects on health (Robles and Kiecolt-Glaser, 2003).

The beneficial effects of social support may be due to “buffering” the individual from stress and stress hormones such as cortisol. Animal studies have shown that the effect of electrical shocks are decreased in the presence of other animals and animals exploring a new environment show less anxiety if introduced into the environment with a con-specific (DeVries et al, 1995; Winslow et al, 2003). Human studies show a similar
effect, wherein the presence of a companion reduces cardiac reactivity (Kamarck et al, 1995) pain perception (Brown et al, 2003) and cortisol response (Heinrichs et al, 2003).

1.1.2 Evolution of social support and importance to human well-being

Evolutionary psychology is the study of how the functions of the human brain have adapted through natural selection to the environment in which we live. The oldest part of the brain (brainstem) has little emotional or cognitive components, but simply controls physiological systems and attends to physical needs. This is sufficient for lower animals, but is not sufficient for the complex environments in which primates evolved. In fact, the primate brain is far bigger than that not only required for physiological functions, but also larger than that required for many other attributes including motor functions and cognition. Considering the energy costs of large brains, there clearly must be an evolutionary advantage to this. Current theories in evolutionary psychology suggest that the selection for large brains in primates was based on the need for pair bonding and on the need for a social brain (Dunbar and Schultz, 2008) – that is the human brain has adapted to be highly socially interactive because the large number of fellow humans in the environment required that learning to coexist and solve problems collectively was not only advantageous, but in fact essential (Van Vugt and Park, 2009; Walker and McGlone, 2013). Charles Darwin made this point very clearly in his second book almost 150 years ago, Descent of Man: “A tribe including many members who, from possessing in a high degree the spirit of patriotism, fidelity, obedience, courage, and sympathy, were always ready to aid one another, and to sacrifice themselves for the common good, would be victorious over most other tribes; and this would be natural selection.”

Coan and colleagues (2010; 2011; 2013) have expanded on these ideas in a theory referred to as Social Baseline Theory. Organisms survive by taking in more energy than they expend – a biological imperative referred to as economy of action. In the Social Baseline Theory, this economy of action is achieved for humans by the positive effects of social support and social interactions. The greatest environmental adaptation humans have made then is to be dependent on the proximity of others who provide familiarity, joint goals and interdependence. Social support systems can be considered to serve a regulatory and protective function in the brain. Essentially, this one brain network which
perceives and responds to social support can modulate multiple other brain systems, resulting in a lower overall energy demand to control many other brain functions. These other brain systems which are protected include primitive functions of breathing, heart rate and cardiovascular systems of the brainstem, immune, sexual, and stress functions of the hypothalamus and endocrine system, emotional processing in the amygdala and related cortical regions and cognitive and memory functions of the hippocampus and cortex. Thus, a strong social support network, with strong attachments leading to a sense of being cared for and relieving emotional stress, can mitigate challenges to many other systems of the human brain – resulting in maintaining a baseline state of relative calm.

The importance of a properly functioning social brain in man is evident in the number of neurodevelopmental and psychiatric disease which result from a failure of this system, including autism, social anxiety disorder and schizophrenia. Even without an underlying psychiatric disorder, lack of social support can lead to loneliness, anxiety and depression. However, the importance of the system is also evident in the increase in physiological harm, when social support is inadequate, such as increased immune dysfunction and cancers.

The need for social bonding in humans has also been suggested to be the major driving force in the evolution of language (Dunbar, 2003) and impoverishment or disorder of language is found in autism and schizophrenia.

1.1.3 Development and plasticity of the social support network

The ability of the brain to learn and adapt to environmental challenges goes on throughout life and understanding the biological mechanisms of adaptations at earlier developmental time points can be used to predict what biological changes must be employed for efficacious adaptations in an adult brain. In the case of the social support system, the adaptation during development is driven by social experience and sufficient and appropriate social interactions are essential at critical periods. Deriving positive soothing relationships from others as an adult depends on having had positive maternal support as an adolescent (Coan et al, 2013). Lack of these interactions leads to deficits of not only the social support network at later times, but also of many key brain mechanisms dependent on it, including cognitive, emotional and physiological systems.
All social bonding experiences in mammals change neuronal structure and all experiences throughout life are based on the first mother-infant bond. Referred to as experience-driven plasticity, connections in the human brain overgrow, peaking at 2 years of age and then are “pruned” back, with only functionally relevant connections being kept. However, these changes in connections go on throughout life, and factors which maintain or destroy synapses during development are also key in understanding how the adult brain adapts to environmental challenges.

Specifically, the substances which promote synaptic connections (serotonin, oxytocin, brain-derived neurotrophic facto (BDNF) and other neurotrophins) also maintain them and re-grow them if broken in adults. Similarly, the substances which damage connections and neuronal cells (cortisol, glutamate) in infancy are also detrimental in the adult. In a plastic neuronal system, such as the social support system, much can be learned about maintenance in the adult, by looking at factors during development. Moreover, since the social support system evolved to lessen brain metabolic demands on other systems, if the social support system is damaged, many other brain systems will be as well. The question then, is: do family and loved ones supply the factors which maintain the social network? And more importantly, in their absence, do the positive factors decrease and the negative ones increase?

Development of the human brain begins with birth of cells, or neurogenesis. Once born, neurons migrate into their final location and only once there, do they differentiate and mature. This maturational stage is crucial – it is when axons grow and cellular connections (synaptogenesis) take place. Synaptogenesis is the stage in development and throughout the lifespan most critical for adaptation to environmental challenges.

Human studies have shown that even as early as in utero, maternal stress can lead to permanent changes in the developing fetus including loss of grey matter content in cortex and severe psychopathologies with social deficits such as schizophrenia and autism (Weinstock, 2008; O'Donnell et al, 2009).

**Neonatal.** The neonatal period in animals and humans represents an intense period of social interactions and the degree and type of interaction determines the extent and quality of social relationships in the adult (Cushing and Kramer, 2005), largely by determining the content and receptor densities of serotonin, oxytocin/vasopressin and
cortisol. Thus, the neuroplastic capacity of the social support network is set early. The peak number of synapses is present and persists until the age of 2. Rapoport (1999) proposes that this is due to the necessity for the great number of synapses which must be available to be modified for adapting to any environment. Infants develop social bonds much more quickly and the bonds are longer-lasting than those acquired at later ages. Stress and adversity at this time can lead to permanent deficits, including of the social network. Documented maltreatment at this time will lead to loss of neuronal structure in anterior cingulate and orbitofrontal cortex (Kelly et al, 2013) and functional differences in the amygdala and anterior cingulate cortex (McCory et al, 2010). All of these are brain regions which take part in the mature social network.

**Adolescence.** The second decade of life represents a time when new demands are put on comprehending and responding to the social environment. In animal studies of rodents, this is a transition from what is referred to as juvenile play behavior to eventually becoming pair-bonding. In humans, adolescence is a peak time for sensitivity to social exclusion from peers and it is when social support first becomes important for maintaining feelings of self-worth. Social cognition improves and theory of mind develops, concomitant with the development of specific regions of prefrontal cortex. Developmental plasticity of the amygdala at this time determines many of the resulting corticolimbic pathways involved in the social circuit (Nelson et al, 2014), strengthening those circuits and connections needed for peer interactions and weakening those used in parental bonding (Scherf et al, 2013). This is also a time when glucocorticoids, such as cortisol have their greatest effect, with peak numbers of glucocorticoid receptors (GR) occurring (Blakemore et al, 2007). Myelination is beginning but continues into early adulthood. In animal studies, this is the peak time for expression of oxytocin and vasopressin receptors (Tribollet et al, 1991) and their final number is set at this time.

**Adult.** It is now clear that neuroplasticity is necessarily a permanent process in the brain. The adult hippocampus is still a site of intense neuroplasticity with ongoing neurogenesis and dendritic and synaptic elaboration (Inokuchi, 2011; Ohkawa et al, 2012) but other regions of the brain are also capable of undergoing plastic changes. This is best evidenced by the known motor cortical reallocation of resources following a lesion or stroke, but this also occurs in other systems, including the social support system. Here,
the factors which are involved throughout development are also still in play. Stress-induced cortisol release can decrease synaptic contacts. Conversely, an enriched environment, that is one with new experiences, can promote synaptogenesis and dendritic elaboration, largely through the release of neuroplastic factors such as BDNF and serotonin. There is little direct evidence as yet, but there are some indications from animal studies that oxytocin may continue to act as a functional and morphological restructuring component of the adult brain as well (Lin et al, 2012).

1.2 Resilience

In detecting changes in the environment, the brain must adapt and change in order to maintain stability, a process referred to by Bruce McEwen as allostasis. This ability to adapt is referred to as resilience. Just as emotionality and the social support system is highly dependent on developmental influences and adult plasticity, so is resilience. Much of the ability to show resilience is based on control of the hypothalamic-pituitary-adrenal (HPA) axis and cortisol. There is a biphasic effect of glucocorticoids, in early stages of a stress exposure cortisol serves to focus the brain’s resources and energy demands, increasing dendritic density in key brain areas. After chronic stress, there can be a loss of dendrites in brain and immunosuppression, insulin resistance and cardiovascular disease can result as well. However, resilient individuals are inoculated from the chronic stress by improved control of the HPA axis. In a study of military personnel exposed to sleep deprivation, those who scored high on the resiliency scale showed the lowest cortisol response (Sun et al, 2014) while parents of special needs children with the highest resiliency scores also have the lowest morning cortisol response (Ruiz-Robledillo et al, 2014).

The adrenal steroid dehydroepiandrosterone (DHEA) is also released during stress; however, this is considered to be protective of long-term stress and to positively contribute to resilience. Neuropeptide Y, a neuropeptide found in the hypothalamus and the amygdala is increased in soldiers who do best in survival training (Charney, 2004). Oxytocin and DHEA-S have been correlated with resiliency and suggested to have use as biomarkers (Yehuda et al, 2006). In animal studies, serotonin, and the 5-HT1A receptor also play a role in increasing resilience.
1.3 Models Systems for the Study of Social Support

1.3.1 Human environmental models

Isolated and Confined Environments (ICEs): There are several environments which can be used as proxies for space travel, and which may make useful models.

1.3.1a Antarctic wintering over. Several nations maintain research stations in the Antarctic, which have been used for studies of the researchers themselves. These stations require people to spend long periods of time in confinement and isolation, with the potential of limited resources, non-24-hour light cycles and monotony. However, they do not last as long as the planned Mars trip, do not have a space mission content, and the stations are much larger and have many more researchers present at a time, so that social support is not dependent on a small number of others. The great advantage to these, however, is that large numbers of subjects can be followed, giving enough power for significant findings. A behavioral response referred to as the winter-over syndrome occurs, which consists of sleep disturbances, impaired cognition, seasonal affective-type of depression (as many as 28% of subjects) and increased interpersonal conflict (Palinkas and Houseal, 2000). These effects peak later in the condition, the so-called third quarter syndrome. In a large study of over 300 subjects, a perceived loss of social support was reported even though it was unchanged, and there was an increase in depression (Palinkas et al, 2004a). It is important to note that groups with high social coherence report far less changes in mood and in conflict (Palinkas, 2003), emphasizing how conditions such as loneliness can lead to hostility and aggression. By following different nations’ researchers at different stations in the Antarctic, important cultural differences have been noted in psychosocial adaptations which will be important to consider when designing a flight crew (Palinkas et al, 2004b). There is decreased function of the immune system and changes in thyroid stimulating hormone have been reported and associated with mood and cognitive findings. In a small study, supplementation of diet with T4 hormone improves cognitive and mood scores (Reed et al, 2001). In a small study, using only 12 subjects, the effects of 100 days of travel in Antarctica on psychosocial well-being were found to be highly individual and to not be an overall effect on the group (Wood et
al, 1999) again emphasizing the need for large sample sizes in order to determine prevention, prediction and treatment strategies. Overall, the data gained from wintering over studies could be substantial and meaningful in planning for long-duration space travel.

**1.3.1b Submarine crews.** This population represents many useful comparisons to long-duration space flights. The space is confined, there is a lack of privacy, there is a risk of accident, there are altered diurnal rhythms, monotony is prevalent and leaving the confinement is slow. High levels of cortisol are reported (Sandal et al, 2003). Overall, this could be a useful model to study the effects of ICEs on social support.

**1.3.1c High-fidelity mock confinements.** Mars 500 refers to studies in a mock confined “spaceship” in a Moscow research institute. It simulates spatial confinement and social isolation, as well as time delays in communication, changes in light cycles, limited resources and simulated landings and work routines. It does not simulate microgravity or radiation exposure. However, the greatest shortcoming to this approach (see important note below) is the very small sample size, in this case only 6, that can be studied at a time. In a pilot study, after only 105 days, sleep fragmentation was observed and correlated with high cortisol; however, there were no changes in cognitive or emotional state (Gemignani et al, 2014). In longer “missions” there are more significant changes. Loneliness has been reported (De La Torre et al, 2012). There is a prominent second half (although not third quarter effect), where mood and hormonal status changes significantly (Wang et al 2014). In a detailed study, using the Profile of Mood States (POMS), the Beck Depression Inventory (BDI) weekly and a conflict questionnaire, significant and interesting behavioral changes were observed. Overall, the crew reported more depressive symptoms in the second half of the mission, and one crewmember reached criteria for depression, while another reported very low mood states, but not reaching criteria. There were significant reports of conflict, more with mission control than with other crewmembers, and again these conflicts were mostly reported by the subjects with the most indicators of a depressed mood. Finally, in a post-mission questionnaire, the two crewmembers with the most depression were also the members with whom other subjects reported the least social communication (Basner et al, 2014). There was also overall, a
loss of sleep quality by all members (Basner et al, 2013). In a companion publication, these authors found increased cortisol and immune markers, including increased tumor necrosis factor – alpha, but no latent virus activation (Yi et al, 2014). There are no effects on three-dimensional vision, which is usually expected in confined spaces where distance is limited and no references to a horizon are possible (Sikl and Simecek, 2014). A more complete battery of biomarkers and a longer follow up period would be worthwhile. HI-SEAS (Hawaii Space Exploration Analog and Simulation) is a test facility which has had two “crews” on missions of 4 months each. There is a new crew currently expected to stay 270 days. There are as yet, no published findings. NEEMO: A permanent undersea (65 feet) station seven miles off Key Largo is referred to as the NASA Extreme Environment Mission Operations (NEEMO). Duration of stay is usually only 7-14 days, but many of the extreme confinement components are present. Elevated cortisol and immune changes have been reported (Crucian et al, 2014). Although time spent at this station can be lengthened to 30 days, the utility of this analog is limited. HERA Human Exploration Research Analog: This is a short-duration analog. It is currently being used in a study of biomarkers as predictors of susceptibility to stress. Duration as long as 60 days is proposed, for a crew of up to 4 in as many as 8 missions (for a total subject number of 32). This analog could be very useful for determining the effects of preflight manipulations to increase cohesion and social support. MARS2013: This is a 4-week analog field test in the Northern Sahara conducted largely by the Austrian Space Forum. Interestingly, it has been used to compare both the astronauts’ and mission controllers’ responses to psychological variables. It also states that the participants had been interactive for more than a month before the beginning of the mission. This could be a very important variable to consider in using any analogue approach. However, the psychological rating scales are not consistent with other approaches, making it difficult to use the information in an overall analysis (Groemer et al, 2014). Microgravity simulation: In the presence of the microgravity in space exploration, fluid shifts take place in the body, resulting in increased intracranial pressure. This effect can be mimicked by 45 days of -6 degrees head-down tilt bed rest. This has been proven to be a good model for predicting bone and muscle changes and for changes in immune function (Hoff et al, 2014). The subjects in these experiments have their usual social contacts, and there is no reason to
expect this could model isolation from family. However, interestingly, there is a loss in the degree centrality (ie how many functional connections with other brain regions) of the anterior cingulate cortex (Zhou et al, 2014). This brain region is relevant as it plays an important role in the functioning of the social support network and suggest that microgravity may have an effect on social behaviors, irrespective of the isolation from family and friends. More research on mood and mental changes are warranted.

It is important to note that meta-analyses of published studies have not been possible, due to the mixed methods and low sample number used in both the simulators and in actual astronauts. Better quality studies and replications are needed (Strangman et al, 2014).

1.3.2 Human conditions

There are several human conditions which can inform our understanding of the social support network, in terms of factors and anatomy of the system, as well as in an understanding of what other physiological and mental functions are dependent on it.

1.3.2a Autism. Autism is classified as a neurodevelopmental disorder, the primary characteristic of which is the lack of a properly functioning social brain. This is a spectrum disorder, which means that loss of social functioning could include loss of understanding of others emotions (theory of mind), loss of motivation and reward for social bonds and loss of social recognition or memory. All of these components of social behavior are essential for proper functioning of the social support network.

Autism can thus be considered as an extreme case of an inadequate social brain and lessons of anatomy and biology can be learned from it. Biomarkers and treatment and/or restorative interventions can be derived from studies of subjects with autism. Secondly, autism may tell us something about the social baseline theory, since it is also often associated with physiological changes (including immune function, sensory function and gastrointestinal issues) and psychiatric co-morbidities such as depression and anxiety. Although this has not been done to my knowledge, an interesting test of the social baseline theory could be to observe these secondary changes in adolescent autistics that have learned to improve their social functioning.
1.3.2b Loneliness. Loneliness arises when the basic human need for social support is not fulfilled, or perceived to not be fulfilled. There are physical health consequences to loneliness, the opposite of those positive benefits of social support. Loneliness increases the incidence of psychiatric problems as well including eating disorders (Levine, 2012) and depression (Hidaka, 2012). Chronic loneliness leads subjects to focus more on negative social interactions and to perceive rejection. Thus, people with loneliness can be considered the opposite of those with a strong social support network, and can be used to inform researchers about the basic underlying mechanisms of both. Many of the same brain regions, beginning with the amygdala, are involved, such as regions of prefrontal cortex, anterior cingulate cortex and reward centers. There are also, however, plastic changes in the bed nucleus of the stria terminalis, which may sustain adverse reactions to social isolation and make interventions more difficult. As well, loneliness can inform researchers about the neuroendocrinology of social support, as in this case, there is increased dysfunction of the HPA axis, directly correlating with immune dysfunction. Chronic loneliness leads to increased salivary cortisol, throughout the day (Cacioppo et al, 2014). There are gender effects in the endocrine effects of loneliness as people age, with women at more risk for inflammatory damage (Hackett et al, 2012).

Loneliness has another important consequence to consider – impulse control deficits, aggression and hostility – because perceived lack of social support can lead to increased self-preservation behaviors. Perceived loneliness as a young child is a positive indicator of later aggression (Schinka et al, 2013). Adolescent loneliness is associated with current aggression (Buelga et al, 2008) and early life stressors (in animal models or humans) leads to later aggression and anti-social behaviors (Haller et al, 2014). Whether an acutely developed loneliness, or a sense of loss of social support, in adulthood can lead to aggressive behaviors is not known, but a possibility worth investigating. Much new information could be gained by studying this population. For example, measures of loneliness, such as the UCLA Loneliness Scale and the Emotional and Social Loneliness scale of De Jong Gierveld could be correlated with potential biomarkers of the social support network. Interventions bringing about change could be tested. The Social Baseline Theory could be tested here as well.
1.3.3 Animal models

1.3.3a Prairie vole. The prairie vole (Microtus ochrogaster) is a prosocial vole, the study of which has led to most of our understanding of the role of oxytocin in social behaviors and is considered an excellent model for the neurobiology of selective social attachment (Resendez and Aragona, 2013). Most importantly, this vole shows mating-induced pair-bonding, which supports theories of biological synchrony in social bond formation. Once a pair-bond is formed, aggression is observed towards novel conspecifics. When separated from their preferred partner, prairie voles show increases in oxytocin receptors (possibly suggesting a loss of oxytocin) but increased plasma cortisol. The preference for the initial partner is lost after 4 weeks. This model may be useful in understanding the plasticity of social bonds, which would not be possible in rodent species which are not monogamous (Sun et al, 2014). The social behavior of these voles relies in part upon the non-synaptic release of oxytocin for the effects on social bonds and much information can be gained about volume transmission effects of oxytocin (Fuxe et al, 2013).

1.3.3b Socially isolated rats. Rats (and to a lesser extent mice: Arndt et al, 2009) have been very useful in studying the biology of social support networks, particularly by the use of isolation at critical periods. Times when bonds change (from maternal to peer for example) can be particularly useful in understanding the factors which lead to development and plasticity of the system. Thus, models include rodent maternal separation (Heim and Nemeroff, 2001, Plotsky and Meaney, 1993, Slotten et al., 2006 and Stevenson et al., 2008) isolation rearing post-weaning (Bellon et al., 2009, Fone and Porkess, 2008, Millan and Brocco, 2008 and Neill et al., 2010) and isolating adult animals.

Maternally deprived rat pups can be used to give information regarding the general factors which are involved in development and plasticity of the social support system; however, the effects of this procedure last throughout the animal’s lifespan and thus cannot be used to test resiliency or plasticity itself. Rats isolated at this time show anxious and depressive behaviors as adults. There is increased stress responding and changes in glucocorticoid signaling. When placed in a stressful situation as adults, the animals respond poorly, due to loss of plasticity caused by loss of BDNF in hippocampus,
prefrontal cortex and striatum (Roceri et al, 2004). There are longlasting changes in both oxytocin and vasopressin receptors, related to the decrease in adolescent social behaviors, such as play fighting which result from an inadequately formed social system (Veenema, 2012).

Post-weaning animals (PND 21, approximately 2 years of age in a human), deprived of littermates and thus the peer interaction referred to as juvenile play behaviors, have been used for over 50 years (Hatch et al, 1965) as a model of isolation-induced loss of the ability to process changing social environments. This model particularly reflects changes in prefrontal cortex in humans (Casey et al, 2005; Paus et al, 2008) and rodents (Counotte et al, 2010; Tseng and O'Donnell, 2005) as this is the time these regions are developing in response to the environment. Post-weaning isolated animals show less severe deficits than animals deprived from infancy but there are still significant changes in behavior and neurochemistry. Isolated animals show increased hyperactivity in a novel environment, increased reward sensitivity (addictive behaviors), increased aggression, and learning deficits (Fone and Porkess, 2008). These animals show sensory changes similar to schizophrenia and increased excitability of the amygdala (Gan et al, 2014) and there is a loss of synapses, suggesting a loss of plasticity and/or maintenance factors (Day-Wilson et al, 2006; Bianchi et al, 2006). Behaviors and neurochemical findings can generally be reversed with subsequent treatments, including by re-socialization. For example, behavioral changes, such as aggression, depression and anxiety can be overcome with a 5-HT1A receptor agonist (Ago et al, 2014) and although these animals show loss of serotonin, dopamine and noradrenaline (Whitaker-Azmitia et al, 2000; Moller et al, 2013) treating these animals, even after 8 weeks of isolation, with an antioxidant, n-acetyl cysteine (NAC) alters the content of monoamine neurotransmitters to levels comparable to that found in socially housed animals (Moller et al, 2013). Some behaviors are not reversed by re-socialization, for example, isolated rats show more addiction to cocaine, which would indicate persistent deficits in the reward/motivation circuit (Baarendse et al, 2014). Thus, these may be the best model for understanding plastic changes in the social network dependent on external environmental factors and how a healthy network can be maintained or restored.
Adult separation models have been used principally to study the beneficial effect of socialization on well-being and there are limited studies on the neurobiological consequences of adult isolation. Social housing improves healing in animal models of wounds and stroke (Karelina and DeVries, 2011). Animals housed with a cagemate show improved behavioral recovery which parallels an increase in BDNF and neurogenesis (Venna et al, 2014). Isolated animals showed decreased BDNF and depressive behaviors (O'Keefe et al, 2014) and slower recovery (Weil et al, 2008). Social interaction in mice decreases pain (Norman et al, 2010) and improves wound healing in hamsters (Detillion et al, 2004). Social housing reduces markers of inflammation such as IL-6, in the periphery, but increases IL-6 in brain where it may act as a neuroprotectant. Further, socially isolated animals show greater microglial activation after ischemia (Karelina and DeVries, 2011).

There have been a number of studies, using a model of social disruption, whereby socially housed animals have cagemates changed periodically (Berry et al, 2012). This approach causes less disruption to biological systems, but has behavioral consequences. This may be a very interesting model to use to further our understanding of maintenance and resilience in response to a changing social environment.

Taken together, the rodent studies show that the social support system is developmentally regulated and studies of different social housing arrangements can be useful in determining the biology of the social support system.

2. Biological Factors

2.1 Principal Factors

There are three principal biological factor involved in development and maintenance of the social support system: serotonin, cortisol and oxytocin/vasopressin. All of these factors have both organizing (developmental and neuroplastic) and activating effects, further emphasizing the role of experience driven plasticity in the social support network, and further suggesting that defects in plasticity would impact the social brain. Moreover, ever changing social environments are adapted to, and some bonds not used
may be lost – an important consideration for the effects of long-term absences from the usual social supports of friends and family.

2.1.1 Serotonin

Serotonin has both neurotransmitter (activating) and neurotrophic (organizing) properties in the brain in general, and in the social support network in particular. Once the brain is mature, serotonin acts as a classical neurotransmitter, although it retains its function as a developmental signal, by its role in experience driven neuroplasticity. Changes in the social environment throughout life, can change serotonin content and secondarily lead to changes in circuitry.

2.1.1a Serotonin in development and plasticity. Serotonin plays a number of key roles in development and plasticity, thus having a lifelong ability to shape neuronal circuits through a number of morphological changes.

Most importantly, serotonin promotes synaptogenesis and dendritic elaboration, thus forming and maintaining neuronal circuits. Animals depleted of serotonin during perinatal development, have a significant loss of synaptic structures throughout their life (Mazer et al, 1997). Depleting serotonin in an adult animal also leads to loss of synapses (Whitaker-Azmitia et al, 1995) but in this case, the role of serotonin in neuroplasticity is important, as the synaptic number can slowly recover as serotonin levels recover. The degree of synaptic plasticity is greater in adolescent than adult animals (Kobe et al, 2012) but recovery in the adult can be promoted by drugs which increase serotonin, such as the selective serotonin re-uptake inhibitors (SSRIs) and the serotonin precursor tryptophan. Loss of synapses, and regrowth in the presence of SSRIs (Liczerski and Duman, 2013) or monoamine oxidase inhibitors (Morais et al, 2014) is considered a major etiological and treatment factor in major depressive disorder.

Serotonin also acts as a neuroprotectant, maintaining cells which are otherwise lost through apoptosis during development. Animals depleted of serotonin perinatally show an earlier loss of cells as they age (Khozhai and Otellin, 2006; Vitalis et al, 2007). Many of the new theories on the mechanism of action of atypical antipsychotics in cognitive recovery, focus on the role of serotonin in neuroprotection (Kusumi et al, 2014).
Finally, serotonin also plays a role in determination of neuropeptides in hypothalamus during development, including vasopressin (Mirochnik et al, 2005) and oxytocin (McNamara et al, 2008).

2.1.1b Serotonin as a neurotransmitter. Serotonin is the most widely distributed monoamine neurotransmitter, making contact with virtually every cortical cell. Thus, as expected, serotonin has a number of important activating properties, most notably in depression and anxiety, both of which can be outcomes in subjects with low perceived social support.

Major depressive disorder has long been known to be associated with loss of serotonin function. Higher levels of serotonin are associated with greater sensitivity to reward and less to negative feedback (Bari et al, 2010). Depletion of brain serotonin in humans leads to mood and anxiety changes.

Fear and acquisition of anxiety states such as post-traumatic stress disorder (PTSD) and panic disorder are inhibited by serotonin and SSRI\textsuperscript{s} are a common therapy for these disorders. Childhood separation anxiety and social anxiety are also successfully treated with SSRIs and prevent the child from developing more severe psychiatric disturbances in adulthood (Mohatt et al, 2014). This effect is through 5-HT\textsubscript{1A} receptors in amygdala, hippocampus and prefrontal cortex. Interestingly, in animal models of early 5-HT\textsubscript{1A} loss, the effects on anxiety cannot be overcome with subsequent 5-HT\textsubscript{1A} treatment, suggesting that changes induced in adolescence or adulthood can be overcome through plasticity, while changes induced in infancy cannot. In further support of this, in humans, depression which is not responsive to SSRI\textsuperscript{s} is associated with early life adversity (Coplan et al, 2014). The 5-HT\textsubscript{1A} receptor in hippocampus is also involved in resilience and stress decreases the number of 5-HT\textsubscript{1A} receptors (Lopez et al, 1998). Serotonin projections from the raphe nuclei into the dorsal horn of the spinal column can regulate pain sensations. Chronic pain, including backache and neuropathic pain, (Jain and Jain, 2011) and fibromyalgia (Ablin and Buskila, 2013) can be effectively treated by SSRIs and the drugs of choice for treatment of migraine pain are the triptan class of drugs which act through the 5-HT\textsubscript{1B/D} receptors receptor. Serotonin projections to the gut slows
movement and leads to satiation but also pain and discomfort as well as nausea and vomiting (Mawe and Hoffman, 2013).

2.1.1c Serotonin role in the social circuit. Serotonin plays a role as both a neurotransmitter/activating factor and a neurodevelopmental/neuroplasticity factor in the social brain.

Serotonin, as a neurotransmitter, regulates social functions by buffering the response to stressors, increasing motivation for social interactions and increasing awareness of the emotions of others. Projections from the raphe nuclei, principally to 5-HT1A receptors play a role in coping behaviors, in the medial prefrontal cortex and amygdala. Serotonin decreases the release of corticotrophin releasing factor (CRF) from projections from the amygdala to the hypothalamus, and thus decreases cortisol. In animal studies, SSRIs decrease infant stress on removal from the mother and prevent the later damaging effects of maternal deprivation (Iijima and Chaki, 2005; Warnick et al, 2008).

Low serotonin in the amygdala is associated with increased aggression (Nelson and Trainor, 2007) and in vervet monkeys increasing serotonin through a variety of pharmacological interventions will increase the extent to which an animal will approach, sit next to and groom another animal (Raleigh et al, 1980). In human studies, increasing brain serotonin with the precursor tryptophan or with SSRIs increases sociability (Young, 2013), increases the amount of time making eye contact, a common measure of orienting to social cues (Di Simplicio et al, 2014), increases awareness of emotions in faces (Browning et al, 2007; Harmer et al, 2003), increases a measure of social affiliation (Knutson et al, 1998), and decreases hyperactivation of the amygdala (Murphy et al, 2009; Godliewska et al, 2012). Conversely, serotonin can be depleted with an amino acid drink, in which case subjects show an increase in irritability and aggression (Young and Leyton, 2002), loss of altruism in the prisoner’s dilemma game (Wood et al, 2006) and decreases in sharing and adjusting self reward to the needs of others (Bilderbeck et al, 2014) Autism, which may include both loss of social motivation and orienting, is associated with loss of serotonin (Azmitia et al, 2011; Chandana et al, 2005).
Much of what is known about the neurodevelopmental role in the social circuit, is based on animal isolation studies. Developmental manipulation of the social environment changes the brain serotonin system. Neonatal (Kosten et al, 2004) early postweaning (Whitaker-Azmitia et al, 2000; Kuramochi and Nakamura, 2009) (Moller et al, 2013) (Ishikawa and Ishikawa, 2013) (Kuramochi and Nakamura, 2009) or adolescent (Brenes and Fornaguera, 2009) isolation leads to loss of serotonin in the adult animal. The loss of serotonin content not only leads to loss of its activating effects in the adult, but also leads to a loss of neuroplasticity and a loss of resilience to stress, evidenced by a failure of SSRIs to reverse effects (Marsden et al, 2011). Singly housed mice do not respond to SSRIs with changes in behaviors, compared to group housed mice, suggesting that ongoing social stressors cannot be completely overcome by increasing serotonin (Dankoski et al. 2014). However, treating with an SSRI during a unique social stress paradigm – group housing but with continuously changed cagemates – reverses the effects on cortisol content (Scharf et al, 2013).

Serotonin has a unique relationship with oxytocin, both during development and in the adult brain. Increasing oxytocin during early development leads to more serotonin terminals in the hypothalamus and the amygdala (Eaton et al, 2011) and disruption of the serotonin system during development leads to loss of oxytocin content in the adult hypothalamus (McNamara et al, 2008). This interaction during development may explain how an infant appropriately bonded to its mother, will have a functioning serotonin system, protecting against anxiety and depression in later life. In the adult, there are projections from the raphe nuclei to the paraventricular cells of the hypothalamus (Sawchenko et al, 1983) which releases oxytocin. Thus serotonin agonists precursors, releasers and SSRIs (Lee et al, 2003; Emiliano et al, 2007) all stimulate the release of oxytocin, largely through 5-HT1A and 5-HT2 receptors (Jorgensen et al, 2003). A reciprocal relationship exists, whereby receptors for oxytocin are found on serotonin cell bodies in the raphe and may underlay oxytocin effects at decreasing anxiety (Yoshida et al, 2009). A recent study of intranasal oxytocin effects, shows that oxytocin may increase 5-HT1A receptor number (Mottolese et al, 2014). Treatment of depression with an SSRI increases oxytocin, but only in those subjects who respond to treatment (Humble et al, 2013).
Serotonin also has a unique relationship with the neurotrophin, BDNF and much of serotonin’s effects as a brain plasticity factor may be due to this relationship. In a rat model of social stress, the SSRI, escitalopram, raises cortical BDNF levels (Schulte-Herbruggen et al, 2009). Treating with 5-hydroxytryptophan in humans increases plasma BDNF (Emanuele et al, 2010) and treatment of depression with an SSRI parallels increase in serum BDNF and improvement in mood (Gonul et al, 2005; Matrisciano et al, 2009; Sun et al, 2014).

In summary, even in the adult brain, social isolation or removal from the typical social supports could lead to loss of serotonin. This in turn, could lead to loss of oxytocin, BDNF and overall a decreased buffering of cortisol. This may then lead to psychological and physiological manifestations of loss of social support, including depression and anxiety and changes in immune markers, increased pain and headaches.

### 2.1.2 Oxytocin

Oxytocin and vasopressin are two related nonapeptide neuromodulators and neurohormones, highly involved in all steps of social bonding, from recognition of emotions in others, motivation for bonding, memory for emotional partners and reward. Moreover, these peptides are involved in all ages, from maternal-infant, to adult behaviors with peers and pair-bonding and thus are proposed to play significant roles in the experience-driven development of the social support system. Both peptides have brain and body effects and as such, are highly localized to the hypothalamus. There is wide species variability in amino acid content and in receptor specificity (Kelly and Gordon, 2014).

Oxytocin and vasopressin differ by only two amino acids and both have a disulfide bridge in the tertiary structure. Cell bodies of oxytocin and vasopressin neurons are found principally in two nuclei of the hypothalamus – the supraoptic nucleus and the paraventricular nucleus. Although found in different cell populations, the two populations are closely related and often in contact. Vasopressin is also produced in the bed nucleus of the stria terminalis and the suprachiasmatic nucleus. Based on the presence of more cells in these regions, it has been proposed that vasopressin action is more important in the male brain. Both oxytocin and vasopressin can be released in the brain volumetrically.
and thus can act in a paracrine manner, and no direct innervation is required. This means that these peptides can be released within the hypothalamus, but influence receptors at a distal location with no direct innervation necessary. A co-ordinated release across many brain regions making up the social network at once, is therefore likely responsible for their effects. Both oxytocin and vasopressin project to brain and to the body, through the posterior pituitary. Receptors for oxytocin (OTR) and vasopressin (VP1, VP2, VP3 and VP4) are said to be “promiscuous” in that all receptors recognize both peptides. Because of the paracrine effects and the promiscuity of receptors it is probably best to consider these peptides as neuromodulators rather than direct neurotransmitters.

Oxytocin has been shown to provide the neurohormonal substrate for virtually all aspects of social bonding including a role in pair-bonding, maternal bonding, social memory and recognition and in decreasing aggression and calming animals in a novel social environment (Feldman, 2012). More importantly, oxytocin is the hormone of biological/behavioral synchrony: when a group collaborates, the same physiological processes take place in all members and a social group is formed through plastic changes in neuronal connections. For example, a nursing mother and infant will both have a rise in oxytocin levels and a permanent bond between them will be formed (Feldman, 2007) and it has been suggested that oxytocin promotes performance in team sports (Pepping and Timmermans, 2012).

2.1.2a Organizing/neuroplastic. It is important to note the role of oxytocin in memory, as this indicates the formation of a bond and that oxytocin functions as an organizing/neuroplastic factor. Early in development, oxytocin influences both maternal and infant care, and biological synchrony. High maternal care, or treatment with oxytocinergic agents, shows increased parent/infant bonding in both rodents and humans (Mogi et al, 2014; Weisman et al, 2012) Oxytocin induces maternal behaviors, such as licking and pup retrieval, even in virgin female rats (Pedersen and Prange, 1979) and correlates with degree of care in rodents. In humans, the amount of increase in oxytocin over the gestational period, correlates with later maternal behavior (Levine et al, 2007). Maternal separation reduces later social behaviors and programs fewer oxytocin and vasopressin receptors in rats (Lukas et al, 2010), while increased maternal care programs
increased oxytocin receptors throughout life (Champagne and Meaney, 2007). In human studies, children neglected as infants do not show the same elevation in oxytocin as typically developing children, when engaged in activities with adopted caregivers (Fries et al, 2005). Directly assessing the role of oxytocin in this neonatal programming, shows that sociability in the adult rodent is influenced by treatment with oxytocin, or oxytocin antagonist, in the first few days of life (Mogi et al, 2014). Children who show high oxytocin synchrony with their mothers as infants, show more empathy and sharing as 3 year olds and more perspective-taking and problem-solving with peers at 13 years of age (Feldman, 2012). Adolescent rats exposed to oxytocin have reduced anxiety and increased social ability as adults, suggesting that the critical period for oxytocin programming of the social circuit continues at least into adolescence (Bowen et al, 2011).

Oxytocin promotes social recognition memories by inducing plastic synaptic changes in the amygdala. Adult rats socially isolated for 7 days show deficits in acquiring social memories and also do not show a plastic response to oxytocin (Gur et al, 2014). These findings imply that the social circuit very rapidly becomes incapable of plasticity after isolation. Social bonds in humans are also greatly enhanced by oxytocin – amount of oxytocin measured in newly falling in love subjects is highest and remain highest in those partners who stay together and show stable reciprocal social bonds (Schneiderman et al, 2012).

**2.1.2c Activating: acute effects.** The role of oxytocin as a mediator of social functions was first described in studies by Insel and Young in 1992, who examined the differences between two species of vole – the prairie vole vs the meadow vole. The prairie vole participates in pair-bonding, while the meadow vole does not. The principal difference between these voles, is the high number of oxytocin receptors in the hypothalamus of the prairie vole. Since those early studies, a great deal of work has been done on the role of oxytocin in all forms of social bonding, in both human studies and animal models.

Oxytocin containing cells project to many brain regions involved in affiliative behaviors: medial preoptic area, the bed nucleus stria terminalis, the lateral septum, nucleus accumbens, amygdala, hippocampus and ventral tegmentum (VTA). This
indicates the widespread activating influence of oxytocin in social behaviors. In imaging studies of intranasal oxytocin, all of these brain regions are shown to be activated. However, the focus of oxytocin’s activity is in decreasing reactivity of the amygdala. Secondarily, there are strengthening of some functional connections within the social circuit, such as the insula and anterior cingulate.

Oxytocin effects can be studied either by acute administration of oxytocin, looking for behavioral changes, or by correlating endogenously released oxytocin with an observed behavior. Both human and animal studies have proven informative.

In the earliest studies of the role of oxytocin in affiliative behaviors, it was assumed that most of its effects were positive – increasing trust, motivation and overall social bonding. However, more recently, the role of oxytocin has been seen to be more nuanced – increasing positive behaviors only towards the in-group and increasing hostility towards others. Overall, these studies have shown an effect of oxytocin in decreasing amygdala reactivity (Kanat et al, 2014).

Starting first with recognition of emotions in others, in a review of published papers, the overall effect of oxytocin is to increase recognition of emotion in faces, particularly emotions which signal the social relationship such as happy or fearful, and less to increase awareness of sad faces (Shahrestani et al, 2013). In those with early life stress, it does not have an effect on emotional recognition (Feesser et al, 2014). There are gender differences, with females rating faces more positively and males, more negatively (Hoge et al, 2014), reflecting the evolutionarily conserved roles, of females tending to promote and increase social bonds, while males increase bonds only to their own existing group and in fact become hostile to outgroup members – the so-called “tend or defend” gender dichotomy. Intranasal oxytocin also increases the perception of bonds and secure attachments one perceives between others (Buchheim et al, 2009).

This role in increasing ingroup bonds preferentially is evident in pair bonding. Intranasal oxytocin activates the VTA and makes men view women as more attractive, however the greatest increase is in response to their own romantic partners, showing that oxytocin effects are specifically greatest in maintaining already existing bonds (Scheele et al, 2013). Moreover, oxytocin increases the physical distance between men and novel
attractive women only if the men are in a committed relationship, suggesting that oxytocin may help promote fidelity in monogamous relationships (Scheele et al., 2012).

Intranasal oxytocin increases bonding to in-group members and can increase hostility to outgroup (Ma et al., 2014). Dishonesty which has gains for the ingroup is increased by oxytocin (Shalvi and De Dreu, 2014). Increased social behaviors occurs most in specific situations, such as when subjects perceive themselves to be in a safe environment. When subjects feel themselves to be in an unsafe environment, anti-social behaviors may actually be induced in humans (Olff et al., 2013) and in a stress-inducing paradigm (a form of the Trier Test) oxytocin increases perceived stress and heightens self-interest (Eckstein et al., 2014). As in emotional recognition studies, there are gender differences. In response to intranasal oxytocin, men show increased self-interest in moral dilemmas, while women suppress self-interest and act more altruistically (Scheele et al., 2014).

2.1.2c Oxytocin as the mediator of benefits of social support. Evidence suggests that much of the effects of social support on physical and emotional well-being is related to release of oxytocin. Direct injections of oxytocin to rats decreases blood pressure and speeds wound healing (Uvnas-Moberg, 1998) and recovery from ischemic damage (Karelina and DeVries, 2011). Conversely, treatment with an oxytocin receptor antagonist, atosiban, slows recovery (Karelina et al., 2011). Many environmental manipulations in humans known to increase well-being can also be shown to release oxytocin – including gentle touch or massage, meditation and music (Chanda and Levitin, 2013). Interestingly, the sound of a loved one’s voice (but not text messages) raises oxytocin levels (Seltzer et al., 2012), emphasizing further the role of verbal communication in maintaining and nurturing social bonds.

Oxytocin may play a dual role in the health benefits of social support – by buffering the effects of cortisol and by directly interacting with receptors in select brain regions and in peripheral organs.

Cortisol Buffering: In animal studies, centrally infused oxytocin has been shown to exert stress-buffering effects (Windle et al., 1997) and chronic stress increases oxytocin receptor number (Liberzon et al., 1997). Oxytocin or social housing heals burns (Iseri et al,
2009) and gastric injuries (Iseri et al, 2005; 2008). In humans, the findings can be much more context specific. Acute stress (Trier) may stimulate oxytocin secretion, (Pierrehumbert et al, 2010) specifically in adults who experienced childhood trauma (Seltzer et al, 2013). Intranasal oxytocin decreases cortisol response in a number of stress-inducing paradigms, including the Trier (Heinrichs et al, 2003), couples conflict resolution (Ditzen et al, 2009) and to the interpersonal stress of social rejection (Linnen et al, 2012). Intranasal oxytocin decreases salivary levels of cortisol in typical males. Interestingly, in males with a history of adverse childhood events, this effect is attenuated, suggesting that a dysfunction of the oxytocin/social axis may arise in development, just as the dysfunction in the HPA axis does (Meinschmidt and Heim, 2007).

**Direct receptor effects:** Oxytocin has specific effects of its own through the oxytocin receptor. Intranasal oxytocin can reduce pain awareness (Goodin et al, 2014; Rash and Campbell, 2014) and a recent study shows that intranasal oxytocin can relieve headaches (Wang et al, 2013). These effects may be directly on oxytocin receptors found in the periaqueductal grey (Yang et al, 2011). Receptors in the brain and periphery combine for a role in energy homeostasis - decreasing food intake and changing metabolic levels and heat production (Chaves et al, 2013). Oxytocin receptors in brainstem and directly in cardiac and blood vessels play a beneficial role in the cardiovascular system, protecting against hypertension and cardiac pathology (Jankowski et al, 2010) In socially isolated rats, oxytocin receptors are downregulated in hypothalamus and heart (Pournajafi-Nazarloo et al, 2013). The interactions between oxytocin and the immune system are complex, reciprocal and sensitive to regulation by feedback (Yang et al, 2013). Oxytocin receptors are found in thymus and on macrophages while cytokine receptors are found on oxytocin-containing cell bodies of the hypothalamus. Considering that immune dysfunction is a prime physiological change in spaceflight (Crucian and Sams, 2009), further investigations into this relationship is warranted.

Given its role in social functioning, intranasal oxytocin has been used in many clinical populations with social deficits and findings are encouraging, although there is much to learn about regulation and plasticity of the oxytocin system itself before reasonable dosing schedules can be determined.
The most successful findings have been in autism, although results are mixed, probably largely due to differences in autism itself (Guastella et al, 2014). However, a review of seven randomized controlled studies, found that at least one measure was improved in each trial for autism (Preti et a, 2014) In autism, oxytocin can improve understanding the emotions of others (Aoki et al, 2014). Oxytocin has proven successful as add on therapy to an SSRI in treatment resistant patients (Scantamburlo et al, 2014) Oxytocin increases emotional recognition and perspective taking in schizophrenia (Gibson et al, 2014). Overall, the effects of oxytocin are attenuated in subjects whose conditions may be in part due to childhood stressors or trauma (Bakermans-Kranenburg and van Ijzendoom, 2013).

2.1.2d Oxytocin as a biomarker. The oxytocin receptor is found in high densities in areas associated with the social circuit – amygdala, ventral striatum (Insel and Shapiro, 1991) as well as in various peripheral organs and tissues. As is typical of factors with organizing properties, the receptors peak at key times of development, both in animal models and in humans (Kang et al, 2011) and are programmable (Bales and Perkeybile, 2012). Receptors are programmed by high maternal care in rodents with increased oxytocin receptors in the amygdala. These effects are long-lasting and lead to behavioral differences as adults (Francis et al, 2002, 2000). Human studies of intranasal oxytocin showing that subjects with adverse childhood events have a decreased response, suggest that human receptors are also programmable. (Meinslschmidt and Heim, 2007). Animal studies, show that in adults, chronic oxytocin downregulates social effects, suggesting that the oxytocin receptor continues to be programmable (plastic) by changes in stimulation (Huang et al, 2013).

Although much has been made of the contributions of different alleles of the oxytocin receptor to social functioning, a comprehensive meta- analysis of genotypes concluded that two of the most intensively studied OXTR SNPs (rs53576 and rs2254298) failed to explain a significant part of human social behavior (Bakermans-Kranenburg and van Ijzendoom, 2014). However, urinary oxytocin may be useful as a peripheral marker of the strength of social relationships. Released oxytocin can be measured 30-60 minutes after a behavioral event relatively non-invasively in urine using RIA and although there
are some questions of how accurately this depicts central oxytocin, it has been used reliably as a measure of social relationships (Crockford et al, 2014; Saito et al, 2014) including studies of interactions between close friends leading to greater memories eventually leading to preference for that friend (Feldman, 2012). Oxytocin levels in plasma of newly arrived immigrants predict loneliness and social functioning months later (Gouin et al, 2015). Plasma levels have been found to correlate with social cognition, in both control and schizophrenics (Frost et al, 2014) and in schizophrenics with severe social withdrawal and few attachments, plasma levels of oxytocin are greatly reduced (Jobst et al, 2014). Plasma oxytocin is also reduced in subjects with borderline personality disorder and becomes even more reduced when subjects experience the social exclusion of cyberball (Jobst et al, 2014). This implies that plasma oxytocin can be used as a measure of resiliency to social exclusion.

Although there is an extensive literature on vasopressin in animals, there is less, and often contradictory, literature in humans. A brief review follows; however, until more research is done, vasopressin is not likely to prove useful as a biomarker.

Vasopressin has been studied in a limited number of intranasal administration studies, where it has been found to increase perception and reciprocal responding of friendliness in faces in females, but to decrease it in males (Thompson et al, 2006). Vasopressin may impair facial recognition in general in males (Uzefovsky et al, 2011) and has no effect on increasing trust (Rilling et al, 2011). High plasma levels in fathers correlate with sharing interest in inanimate objects with infants, but not with social interests (Apter-Levi et al, 2014). Plasma levels have been associated with marital distress in men, but not women (Taylor et al, 2010). Higher levels of plasma vasopressin correlate with more community social interactions, but also with more negative marital interactions and avoidance of attachment (Gouin et al, 2012). However, this same group has found higher levels of vasopressin to be associated with fewer negative interactions in a married couple, in both males and females (Gouin et al, 2010), making the use of vasopressin as a biomarker for social interactions problematic.
2.1.3 Brain-derived neurotrophic factor

Neurotrophins are a family of proteins which include nerve growth factor (NGF), neurotrophins 2 and 3 and BDNF (Reichardt, 2006). All of these factors are related by highly conserved amino acid sequences, close molecular weights and all form dimers for activity. They all have some biological activity through stimulation of the p75 receptor; however, each also has a specific tyrosine kinase (Trk) receptor, and for BDNF this is the TrkB receptor. In the developing brain, BDNF has a role in proliferation, migration, survival and differentiation (Lee et al, 2002). In the adult brain, BDNF is found throughout the brain, but is especially high in brain regions which require high levels of neuroplasticity for proper functioning, including the hippocampus, amygdala, striatum and frontal cortex. BDNF is produced in all brain cell types, including neurons, microglia, astroglia and oligodendroglia. The neurotransmitter glutamate is most often involved in release, through a metabotropic receptor, although serotonin and acetylcholine can also cause release. Released BDNF can be transported to the pre-synaptic or post-synaptic neighboring neuron, and thus influence cell morphology (Tapia-Arancibia et al, 2004).

BDNF translates activity signals, arising from environmental manipulations, into plastic changes in the neuronal structure. Positive environmental influences, such as receiving maternal or other care, increases BDNF and strengthens neurons. There is a large literature on the effects of exercise in increasing BDNF and it has been suggested to be the intermediary, by which exercise prevents or attenuates brain degenerative disorders, including Alzheimer’s disease. Serotonin may have much of its effects in neuroplasticity through release of BDNF and the actions of the SSRIs in improving depression are likely to be dependent on this action. BDNF has a reciprocal effect on serotonin maintenance (Altar, 1999). BDNF’s effect on dopamine neurons enhances rewarded-mediated behaviors (Nikulina et al, 2014). Acute increases in cortisol increase BDNF expression, and this is a mechanism by which cortisol can induce neuroplastic changes necessary for memory (Marnigere et al, 2003). Conversely, chronic stress or a dysregulated HPA axis, decreases BDNF and synapses and neurons are damaged (Duman, 2004). BDNF is lost with normal aging (Primiani et al, 2014), in neurodegenerative diseases such as Huntington’s Chorea (Zuccato and Cattaneo, 2014) and with chronic sleep loss (Zielinski et al, 2014).
In the post-weaning social isolation model in rodents, BDNF is decreased in hippocampus (Bjornebekk et al, 2007; Djouma et al, 2006). Interestingly, the loss of BDNF is not related to corticosterone levels. In socially isolated adult rats, BDNF expression is decreased (Barrientos et al, 2003, Scaccianoce et al, 2006) and BDNF is decreased after social defeat (Fanous et al, 2010). Social deprivation stress leads to loss of BDNF in adult mice; however it is not decreased in the continuous changing of cagemates model of social stress (Berry et al, 2012). In a mouse model of stroke, social interactions increase behavioral and neuronal recovery, paralleled with changes in BDNF (Venna et al, 2014) while social isolation after stroke decreases BDNF and decreases recovery (O'Keefe et al, 2014). These latter studies suggest that BDNF may be a good marker for resilience and adaptation to social environmental changes – it is decreased in chronic stress, but this decrease is attenuated in the face of a changing/challenging environment.

BDNF genetic variations result from a single nucleotide polymorphism (SNP) which substitutes valine (Val) for methionine (Met) at codon 66 and is referred to as the Val66Met polymorphism. Although extensive research has shown that this substitution should effect expression and secretion, the human studies comparing genetic variation with cognitive or emotional tasks or hippocampal volume, have been largely negative (Kim et al, 2015).

However, BDNF levels can be measured in plasma (Sen et al, 2008) using a commercially available ELISA kit and this has become a reliable biomarker for brain plastic events. Interesting human studies have shown changes in BDNF to parallel SSRI response in depression and studies showing it is negatively correlated with avoidance of social bonding – e.g., the more likely someone is to say they do not want others to know their true feelings, the less BDNF is found in plasma (Marazziti et al, 2009). Measures in subjects recovering from a romantic loss show improvement with mood correlates with changes in BDNF levels (Emanuele et al, 2010).

2.1.4 Cortisol

While serotonin, oxytocin and BDNF are all primarily positive modulators of the development and maintenance of the social circuit in brain, cortisol is the major negative
modulator. Stress, including social stress, can increase cortisol, resulting in significant mental and physiological impairments. Social support has its beneficial effects largely by buffering cortisol.

Brain pathways from the amygdala, prefrontal cortex, hippocampus and sensory cortex send messages to the paraventricular nucleus of the hypothalamus to release CRF to the pituitary, which releases adrenocorticotropic hormone (ACTH) into the bloodstream. ACTH then releases cortisol from the adrenal glands. CRF, ACTH and cortisol levels can all be monitored to determine the reactivity of the hypothalamic-pituitary-adrenal (HPA) axis. Cortisol is a steroid hormone, passing easily into the brain from the adrenals, with specific glucocorticoid (GR) and mineralocorticoid (MR) receptors in the prefrontal cortex, hippocampus, amygdala and anterior cingulate. These are nuclear receptors, and thus remodeling of circuits can result throughout the lifespan. Cortisol also has direct effects on peripheral systems including mobilizing glucose for energy, suppressing immune and inflammatory responses and decreasing sex hormone synthesis.

Initially, cortisol release is essential for homeostasis, by increasing arousal, sharpening mental acuity and attention and increasing energy. After the initial stressor passes, cortisol levels return to baseline. There is a significant negative feedback loop to the hypothalamus, minimizing the chance of long-term overexposure to cortisol. However, in susceptible individuals, cortisol levels remain high, even when the stress is gone. In this case, the HPA is unregulated or dysregulated and pathologies can result. The hippocampus and prefrontal cortex can lose dendrites and cells, while the amygdala undergoes plasticity to increase synapses. This could result in mental disorders such as depression and anxiety. Consequences to the peripheral system include metabolic syndrome (due to insulin resistance), cardiovascular damage, gastrointestinal disturbances and severe damage to the immune system, leading to an increased risk of cancers. There are changes in cortisol content in spaceflight crewmembers, which vary by the length of the flight, with short flights showing pre-and post-landing increases, but long duration, showing increases only on landing (Stowe et al, 2011). In the 520-d isolation paradigm, morning cortisol levels were elevated throughout and the immune
response was concomitantly dysfunctional (Yi et al, 2014). Clearly cortisol levels should be constantly monitored during space flight.

The HPA axis is programmed by early life experiences. In animals, maternal neglect or prenatal stress, results in behavioral changes in the adult, similar to depression and anxiety, as well as social disorders and changes in reward responding (Matthews and Robbins, 2003). There are structural changes to the hippocampus, prefrontal cortex and amygdala. In humans early or prenatal stress is associated with anxiety and depression (Charil et al, 2010) but importantly, also an increase in the incidence of autism (Ronald et al, 2011; Walder et al, 2014; Whitaker-Azmitia et al, 2014), a disorder best known for its social deficits. As in the animal studies, there are structural changes in prefrontal cortex, amygdala, hippocampus and striatum. In addition to behavioral changes, there are lifelong changes in reactivity – early life stress leads to over-reactivity and increase in cortisol to stress later in life (Finn and England, 1997). Toddlers with insecure attachment to their mothers show increased cortisol reactivity in strange situations (Nachmias et al 1996). In adolescence, cortisol programming continues to be important. Post-weaning isolated rats show normal corticosterone but accentuated response of the HPA axis in acute stress (Serra et al, 2007). In young non-human primates isolated, cortisol is increased and neurogenesis in the hippocampus is decreased (Cinini et al, 2014).

Social support can buffer against the effects of stress and high cortisol at all periods in life (Davidson and McEwen, 2012). Cortisol levels increased by aversive stimuli are moderated when a friend is present (Kirschbaum et al, 1995; Devries et al, 2003) and the more social support someone has in general, the less cortisol is activated during a social stressor (Eisenberger et al, 2007). In married partners, cortisol levels are physiologically synchronous, co-varying over the day (Papp et al, 2013). The more time spent in an intimate relationship, the lower the cortisol level becomes (Ditzen et al, 2008). Cortisol is decreased by massage (Field, 2014). Conversely, subjects with marital discord, show dysregulation of the HPA axis (Barnett et al, 2005). On receiving counselling, and noting improved relationships, cortisol regulation improves (Ditzen et al, 2011). In human conditions associated with deficits in social functioning, cortisol dysregulation is commonly found. Subjects experiencing loneliness have a dysregulated
HPA axis (Cacioppo et al, 2002; Adam, 2006; Doane and Adam, 2010; Matias et al, 2011) Subjects with autism show heightened HPA reactivity to social situations, but blunted activity during isolation or physiological challenge (Taylor and Corbett, 2014).

In addition to decreasing cortisol response, social support also increases oxytocin response. Together, less cortisol and more oxytocin, can be the major mechanism by which social support buffers from stress.

### 2.2 Modulating Factors

#### 2.2.1 Dopamine

The catecholamine neurotransmitter dopamine is involved in reward and motivation – that is the process of working to achieve a reward. This function depends on the individual as well as the intensity of the reward (drugs such as cocaine representing a large reward). In the social system, an individual’s desire for the reward of social interaction is dependent on a dopamine process. Dopamine is produced in the ventral tegmental area (VTA) and substantia nigra and the nucleus accumbens (part of the ventral striatum) is often thought to be the important projecting region (Berridge, 2007). The VTA is capable of conditioning and the recurrence of a pleasurable stimuli will lead to increased activity in these neurons when a cue for a stimulus is present (Depue and Collins, 1999). Dopamine neurons in the VTA are highly dependent on BDNF for trophic support, development and plasticity. After repeated pairing of cue and reward, synaptic plasticity takes place, and circuits are remodeled in response to repeated pleasurable/rewarded experiences (Grueler et al, 2012).

In the social support context, dopamine activity can be seen as a motivator to acquire attachment and this motivation increases the more often the attachment is rewarded and when cues (such as the voice or picture of a loved one) are present. Social support is associated with density of D2/3 receptors in the nucleus accumbens (Martinez, 2010) and giving support to a loved one (particularly one in need) is associated with increased activity here as well (Inagaki and Eisenberger, 2012).

Oxytocin mediates the reward value of social stimuli by stimulation of its receptors in the VTA, leading to release of dopamine in the nucleus accumbens. This leads to an increased synaptic density for the original social stimuli (Love, 2014). Maternal-pup
interactions release dopamine in the nucleus accumbens, and treatment with a dopamine receptor antagonist leads to decreased interactions. Interestingly, in maternal rats with the highest degree of interactions, the amount of oxytocin projecting to the VTA is greatly increased, showing that the motivation for dams to interact with their pups is oxytocin driven. Using fMRI, human mothers shown pictures of their young, activate a similar reward circuit and the degree of activation correlates with oxytocin blood levels (Strathearn et al, 2009).

A similar dopamine/reward system is activated in pair bonding. In studies of the monogamous prairie vole, blocking dopamine receptors leads to loss of pair bonding after mating, in spite of there being an increase in oxytocin (Aragona et al, 2003). As in maternal/infant bonding, it is oxytocin driven changes in dopamine which are responsible and it appears that both systems must be functioning for pair bonding to take place (Love, 2014). In human fMRI studies of subjects viewing their partners’ faces, the same mechanism appears to be at work (Aron et al, 2005).

Clearly, dopamine is important for social bonds to be rewarded and thus maintained. What happens during isolation? Post weaning isolation causes loss of dopamine (Moller et al, 2013) and loss lasts after re-socialization. In adult rats, isolated as adults, there is a decrease of dopamine function in the nucleus accumbens and a decrease in dopamine response to novelty (Miura et al, 2002) with a resultant decrease in exploring a novel environment. Decreased dopamine has also been reported in the prefrontal cortex (Fabricius et al, 2011).

However, in stressful situations, dopamine responses change significantly – a phenomena referred to as dopamine sensitization. A stressed rat in response to psychostimulants, shows increased dopamine activation (Trainor, 2011; Shimamoto et al, 2014). This leads to an increased vulnerability for addiction. Similarly, in humans, acute stress downregulates the reward system (Montoya et al, 2014) but in subjects reporting loneliness there is a heightened response to amphetamines (Gevonden et al, 2014). The social defeat or social exclusion hypothesis of schizophrenia, centers on findings of sensitization to dopamine following a lifetime of being socially excluded (Selten et al, 2013). This suggests that in humans, long-term stress sensitizes dopamine systems, while short term decreases it. In terms of social behaviors, this would suggest that a
subject would have a larger reward when experiencing social interactions and would more readily form bonds, under stressful situations, as in the experience of a long spaceflight. This suggestion would also explain the lifelong bonds formed between college roommates or between military personnel serving together – although these observations are well known, they have never been explored for the biological basis.

### 2.2.2 Neurosteroids and steroid hormones

There is a growing literature on the role of neurosteroids in the development and maintenance of the brain. In particular, allopreganaolone (ALLO) has increasingly become a neurosteroid worth studying. ALLO is one of the neurosteroids found in brain, either synthesized there directly from progesterone, or synthesized from progesterone produced by the ovaries. ALLO binds to subunits of the GABA-A receptor and leads to increased inhibition of glutamate firing, particularly in hippocampus, amygdala and prefrontal cortex and promotes proliferation of both human and rodent neural precursors (Wang et al, 2005). ALLO is decreased in both post-weaning and adult socially isolated rats (Bali and Jaggi, 2013; Serra et al, 2008). Treating with ALLO, either during or after isolation, restores function (Evans et al 2012). Isolated mice also show loss of ALLO in corticolimbic circuits (Agis-Balboa et al, 2007). In humans, lowered blood ALLO is found in depression and PTSD and is found to increase after successful treatment with an SSRI (Nin et al, 2011). There is an interest in producing ALLO agonists to act as antianxiety and sedating agents, without the addictive properties of benzodiazepines. The potential of these agents to maintain the social support circuitry may be worth exploring.

Competition and tension are commonly found in space travel simulations (Sandal, 2001) and testosterone levels are increased during competition and social challenges, which may produce a lasting effect on neuronal morphology. Testosterone levels have been measured in the crew of a simulated 105-day space mission and found to be correlated with behavioral changes (Ushakov et al 2012). In a recent review, the hypothesis has been put forward that testosterone is the balance to oxytocin – for example where oxytocin increases trust and decreases amygdala activation, testosterone decreases trust and increases amygdala activation (Crespi, 2015). In acute placebo-controlled administration studies of testosterone, it does indeed decrease trust, increase
risk taking, reduce empathy, activate the amygdala and reduce orbitofrontal control of the amygdala (as reviewed in Bos et al, 2012). Salivary levels of testosterone correlates with high dominance in adolescents (Rowe et al, 2004) and adults (Carre et al, 2009). Winning various competitions increases testosterone in general. Putting these observations together, it has been suggested that high testosterone subjects in a high status position do well in cognitive and social tasks, while high testosterone individuals in low status positions do poorly in testing (Newman et al, 2005). More work on the role of testosterone in the biology of social support is clearly worthwhile.

Testosterone plays a role in neurogenesis in the hippocampus. Typical levels prevent the loss of neurogenesis induced by social isolation, but high levels are detrimental (Spritzer et al, 2011). Loneliness increases testosterone in females, although there are no changes in males (Fujisawa et al, 2011).

### 2.2.3 Endorphins

The endogenous opiate system, the endorphins and its receptors, is also important for pair-bonding in primates and there are interesting proposals that the pain of social rejection or isolation is similar in brain and hormonal substrates to those underlying physical pain (Eisenberger et al, 2006). Some researchers have suggested that although oxytocin facilitates social interactions, it is actually beta-endorphin which forms and maintains bonds (Depue et al, 2005). Removing infant animals from their mothers results in crying, which is blocked by the addition of low doses of morphine (Panksepp et al, 1978). Endorphins buffer against the increase in cortisol after monkey pairs are separated (Ragen et al, 2013) and increase maternal care (Martel et al, 1993) and other non-familial bonding (Keverne et al, 1989; Schino and Troisi, 1992; Martel et al, 1995). In human PET studies, endogenous opiates, acting at the μ-opioid receptor act to buffer social rejection (Hsu et al, 2013). Although not near so well studied as other modulators, this system should not be overlooked, particularly in rewarded or motivated social behaviors (Chelnokova et al, 2014).
2.2.4 Neuropeptide Y

Neuropeptide Y (NPY) is a 36 amino acid peptide found in both the peripheral and central nervous systems. In general, NPY has action as an anxiolytic and CNS depressant, serving as an antiepileptic and neuroprotectant, inhibiting excitotoxicity (Malva et al, 2012). It is often co-localized with CRF containing neurons and thus may have a direct effect in mitigating the effects of stress. In addition to effects on the HPA axis, NPY also modulates the catecholamine and fight or flight response to acute stress and mediates the central response to an immune challenge (Painsipp et al, 2008), by downregulating microglial activation through a metabotropic Y receptor. NPY also plays a role in feeding (Malva et al, 2012). NPY is one of the most abundant neuropeptides and can be found in widespread regions, including amygdala, hippocampus and hypothalamus. NPY has been suggested to be a necessary component of resilience (Enman et al, 2015) and may be used as a biomarker for this purpose (Morgan et al, 2000; Yehuda et al, 2006).

3. Brain Regions and Networks in the Social Support System

3.1 Cellular Components

3.1.1 Von economos neurons

Recent work has suggested the importance of large spindle-shaped cells in layer V of specific brain regions associated with the social brain, such as the frontoinsular cortex and the anterior cingulate cortex (Nimchinsky et al, 1999; Cauda et al, 2014). These cells are first evident in the late stages of gestation and increase dramatically during the first 8 months of life. They have evolved relatively recently and are involved in fast communication supporting social networks (Allman et al, 2005). They are found in humans and non-human primates (Cauda et al, 2014). Since they are increasingly found in species with a highly developed social life, they are sometimes used as “markers” of social areas (Allman et al, 2010). These neurons are rich in both dopamine and serotonin inputs (Cauda et al, 2014).
3.1.2 Oligodendroglia

Myelination, the primary function of oligodendroglial cells, is key in developing and maintaining fast communication between specific brain regions involved in any circuit, including the social circuit, and is therefore an important component of adult plasticity. Myelin deficits are observed in autism (Deoni et al, 2014) and the demyelinating disease, multiple sclerosis, is associated with social deficits (Charvet et al, 2014). In animals suffering from early life adversity, high cortisol levels correlate with decreased myelin in the adult (Howell et al, 2013) and in the post-weaning isolation model, socialization does not restore myelin (Liu et al, 2012; Makinodan et al, 2012). However, in adult mice isolated and resocialized, myelin is restored, suggesting that myelin plays a role more specifically in adult plasticity and network formation (Liu et al, 2012). Oligodendroglial cells are susceptible to attacks from oxidative stress, stress hormones such as cortisol and from the immune system, in all cases leading to a secondary demyelination (El Waly et al, 2014). Once lost, however, myelination can be restored if trophic and maintenance factors are sufficient (Bartzokis, 2011). Plasticity factors such as BDNF (Lundgaard et al, 2013) and serotonin (Fan et al, 2014) have been associated with remyelination. SSRIs can improve myelination in disease states where it has been lost (Bartzokis, 2012).

3.2 Regions of Interest

3.2.1 Amygdala

The amygdala is widely recognized to be involved in emotions and is the most important brain region in focusing attention and brain resource allocation in responses to threats in the environment (Phelps and LeDoux, 2005), particularly in a social context (Adolphs, 2010; Sander et al, 2003 Thomas et al, 2001). Indeed, the amygdala has been described as the “hub” of brain networks supporting social life (Bickart et al, 2014) and the strength of connections between it and other regions determines all aspects of social functioning, including perception, affiliation and motivation. The amygdala learns which situations are most likely to lead to aversive outcomes (Delgado et al, 2006) and neuroplasticity takes place. Consequently, the amygdala re-organizes other neural networks in other cortical and subcortical regions (Scherf et al, 2013). Children who have been maltreated when infants show amygdala hyper-reactivity as adults (McCrorry et al,
and young children who experience peer rejection also show hyperactivity of the amygdala (Lee et al, 2014). Patients with social anxiety disorder show hyperactivation (Bruhi et al, 2014). Conversely, people with greater perceived social support show less activation of the amygdala during stress (Hyde et al, 2011) and viewing pictures of loved ones, decreases activity in the amygdala (Bartels and Zeki, 2000). Neurochemically, the amygdala receives both serotonin and dopamine inputs and social isolation of rodents results in loss of both in the amygdala. There are oxytocin receptors and intranasal oxytocin decreases amygdala activity (Zink and Meyer-Lindenberg, 2012). Finally, there are glucocorticoid receptors and corticotrophin releasing hormone cell bodies and the amygdala plays a role in the control of the HPA axis. Increased cortisol may activate expression of BDNF in the amygdala, leading to increased dendritic density and thus leading to plasticity within secondary neural circuits (Bennett and Lagopoulos, 2014).

3.2.2 Prefrontal cortex

Several areas in the prefrontal cortex (PFC) are part of the corticolimbic emotional system and play a role in the social circuit. Much of the prefrontal cortex shows hypoactivity in social deficit syndromes, including autism and schizophrenia (Dichter, 2012). The PFC has connections with both the amygdala and hippocampus and finds the emotional value of a stimulus and links it to a primary reinforcer, such as social information. (Rolls, 2007). The medial prefrontal is required for understanding the feelings of others as opposed to one’s own (Theory of Mind) and is also activated when feeling socially isolated by others. It develops around the time that juvenile play develops, and is assumed to be important for responding and interpreting the actions and needs of others (Bell et al, 2010). This region is activated by intranasal oxytocin (Aoki et al, 2014) and activity is decreased by cortisol (Pruessner et al, 2010). There is a strong serotonin innervation and serotonergic 5-HT1A receptors are present (Savitz et al, 2009). The orbitofrontal prefrontal cortex also develops during adolescence (Bell et al, 2010) and is important for making emotional decisions based on expected reward. The ventromedial prefrontal cortex is important for coping behaviors and resiliency. The orbitofrontal and ventromedial prefrontal both have extensive serotonergic innervation.
3.2.3 Hippocampus

The hippocampus is critical for processes related to memory and the flexible use of memory. In social behaviors, the hippocampus is involved in regulating opinions and strengths of bonds to others, in the face of changing environments. Patients with hippocampal amnesia, are not capable of making new friends, in part because they cannot recall details of communications with social salience (Rubin et al, 2014). Both glucocorticoid and mineralocorticoid receptors are found here, and the region is exquisitely sensitive to cortisol, playing a major role in feedback inhibition. Stress and cortisol inhibit synaptic plasticity here and can lead to memory deficits and malfunctioning of many behaviors, social, cognitive and linguistic to name a few. Conversely, serotonin, and the 5-HT1A receptor, is important for maintaining synaptic plasticity and possibly neurogenesis in the hippocampus (Mehar et al, 2014).

3.2.4 Anterior cingulate cortex

The anterior cingulate cortex (ACC) is considered part of the fear and anxiety circuit, which originates in the amygdala. Social exclusion, rejection or loss of a relationship all activate the ACC (Eisenberger et al, 2003; Rogoe et al, 2014). Conversely, the more social support an individual has, the less activation of the ACC takes place in a socially stressful situation (Eisenberger et al, 2007;Barbas et al, 2003). Therapeutic massage also decreases activation (Field, 2014).

3.2.5 Ventral tegmentum, ventral striatum/nucleus accumbens

These regions of the reward circuit are involved in motivation for social interactions, or heightening anticipation of reward for social interactions as well as in cooperating, competing, and following social norms (Bhanji and Delgadao, 2014). Both the striatum and ventral tegmental area are activated when viewing a romantic partner’s face (Fisher et al, 2005). Interestingly, this activation is greater when the relationship has ended (Aron et al, 2005). Subjects with autism show diminished activity in this region in social tasks (Dichter, 2012). The primary neurotransmitter involved in this circuit is dopamine; however, oxytocin (Scheele et al, 2013), also shows activation. A major role for serotonin in reward processing is unlikely (Faulkner and Deakin, 2014).
4. Summary of the Biology of Social Support System

4.1 Summary of Principals

The social support circuitry of the brain developed evolutionarily to not only make it easier for humans to live in close proximity, but to actually benefit from it. This is further supported by the Social Baseline Theory, whereby a properly functioning social circuit saves energy and removes burdens from other brain and body functions. The social support circuit shows experience-driven plasticity, that is there are neurochemical and cellular changes which are necessary in order to respond to a changing environment. The same factors are used across the lifespan, from maternal/infant bonding, to peer bonding to pair-bonding. Much can thus be learned by studying the circuitry and biology at all ages.

To further our understanding of the biology of social support, several different model systems may prove useful in humans. ICEs may provide a large number of subjects, not available in the high-fidelity environments. However, in either case, more uniform research questions should be applied. In human disease states, both autism and loneliness are worth studying – in particular loneliness should be further explored as it has been reported in flight crews and it can lead to hostility. In addition, loneliness may model maladaptation to long-term social isolation best. In animal studies, social isolation of rodents can be very useful, in particular studies with the pair-bonded prairie vole.

4.2 Biological Factors

The principal factors involved in the experience-driven plasticity of the social support network are serotonin, oxytocin and BDNF (which increase the integrity of the network) and cortisol (which leads to damage to the network). It will be important to further study the cellular changes brought about by these factors, in particular more extensive studies of oxytocin should be undertaken. Dopamine is involved in the reward to social interactions and may be a particular target of changes brought by about long-term stress. Allopregnanolone and endorphins should be further explored for a role in maintaining the social support circuitry.
BDNF, cortisol and oxytocin can all be measured in biological fluids and intensive efforts should be undertaken to develop these as biomarkers of the functioning of the social support. Further, having useful biomarkers can lead to testing the effects of pharmacological agents, including SSRIs.

5. Future Directions for Research

The previous sections have presented a literature review of our current understanding of the evolution and necessity of social support in maintaining human mental and physical health, as well as describing some predisposing factors to understand individual differences.

Exploration class missions will necessarily put a severe strain on an individual’s typical social support and understanding and mitigating this risk is essential. This final section will include a summary of research recommendations to gain the knowledge necessary for monitoring the biological systems sustaining social support and how to predict and mitigate any detrimental changes.

5.1 First Priority: Establish the Biomarkers of Social Support

The primary signal controlling development, plasticity and activation of the social support system is a balance between cortisol release (regulated by corticotropin releasing factor, CRF) and oxytocin. Reciprocal connections between the amygdala (AMYG) and the paraventricular nucleus (PVN) of the hypothalamus, are further regulated by the developmental and activating effects of serotonin neurons in the raphe nuclei (in blue) and by the levels of BDNF. All four of these are thus considered to be the primary biological components of the
system and should be the subject of further research. Secondary signals to study include endorphins, NPY, neurosteroids and interleukins. Finally, anatomical and functional imaging studies should be expanded.

To begin validating these biomarkers, both animal and human studies will need to be used.

5.1.1 Animal models

**Post-weaning social isolation rat:** Plasticity is greatest in the brain during times of transition. Thus, using the post-weaning model of isolation, when rodents are changing from maternal to peer social bonds, is an ideal time to gain a significant amount of data in a short period. This model is particularly good at showing deficits in adapting to novel social environments. This social isolation model has previously been shown to include changes in the biomarkers as reported above, including BDNF, IL-6 and corticosterone (reviewed in Fone and Porkess, 2008) as well as showing increased excitability of the amygdala (Gan et al, 2014) and increased sympathetic tone. The animals show a profound loss of serotonin and many of the effects of isolation can be overcome by serotonergic drugs, making this model ideal for testing the utility of biomarkers as indicators of social support function over the course of treatments and re-socializing. It is also ideal because it may more accurately predict the physiological responses to long-term social stress.

**Prairie vole (Microtus ochrogaster):** The prairie vole, found extensively in the grasslands of the central United States, has adapted well to a laboratory setting and continues to show its monogamous bonding behaviors. The prairie vole has a more limited behavioral repertoire than other rodent species, but it has the advantage of being monogamous. Isolating bonded pairs thus make an ideal model of disruption of established social bonds. Adult prairie voles isolated from their partners show anhedonia (Grippo et al, 2007a) and anxiety (Stowe et al, 2005) Changes in biomarkers include increased resting heart rate (Grippo et al 2007b) and corticosterone (McNeal et al, 2014). Heart rate responses to stress are magnified in the isolated prairie vole (Grippo et al, 2007b). Neurochemically, the prairie vole shows increased dopamine functioning (Young et al, 2008), while depletion of serotonin during development (in a model system derived
in my laboratory) caused a loss of affiliative behaviors (Martin et al, 2012) and an SSRI increases affiliation (Villalba et al, 1997). These animals could prove highly useful in further defining the biology of the social support network, as well as understanding what will happen during separation from a partner and how to re-establish bonds when re-introduced.

Once definitive markers of the function and plasticity of the system have been established in the animals, an intensive validation of biomarkers in humans can begin. These markers will be essential for predicting responses to isolation, and proposing means of mitigating any adverse effects.

5.1.2 Human studies

Several human populations will prove useful, as each has its own limitations and advantages.

The stress imposed by changing social environments is the most common form of stress humans experience (Almeida, 2005). In the context of long-distance space travel, appreciating the chronicity of this exposure will be very important in planning and interpreting studies. Acute stress responses are adaptive, while chronic stress responses are often maladaptive. Looking at the immune system as an example, short-duration stress (up to several weeks) may positively affect the functioning of the immune system, while chronic stress, associated with a long-duration flight could change into a dysfunctional state and have a negative impact (Crucian et al, 2014). Metabolic syndrome may also arise after long-term stress combined with these immune changes. This is a syndrome characterized by increased morbidity through diabetes and cardiovascular events, and should be considered as a possible outcome after a long-duration flight. There are few studies to date which have studied a long enough time period to measure this adaptive negative impact. Thus, populations to be studied should be considered as their utility for modelling acute or chronic exposure. Loneliness and Antarctica wintering over are thus considered the most useful models for chronic adaptations awhile the mock analogues are most useful for acute and assessing predictive markers.
**Loneliness:** Approximately 12% of an adult population will report often or always feeling lonely making the contributions which this population could make in numbers, significant. This population would be very useful in understanding the effects of long-term poor adaptation to social isolation, as loneliness is associated with the metabolic syndrome (Whisman, 2010) as well as in predicting who copes with isolation, in spite of similar social environmental changes – such as the individual responses to bereavement.

**Antarctica wintering over:** Studies in this population may also give very useful information, since the numbers of participants are relatively high, and the duration can be up to 1 year. The stress of this environment has been documented to produce significant psychological changes in particular related to social isolation. There are inland stations, which are more isolated than coastal, with no evacuation possible for up to 9 months and there are restricted telecommunications. These stations may prove most analogous (Crucian et al, 2014).

**Mock analogues:** These are severely limited both for the number of subjects and also for the time of isolation, but they have increased ability for monitoring biomarkers and psychometric changes in the acute response phase. These could have unique uses in defining predictive markers and testing preflight social bonding exercises to increase team cohesion.

**5.1.2a Development of quantitative markers.** More scientific rigor must be applied to understanding and measuring the social support system in the human brain. Selecting some key markers, to be used across populations, will greatly increase the power of those studies.

**Psychometric Testing.** Objective psychological measurements can be obtained using validated assessment instruments such as questionnaires with graded responses. Most rating scales, including the five proposed here, use an ordinal scale referred to as the Likert scale, where a statement is made and the response assigned a number based on “Strongly agree” to “Strongly disagree”, or a question is asked and the response can
range from “Never” to “Always”. The scales given here all have been assessed for internal consistency and reliability and are therefore being listed as suggestions for promoting uniformity across studies. As indicated above, previous psychometric testing has not been consistent among studies, and meta analyses have not been possible. It is assumed that standard psychometric tests of anxiety and depression, such as the Profile of Mood States and the Beck Depression Inventory (BDI), will also be used.

It is important to note that the original definition of social support, including such factors as empathy, caring, love and trust, does not have an adequate psychometric measure to be used in these populations, but it is essential that one be developed in order to further research studies.

**Emotional and Social Loneliness scale of De Jong Gierveld (DeJong Gierveld and Van Tilburg, 2006):** This is a six-item test with questions such as “There are plenty of people that I can lean on in case of trouble” and “I miss having people around”. This test has been validated and found reliable in a multinational cohort (De Jong Gierveld et al, 2010).

**Positive and negative social exchanges (PANSE):** Stable negative social exchanges, that is ongoing stressful interactions with family or friends, also affect health (Newsom et al, 2008) and indeed may be more detrimental to health than is the lack of positive exchanges (Newsom et al, 2005). It is important to have a reliable rating scale for this, as there are new social interactions which may arise during long-term spaceflight which are negative but will be ongoing and inescapable. A means of measuring these interactions and predicting outcomes and interventions will be essential for mitigating their effects. The PANSE scale, developed by Newsom et al (2003) can be used for these studies. The scale consists of 24 questions and a 5-point Likert scale. Twelve questions center on positive social exchanges (eg. In the past month, how often did people do things to make your life easier?) or negative exchanges (eg. In the past month, how often did people do things to make your life more difficult?) Although the original study was based on a monthly sample, the scales have also been used daily.
**UCLA Loneliness scale (UCLA-LS)** measures the extent to which one feels connected to others (Russell, 1996). This is a 20-item questionnaire using a 4 point Likert scale. This scale has been used in over 100 published studies and is well validated. Sample questions include: How often do you feel that you are no longer close to anyone? And How often do you feel that there is no one you can turn to?

**Connor-Davidson Resilience Scale (CD-RISC)** is a 25-item scale using a 4-point Likert scale (Connor and Davidson, 2003).

**Multidimensional Scale of Perceived Social Support (MSPSS)** is a 12-item scale using a 7-point Likert (Zimet et al, 1988).

**Biomarkers.** Measuring changes in substances in blood, urine or saliva has long been an important component in diagnostics and consequently an intensive search for such biomarkers in understanding brain functions of all types has been underway. Some biomarkers can be used to predict response to stress and others may indicate stress has occurred and whether or not a healthy adaptation has taken place.

**Primary biological factors**

**BDNF:** Blood levels of BDNF have been used reliably as a biomarker in depression and social attachments and these levels are responsive to treatment with SSRIs (Shimizu et al., 2003; Marazziti et al, 2009; Emanuele et al, 2010). Blood samples should be collected in the morning after an overnight fast (Sen et al, 2008) and can be analyzed using a multiplex immunoassay panel. This marker may be a very useful marker of the ability for the social support system to adapt to changing social environments. It has been shown to increase in the later timepoints in the Mars 105-day simulation (Strollo et al, 2014).

**Cortisol:** Cortisol can be accurately measured in saliva and is a good measure of plasma levels. It is easily collected and stable for long periods at room temperature. Cortisol peaks about 20 minutes after an acute stressor. Sampling time must be
controlled, as there is a daily rhythm, with a peak awakening response. It is best to look at changes, rather than a single measure – for example before and after a stressor such as the Trier or the level on immediate awakening and 20 minutes after awakening. Finally, the dexamethasone suppression test – which involves using the synthetic hormone dexamethasone to test the negative feedback capacity of the HPA axis – is particularly important in studying the long-term maladaptive response to chronic stress.

**Oxytocin:** can be measured in both blood (Frost et al, 2014; Jobst et al, 2014) and urine (Crockford et al, 2014; Saito et al, 2014) and has been used reliably as a measure of social relationships including immediate responses to an interaction, and as a baseline measure for predicting future responses. Unfortunately, salivary samples do not appear to be accurate (Javor et al, 2014).

**Serotonin:** Plasma or blood levels of serotonin are not indicative of central levels.

**Autonomic nervous system:** Heart rate – In the “fight or flight” stress response sympathetic outflow increases adrenaline release from the adrenal glands, resulting in a raised heart rate. Over time (15-20 minutes) the HR should return to baseline. Over-reactive changes induced by stress paradigms may be in particular associated with aggressiveness and hostility after social isolation (Sgoifo et al, 2014) and PTSD. However, recurring or constant exposure to a stressor leads to chronically elevated HR. Higher resting heart rates are found in subjects with greater social disadvantages and isolation (Chaix et al, 2011; McCrory et al, 2014). Interestingly, effects of social stress on heart rate may be attenuated by a serotonin agonist because serotonin can suppress stress-induced sympathetic outflow (Nalivaiko et al, 2009). Thus, this biomarker fits in well with the overall hypothesis of the social support system, and is easily measured.

**Alpha amylase** – Alpha amylase can be measured in saliva as an index of sympathetic activation in response to acute stress. There is a daily rhythm which must be controlled for. Unlike cortisol, levels rise in saliva in the first few minutes after a stressor. It is also useful in the context of the studies proposed here, as it adapts differentially over length of exposure- for example levels can be correlated with burnout scores and response to
mindfulness meditation (Duchemin et al, 2015). It has been suggested that a ratio of alpha amylase over cortisol is a good indicator of long-term stress (Ali and Pruessner, 2012). However, it is relatively unstable and samples would need to be quickly measured and it is overly responsive to physical stressor.

**Genetic factors:** Many of the biological factors known to play a role in the social support system have also been studied extensively for possible genetic underpinnings and there are two genes which could be studied to gain useful information. The serotonin transporter-linked polymorphic region (*5-HTTLPR*) is the most extensively studied candidate gene in neurobiology and may show proneness to psychological distress, amygdala reactivity (Jonassen and Landro, 2014) and loneliness (van Roekel et al, 2010), likely through development expression differences between the two alleles (Parsey et al, 2006). Cortisol responsiveness, and thus negative feedback, is determined by mineralocorticoid (MR) and glucocorticoid receptors (GR). There is considerable individual variation in the sensitivity to cortisol, through various common single nucleotide polymorphisms (SNPs) in both receptor genes. Studies also found that these polymorphisms were associated with onset and presence, but not recurrence, of major depression (Hardeveld et al, 2015) and these may prove useful in predicting response to long-term stress.

The Val66Met BDNF gene and the oxytocin receptor gene have not proven to be useful markers and should not be explored further in the context of the social support system.

**Immunologic/inflammatory markers:** Increasingly, inflammation has been seen as an indicator of pathological neuronal and psychological processes, including depression and anxiety (Anisman, 2009) and may be correlated with other biomarkers, for example, IL-6 has been shown to correlate with amygdala reactivity to acute stressors (Muscattell et al, 2015). A recent review finds that salivary markers IL-1β, TNF-α, and IL-6 have been reliably determined from saliva and have increased in response to stress across multiple studies (Slavish et al, 2015). TNF-α was shown to be increased in a 520-day mock isolation study (Yi et al, 2014); however, it was not correlated with psychological findings, which would be an important future study.
**Neuropeptide Y (NPY):** Plasma NPY levels have been proposed as predictors of resilience; however, much more work is needed, particularly determining changes after stress-inducing paradigms such as the Trier Test. Samples are generally drawn in the morning after fasting and analyzed by a commercial ELISA.

**Imaging Studies (fMRI and PET)**

There are two areas of research studying social support and reactivity and using functional MRI techniques. Threat-related amygdala reactivity to fearful and angry faces has been used extensively. Amygdala reactivity is a good marker of heightened and maladaptive response to chronic stress and can be used as a biomarker to predict likelihood of developing PTSD, anxiety and or depression up to 4 years later (Swartz et al, 2015). Secondly, the social rejection task, referred to as cyberball has been very useful in delineating brain regions and subject characteristics of sensitivity to social isolation. In this task, the subject “plays” a game of toss with two computer-generated players and over time the subject no longer receives tosses. This paradigm also shows changes in acute responses, such as heart rate changes, and should be useful in assessing other biomarkers. Interestingly, healthy individuals do not show loss of oxytocin when excluded in cyberball, while those with psychological predisposition to rejection sensitivity do (Jobst et al, 2014).

PET studies may prove the most useful means of assessing neurotransmitter system, as there are no direct peripheral biomarkers of neurotransmitters such as serotonin or dopamine. If necessary to studies, binding potential of labelled transporters or receptors are available for both neurotransmitters.

5.2 Priority Two: Experiments to Predict and Improve Outcomes

Once reliable biomarkers and psychometric tests are established, studies aimed at predicting individual responses, and how to mitigate any adverse effects can begin. Some information from basic studies (such as treatments with SSRIs or exercise studies) would be used to inform these studies.
5.2.1 Time periods of testing

In models of responding to stressors, such as changes in the social environment, it is important to define the period of responding – before the stressor can be used for predictive studies, during can be used for coping and resilient measures, and after the stressor has passed can be used for determining if adaptability and return to baseline is possible. All these could be studied in both animals and human populations.

Prior to flight, markers of plasticity, such as BDNF and oxytocin would be useful. Experimental stressors such as the Trier or exclusion in the cyberball paradigm could predict responses to the later loss of social support. Studies to improve bonding, such as using intranasal oxytocin in conjunction with experimental manipulations to increase closeness (Aron et al, 1997) would also be very informative at this time. Studies of biomarkers and psychometrics after flight are also very important. Very little is currently known about the long-term consequences of separation from social support systems.

5.2.2 Correlations of biomarkers with psychometric and physiological responses

The first step in future studies is in being sure of reliable psychometric measures for defining and quantifying functioning of the social brain, much in the way that agreement on DSM criteria for mental disorders is necessary before research can begin. Once established, correlations between, and among, biomarkers can begin. For example, it is surprising that correlations between oxytocin release and functioning of the immune system have never been done – although this is a straightforward experiment testing the social baseline hypothesis. Similarly, BDNF levels have never been correlated with loneliness and high cortisol, nor BDNF and NPY, although both are important in coping and resilience. Overall studies, in animals and humans, can be used to further define the biological components of the social support system. Tryptophan depletion and psychological responses should also be determined as this could predict vulnerability to depression.
5.3 Priority Three: Evaluating Manipulations for Maintenance and Repair of the Social Support Network

Although pharmacological interventions can prove very useful in restoring the social support system, it is not likely that this can be relied upon in the context of long-distance space travel – first, because the storage area for drugs is predicted to be very limited, and secondly, pharmaceuticals which are stable for up to 4 years (and resistant to radiation) may not be available. Thus, understanding and evaluating non-pharmaceutical interventions is necessary. Specific sensory stimulation, such as hearing a loved one’s voice or familiar music will likely prove useful. Tactile and visual systems should also be explored, as well as the role of taste of familiar food in eliciting comfort. Finally, the role of meditation (specifically mindfulness meditation) and relaxation techniques should be explored. These interventions can then be correlated with changes in biomarkers and psychometric tests. For example, mindfulness mediation can lower salivary Alpha-amylase (Duchemin et al, 2015) and cortisol (Bergen-Cico et al, 2014) as well as improve depression, anxiety and suicidal.

6. Conclusions

A thorough understanding of the biology and plasticity of the social support circuit is essential in planning for the effects of separation from one’s typical social support during long-term space travel, as this circuit is ultimately responsible for many other features of human physical and mental well-being.

A means of accurately and reproducibly measuring human behavior is essential to any endeavor to understand that behavior. In the case of the social support circuit, there are several important biomarkers which, with more validation, could proof highly useful. These include BDNF, oxytocin and cortisol. Psychometric tests are also becoming more reliable. Animal models and human situations and extremes can be used to further understand, predict and maintain the social support network.
Literature Cited


Carre JM, Putnam SK, McCormick (2009) Testosterone responses to competition predict future aggressive behaviour at a cost to reward in men Psychoneuroendocrinology, 34:561–570


Coplan JD, Gopinath S, Abdallah CG, Berry BR. (2014) A neurobiological hypothesis of treatment-resistant depression - mechanisms for selective serotonin reuptake inhibitor non-efficacy.Front Behav Neurosci. 8:189.


Crockford C, Deschner T, Ziegler TE, Wittig RM. (2014) Endogenous peripheral oxytocin measures can give insight into the dynamics of social relationships: a review. Front Behav Neurosci. 8:68.


Hyde LW, Gorka A, Manuck SB, Hariri AR (2011) Perceived Social Support moderates the link between threat-related amygdala reactivity and trait anxiety Neuropschologia, 49:. 651–656


Joseph NT, Myers HF, Schettino JR, Olmos NT, Bingham-Mira C, Lesser IM, Poland RE (2011) Support and undermining in interpersonal relationships are associated with symptom improvement in a trial of antidepressant medication. Psychiatry. 74(3):240-54


Keverne E B, Martensz ND and Tuite B (1989). Beta-endorphin concentrations in cerebrospinal fluid of monkeys are influenced by grooming relationships. Psychoneuroendocrinology 14, 155–161


Kuramochi M, S, Nakamura (2009) Effects of postnatal isolation rearing and antidepressant treatment on the density of serotonergic and noradrenergic axons and depressive behavior in rats Neuroscience, 163: 448–455


Machado CJ and Bachevalier J (2006) The impact of selective amygdala, orbital frontal cortex, or hippocampal formation lesions on established social relationships in rhesus monkeys (Macaca mulatta) Behav. Neurosci., 120:761–786


Marsden CA, King MV, Fone KC. (2011) Influence of social isolation in the rat on serotonergic function and memory--relevance to models of schizophrenia and the role of 5-HT₆ receptors. Neuropharmacology. ;61(3):400-7.


86


Biological Basis of Social Support

Patricia M. Whitaker-Azmitia

Lyndon B. Johnson Space Center
Houston, Texas  77058

National Aeronautics and Space Administration
Washington, DC  20546-0001

Unclassified/Unlimited
Available from the NASA Center for AeroSpace Information (CASI)
7115 Standard
Hanover, MD  21076-1320

Category: 53

Unclassified/Unlimited

The social support circuitry of the brain developed evolutionarily to not only make it easier for humans to live in close proximity, but to actually benefit from it. The beneficial effects of a healthy social support circuit are seen in improved cardiovascular, immune and emotional health. The social support circuit depends on experience-driven plasticity, that is, there are neurochemical and cellular changes which are necessary to respond to a changing environment. The same factors are used across the lifespan, from maternal/infant bonding, to peer bonding to pair-bonding. The principle factors involved in the experience-driven plasticity of the social support network are serotonin, oxytocin and BDNF (which increase the integrity of the network) and cortisol (which leads to damage to the network). These factors can be measured and used to study and assess the integrity of the circuit in individuals in different environments. To further our understanding of the biology of social support, several different model systems may prove useful in humans. Isolated and confined environments may provide a large number of subjects, not available in the high fidelity environments. In human disease states, both autism and loneliness are worth studying – in particular, loneliness may model maladaptation to long term social isolation best. In animal studies, social isolation of rodents can be very useful, in particular studies with the pair-bonded prairie vole or with rodents transitioning from parent to peer bonding. A thorough understanding of the biology and plasticity of the social support circuit is essential in planning for the effects of separation from one’s typical social support during long term space travel, as this circuit is ultimately responsible for many other features of human physical and mental well-being.