Research Topic White Paper #3
Institute for Research on
Unlimited Love
Altruism, Compassion, Service.

APPROACHES TO DEFINING MECHANISMS BY WHICH ALTRUISTIC LOVE AFFECTS HEALTH

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I. Introduction

The Stress Model: Many studies have now convincingly shown that acute and chronic stress negatively impact health (Cohen, Tyrrell et al. 1991; Kiecolt-Glaser 1999; Sternberg 2001). Furthermore an extensive body of literature exists that identifies the brain regions, neuroanatomical pathways and neurotransmitter and neuroendocrine systems that mediate these effects of stress on health (Chrousos and Gold 1992). These effects of emotional responses to external events are mediated through stress hormones and neurotransmitters released during stress, that in turn influence immune function through ligand-receptor mediated effects on specific aspects of immune cell function. In addition more recent studies indicate that different forms of stress (whether psychological, social, physical, physiological etc.) activate different components of the central nervous system to affects different components of the immune system, leading to varying effects on overall pattern of disease (Ericsson, Kovacs et al. 1994; Sawchenko, Brown et al. 1996).

Altruistic love: However, while the chain of events leading from negative emotional responses to external events to impact on disease has been well worked out, less research has been done applying the same model to studying the effects on health of positive emotional responses. The following white paper proposes to apply the same approaches and standards that have been used in the stress literature to studying the chain of events leading from altruistic love to beneficial effects on health. It is possible that the mechanism by which altruistic love has a beneficial effect on health occurs through blocking or attenuating the stress response or through activating positive neurotransmitter pathways in the brain.

II. Key Research Questions

Question 1

Define the neurobiology of altruistic love.

Altruistic love is composed of many components that have been well studied in other contexts, including maternal-child bonding; social interactions; positive/supportive behaviors (e.g. hand-holding); positive emotional states (happiness, pleasure, reward); placebo effect. The range and combination of such emotional responses and behaviors set into play during the state defined as altruistic love should be defined in order to define the neurobiological and neuroanatomical circuits of altruistic love. Thus, psychological instruments that parse these emotional and behavioral components of altruistic love should be developed and validated to be applied as quantitative objective measures of states of altruistic love. Neuroimaging studies should then be designed to be applied in which subjects who are deemed to be in a state of altruistic love. The aim of these studies would be to define brain regions, neurophysiological responses and neurotransmitter systems activated or suppressed during states of altruistic love. The main methods of study would involve brain imaging – fMRI; PET; EEG. Neuroimaging study approaches that have been successfully applied to identify the neurobiology of happy and sad states (George, Ketter et al. 1996; Damasio, Grabowski et al. 2000) should be adapted to evaluate the neurobiology of altruistic love.

In such studies, questions that could ultimately be explored include determination of whether brain regions activated by altruistic love correspond to brain regions activated during positive states (happiness), pleasure, addiction, maternal behaviors. In addition, since resilience and health are associated frontal lobe asymmetries (Davidson 2000), such studies could also address the question as to whether induction of a state of altruistic love is associated with differences in asymmetries of brain region activation during altruistic love that correspond to brain region asymmetries activated in resilient versus non-resilient individuals. Since the nucleus accumbens and dopamine associated brain regions are activated during pleasurable states and addictive behaviors, such studies should also explore whether one aspect of the neurobiology of altruistic love involves activation of these limbic pathways involved in addiction. Activation of such pathways might provide insights into the motivational aspects of altruistic love.

Question 2

Define the neurohormonal and neurotransmitter transduction mechanisms associated with altruistic love.

Much research has been performed identifying transduction pathways by which activation of the stress response affects physical health, however little research has been done in this regard in relation to transduction pathways activated or blocked by emotions associated with altruistic love. Stress itself does not alter immune cell responsiveness and susceptibility and resistance to infectious or inflammatory diseases. Rather the neurohormones and neurotransmitters released during stress alter immune cell function through receptor-mediated mechanisms to affect the immune system's ability to fight infection or respond to pro-inflammatory stimuli. The methods that have been applied to studying stress effects on immunity should be systematically applied to studying the effects of altruistic love on various health outcome measures. In this context the effects of altruistic love on disease outcome should not only be measured, but the intermediate neurohormonal and neurotransmitter systems that might transduce the effect of the emotional response should be quantitated.

Several intermediate stress pathways that impact health that could explain the effects of altruistic love can be measured in a sensitive and quantitative manner. These include the neuroendocrine stress response (outcome measure in ambulatory settings: salivary cortisol) (Pruessner, Wolf et al. 1997); sympathetic and parasympathetic autonomic tone (heart rate variability and cardiac impedance) (Cacioppo, Berntson et al. 1998; Jacob, Thayer et al. 1999). It is possible that altruistic love might either activate or block these stress pathways and could therefore positively affect health through blocking some of the deleterious effects of stress on the body.

It is also possible that altruistic love might activate certain aspects of the "relaxation response" in addition to blocking aspects of the stress response. Thus, measures of exhaled nitric oxide (Stefano, Fricchione et al. 2001; Stefano, Murga et al. 2001) could shed light on positive transduction pathways activated by altruistic love. Studies aimed at measuring changes in all these transduction pathways will shed light on the mechanisms by which altruistic love might positively affect health.

Activation of the stress response involves two major neural and neuroendocrine response pathways: the neuroendocrine hypothalamic pituitary adrenal axis (Sternberg and Gold) and the autonomic nervous system, comprised of the sympathetic and parasympathetic nervous system (Stevens-Felten 1998; Elenkov 2000). The main sympathetic neurotransmitter is norepinephrine, and the main sympathetic neuropeptide is neuropeptide Y (NPY). The adrenal medulla is a glandular component of the sympathetic nervous system that releases epinephrine (adrenalin) into the bloodstream during stress activation. Together, adrenalin, released from the adrenal medulla, and norepinephrine and NPY released from nerve terminals, produce a variety of effects during stress. These include increased heart rate and peripheral vasoconstriction with resultant increased blood pressure and diversion of blood flow away from skin and to muscles – a pattern of cardiovascular response known as a 'threat' pattern. In physiological studies the degree and pattern of sympathetic activation can be sensitively and non-invasively quantitated by continuous measures of heart rate variability. Similarly, HPA axis activation can be sensitively and non-invasively quantitated by measures of salivary cortisol (Hellhammer, Buchtal et al. 1997; Pruessner, Wolf et al. 1997; Kirschbaum, Kudielka et al. 1999).

The effects of activation of the sympathetic nervous system together with behavioral responses resulting from activation of the HPA axis produce the physiological stress response commonly known as the 'fight-or-flight' response. The parasympathetic nervous, whose major nerve is the vagus nerve and whose main neurotransmitter is acetylcholine (Ach) both sends signals to and receives signals from the CNS, and innervates the gut, liver, spleen, lungs and heart. The parasympathetic nervous system also innervates the skin, sweat glands, and internal organs including the uterus and bladder. The vagus nerve is tonically activated and generally provides a brake to the system, tending to slow heart rate and reduce blood pressure. Removal of the brake by inhibition of vagal tone, as occurs during a stress response, is the fastest way to increase heart rate and blood flow and activate the stress response, and occurs on the order of milliseconds, compared to sympathetic activation that occurs on the order of seconds, and HPA axis activation that occurs on the order of minutes. The pattern of enhanced cardiac performance and reduced peripheral resistance seen during vagal activation is known as a 'challenge' pattern of response. Activity of the parasympathetic nervous system can also be sensitively and non-invasively quantitated by HRV measures (Jacob, Thayer et al. 1999).

Measures of activation of these various components of the stress response during altruistic love would provide insights into the nature of the transduction mechanisms set into play during altruistic love, and would provide mechanisms by which an emotional response might impact physical health through release or blockade of release of neurohormones and neurotransmitters of the stress response or activation of relaxation response pathways.

<u>Question 3</u>

Does altruistic love positively affect specific aspects of immune cell function or other measurable elements of health or disease? If so are these effects mediated through the neurophysiological pathways neurotransmitters, neuropeptides and neurohormones activated by altruistic love?

If altruistic love has a positive impact on health, specifically on conditions mediated by the immune system such as inflammatory or infectious diseases, these effects should be mediated by neurotransmitters and neurohormones activated by altruistic love. In the stress model, the impact of stress hormones on many aspects of immune responses and disease has been extensively studied. Similar approaches should be applied to the study of the effects of altruistic love on immunity and immune mediated illnesses.

Three types of studies evaluating the effects of either interruption of stress responses or activation of positive or negative emotional responses provide quantitative approaches that could be applied to measuring effects of altruistic love on immunity and immune mediated disease.

Smyth et al (Smyth, Stone et al. 1999) have, using the Pennebaker method (Pennebaker and Seagal 1999) of writing about a stressful event, that a 15 minute writing session in which the subject wrote about a stressful event, had significant and measurable positive effects on quantitative outcome measures in asthma and rheumatoid arthritis. Outcome measures applied included joint scores in RA and FEV1 in asthma. It should be noted that in defining the question in this manner, the outcome measures selected were not intermediate immune cell in vitro responsiveness, but practical disease outcome measures that sensitively and quantitatively provided information on the effects of this approach of reducing negative emotion on disease outcome. Similar studies could be performed using a manipulation involving induction of a sense of altruistic love. Pilot studies would have to determine if such manipulations induce a sufficiently powerful reproduction of the state of altruistic love that for any measurable changes in disease outcome to occur.

Typically in order to induce stress or other negative responses in the laboratory setting, a series of negative (stressful, fearful, disgusting) pictures are shown to subjects in order to elicit a given emotional response. It is not clear that being exposed to a similar series of positive pictures would be powerful enough to elicit a positive state of altruistic love. However, studies in which movies are used to elicit emotional responses provide a potential approach to induce such positive states. Bruce Miller et al. al (Miller, Spencer et al. 1993; Miller and Wood 1997) performed studies using the movie E.T., in which children with asthma were asked to score their emotional responses to various segments of the movie (scary, happy, sad etc.) and objective observers also scored a videotape of the children watching the movie. During this time physiological measures of sympathetic activation and salivary cortisol, airway responsiveness (FEV1) and heart rate variability were performed. Subjective and objective emotional states were correlated with physiological and disease outcome measures. Similar studies could be performed using a movie in which emotions associated with altruistic love are elicited, in order to determine whether such emotions correlate with either beneficial effects on disease outcome measures or activation or inhibition of physiological response pathways.

In separate independent studies, John Cacioppo (Cacioppo, Ernst et al. 2000) and Julian Thayer (Jacob, Thayer et al. 1999) have shown that in isolated individuals – either lonely students or isolated aging individuals in the inner city – show a threat pattern of heart rate variability and blood pressure response. Similar approaches could be applied to socially connected individuals, as has been done in studies by Sheldon Cohen et al. linking social connectedness to common cold resistance.

Other sorts of approaches that have been successfully applied to studies of effects of stress on immune responses include the effects of exercise on *ex vivo* immune cell cytokines production (DeRijk, Petrides et al. 1996). This approach allows quantitation of effects of neurohormones on specific aspects and patterns of immune responsiveness. It is not clear whether induction of states of altruistic love would be powerful enough to release sufficient quantities of hormones or to block their release in this assay system. Pilot studies should be performed to evaluate whether such an approach might be sensitive enough for application to altruistic love effects on immunity and health.

Question 4

Define the role of learning and memory and early maternal environmental factors in development of altruistic love behaviors.

Carrying out acts of true altruism at times might involve serious risk or danger to the person carrying out the act. This research question would address the degree to which the impulse to help others is learned/trained or motivated by innate biological responses more akin to the stress response. It is likely that both nature and nurture contribute to the impulse to carry out an altruistic act, and the relative contribution of each may depend upon the specific situation. Studies addressing this question should compare the previously described neurobiological and/or neurophysiological responses in untrained versus trained individuals who are presented with the opportunity to perform an altruistic act. This could be addressed through systematic study prior to the beginning of and during training of professionals trained to perform altruistic acts. Firemen are an example of such professionals trained to rush into a fire rather than to run away. Such studies could address whether risking one's life to save others involves suppression of nerve pathways and neuroendocrine responses (i.e. the stress response) that would otherwise predispose an individual to act differently, or activation of positive motivational nerve pathways, and the degree to which such physiological responses change with training.

Certain components of altruistic behaviors are reminiscent of maternal-infant interactions in all species. Animal studies could be selectively applied to address certain aspects of the question of the degree to which the tendency to perform altruistic behaviors are innate and related to genetic determinants. Much research has been performed in the area of effect of separation in rodent models on the adult set point of the neuroendocrine stress response. Thus, pups separated from their mothers for as little as 15 minutes per day for the first two weeks of life exhibit a significant and permanent increase in the set point of the neuroendocrine stress response that lasts into adulthood (Levine 1988; Sutanto 1996; Francis 1999) (Plotsky 1993). Inbred rat strain dams with high and low hypothalamic pituitary adrenal axis responsiveness exhibit differential maternal behaviors when pups are separated from them (Gomez-Serrano in press). Cross-fostering of pups between these strains alters the adult set-point of the hypothalamic pituitary adrenal axis response in a strain and gender dependent fashion, indicating that both maternal environmental and genetic factors contribute to the adult set point of the stress response (Gomez-Serrano in press). Similar studies could be performed in inbred rodent strains in which maternal behaviors are well characterized, where the read-out is adult maternal protective behaviors, in order to determine the degree to which apparently innate maternal protective behaviors are related to early developmental environmental factors.

Summary.

Studies such as those outlined will define the neurobiological pathways set into play during altruistic love, including brain regions that might be activated or suppressed, intermediate neuronal and hormonal pathways that might be activated or suppressed, and specific aspects of disease and immune system activity that might be affected by activation or suppression of these pathways. Together such studies will provide insights in a quantitative and objective manner on mechanisms by which altruistic love might affect disease outcome or health.

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