SOCIAL CONTACTS AS MODIFIERS OF DIURNAL CORTISOL PRODUCTION: A POTENTIAL PATHWAY BETWEEN SOCIAL RELATIONSHIPS AND HEALTH

by

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M.A., Washington University in St. Louis, 2003

A THESIS SUBMITTED IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

in

The Faculty of Graduate Studies

(Psychology)

THE UNIVERSITY OF BRITISH COLUMBIA

May 2007

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Abstract

Social connections have been linked with morbidity and mortality across decades of research. Although stress buffering and health behavior models have been extensively detailed as pathways for this effect, the direct effects of social contacts on physiology have received less attention. Social contacts may help to regulate biological rhythms, particularly within the hypothalamic-pituitary-adrenal (HPA) axis, a hormonal system known to be influenced by the social environment. Dysregulation of the HPA axis has been associated with psychiatric illnesses such as depression. The current thesis includes three studies that investigated the relationship between social contact and the diurnal pattern of cortisol secretion, as well as the moderating role of depression. These relationships were examined both cross-sectionally and prospectively via daily diary assessment of daily social contacts and salivary cortisol levels. In the first study, depressed women had a blunted cortisol response to waking compared to non-depressed women. Among the non-depressed but not among depressed women, the number of social contacts (especially positive ones) was associated with cortisol response to waking. In the second study, data were analyzed using hierarchical linear modeling and within-person results revealed that cortisol slopes following a day with more social contacts were steeper compared to cortisol slopes following a day with fewer social contacts. In the third study, daily social contacts were manipulated using a within-subjects design. Participants experienced both high and low social contact conditions in the laboratory while continuing to collect ambulatory data on their daily social contacts and cortisol levels. Results show that the manipulation successfully altered daily social contacts, but had no significant effect on cortisol slope. However, there is some evidence to suggest
that frequency of contact may be an important moderator of the effect. Although causality has not been definitively demonstrated, findings from these studies suggest that in addition to previously articulated pathways, social relationships may influence health via a direct effect of social contact on physiology.
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Acknowledgements

I would like to express my sincere appreciation and gratitude to Dr. Gregory E. Miller. I was very fortunate to have him as an advisor during graduate school and will continue to consider him a mentor and a friend. I would also like to thank my delightful team of volunteers who assisted me with data collection: Erica Bennett, Kim Johnson, Jennifer Munch, Shivani Nair, Khrystyna Savchuk, Adeline Sawsurachai, and Jane Woo. Without the informational and emotional support of my friend, Elizabeth Stanford, this process would have been much, much more difficult. And finally, thank you to the members of the Psychobiological Determinants of Health Lab at UBC for their support, patience and friendship.
Dedication

To my love, JMH
Co-Authorship Statement

Although the data for the first study in this thesis were collected as part of a larger study of inflammatory markers during depression, the ideas for the current research program were that of the first author, Cinnamon Stetler. For all three studies, she participated in all aspects of the research from interviewing participants and collecting data (except for performing the cortisol assays) to performing the data analyses, interpreting the results, and writing the manuscripts.
Introduction

Social relationships, the web of connections that ties an individual to larger society, have been repeatedly associated with better health outcomes and decreased risk of disease or mortality. Decades of research have explored this link. In 1979, Berkman and Syme were among the first to conduct prospective research on epidemiological data; their results revealed an increased risk of dying for those people who reported the fewest social connections, with the best outcomes coming for the people who reported having the most social ties. House, Landis, and Umberson (1988) coalesced the existing studies into a seminal statement about the importance of social relationships for survival, and noted that social isolation has as big an impact as cigarette smoking on mortality rates. A more recent synthesis of high quality studies described evidence for the important role that social ties play in health maintenance and disease recovery, particularly in aging populations (Seeman, 2000). Specific disease outcomes have also been linked with social relationships. Helgeson, Cohen and Fritz (1998) reviewed the literature and found good support for a link between social integration and mortality due to cancer. A lack of social ties has also been implicated as a major risk factor for mortality following a heart attack, on par with well-known medical risk factors such as elevated cholesterol and hypertension (Mookadam & Arthur, 2004).

How Social Relationships Influence Health

While social relationships have been identified as an important factor for future health outcomes across a range of populations, the underlying mechanisms still remain to be clarified and refined. Theorists have argued that social relationships may exert their influence on physical health via at least three primary pathways. They may act as a brake
on reactivity in times of stress (the stress-buffering hypothesis), they may promote better health behaviors and coping strategies, or they may have a direct effect on physiological functioning (Cohen, 1988; Cohen, Gottlieb, & Underwood, 2000). These pathways are not mutually exclusive, to be sure. In a comprehensive review, Uchino, Cacioppo & Kiecolt-Glaser (1996) concluded that there was good evidence to support the buffering effect of social relationships on physiological reactivity in times of stress. Having social support in the context of a stressful experience seems to attenuate cardiovascular and hormonal reactivity. Seeman and McEwen (1996) reviewed studies that tested the association between social environment and cardiovascular or neuroendocrine outcomes, and found that aspects such as status within a social hierarchy or support experienced during an interaction can influence physiology, but again this effect was primarily during times of stress. Studies that find an effect of social relationships on health outcomes often control for health behaviors (although this may be an important pathway itself) and continue to find effects for physiological outcomes, indicating that social ties influence biological processes directly, above and beyond their ability to influence health behaviors (Seeman, 2000). Taken together, the literature gives ample reason to suggest that the direct impact of social relationships on physiology is worth examining in greater detail, although the number of studies in this area to date is very small.

How Social Relationships are Conceptualized

Differing theories about the underlying mechanisms through which social relationships influence morbidity and mortality have given rise to disparate ways to conceptualize and operationalize this construct. Research arising from the view that relationships serve a stress-buffering function has generally focused on the supportive
features of social contacts. The idea here is that during times of stress, friends and family provide information, tangible support, and emotional guidance that helps to minimize the impact of the situation and reduce perceived stress. Thus, researchers in this area use measures that assess the quantity and nature of the support received during a time of stress. Research that arises from the view that social relationships operate through health practices generally focuses on whether a person has a few critical network members, i.e. typically a spouse, child, or close relative. These individuals are thought to shape decisions and behavior regarding nutrition, smoking, alcohol use, etc, and motivate the person to seek medical care when necessary. Also, the presence of close relatives and friends is thought to help a sick person deal with many of the chronic difficulties that arise in managing an illness. Research focusing on the direct benefits of social contact views the presence and frequency of interaction as important for health outcomes. In this work social contacts are thought to promote health by directly stabilizing biological processes and helping to regulate circadian rhythms. Thus, research in this tradition focuses on the number, frequency, and quality of social interactions that people have in their daily lives.

Social Contacts and Hormonal Rhythms

The primary theme in the current line of research is that social contacts have a direct effect on health via their ability to regulate and maintain the proper timing of biological processes. These patterns of proper timing, or rhythms, are critical for adaptive mental and physical functioning. If bodily systems become out of sync with one another or with the environment, then illness or distress is the likely consequence. Given that proper timing of biological processes is a crucial part of adaptive functioning, regular
patterns of social contact are therefore viewed as the important aspect of social relationships in this model. Specifically, the studies in this dissertation focus on the hypothesis that having regular social contact influences the magnitude and timing of cortisol secretion, a process that has important implications for future mental and physical health outcomes.

Cortisol is a glucocorticoid hormone that is the primary product of the hypothalamic-pituitary-adrenal (HPA) axis. In addition to being a key component in the body's response to stress, it is secreted throughout the day even in the absence of an acute stressor. A portion of the cortisol secreted into circulation remains active, or unbound, and makes its way into the saliva. Cortisol levels in saliva are highly correlated with cortisol levels in circulation (Kirschbaum & Hellhammer, 1994). This hormone has effects on multiple systems throughout the human body, including the cardiovascular, immune and nervous systems, as well as metabolism. For example, corticosteroids such as cortisol are critically involved in blood pressure regulation (Hammer & Stewart, 2006). Cortisol promotes gluconeogenesis in the liver, providing a vital source of energy for the body's tissues. Cortisol has been shown to modulate several aspects of immune function, including T and B cell function, cytokine and adhesion molecule expression, cell trafficking and cell proliferation (Webster, Tonelli, & Sternberg, 2002). Because of its pervasive effects, proper regulation of cortisol secretion is considered important for physical and mental health. A number of diseases have been associated with disturbances in cortisol levels, including depression (Young, Haskett, Grunhaus, Pande, Weinberg, Watson, et al., 1994), post-traumatic stress disorder (Yehuda, Giller, Southwick, Lowy,

Under normal conditions, cortisol levels follow a distinct circadian pattern, with cortisol levels highest early in the day soon after awakening, and declining throughout the day to a nadir in the late evening/early morning hours. Overnight, cortisol levels climb steadily and reach a rapid peak in the morning hours, usually just after awakening. The current research examines two aspects of this circadian pattern: the peak levels of cortisol reached just after awakening, and the diurnal decline in cortisol during waking hours. These specific aspects of cortisol secretion were chosen as outcomes because they not only indicate HPA axis function, but they also may be markers of broader biological rhythms as well (Desir, Van Cauter, Golstein, Fang, Leclercq, Refetoff, et al., 1980). Measuring cortisol levels non-invasively, in saliva, permits frequent but meaningful assessment required for accurate estimation of the morning peak and diurnal decline, increasing its appeal as a marker of biological rhythms. Furthermore, a disrupted circadian pattern of cortisol secretion has been shown to predict greater risk for cardiovascular disease (Rosmond & Bjorntorp, 2000; Matthews, Schwartz, Cohen & Seeman, 2006), reduced longevity among breast cancer patients (Sephton, Sapolsky, Kraemer, & Spiegel, 2000) and greater risk for relapse following a major depressive episode (Zobel, Nickel, Sonntag, Uhr, Holsboer, & Ising, 2001).

Timing physiological functions

Many physiological processes run in a consistent pattern, known as a circadian rhythm, that is timed to correspond to the 24-hour day dictated by the earth’s rotation on its axis. Circadian rhythms are endogenously generated in humans by the suprachiasmatic
nucleus (SCN) of the hypothalamus, and synchronized with the environment via external cues called zeitgebers, a German term roughly translated as “time giver” (Moore, 1999). While the primary zeitgebers in the environment are the rising and setting of the sun, social zeitgebers are tasks, demands, or social interactions that also help to program daily biological rhythms (Wever, 1988). These cues that help to entrain biological processes are derived from the daily regularities of a modern lifestyle, such as meals, employment, and entertainment, and are often, but not necessarily, driven by interpersonal interactions and participation in a larger community (Ehlers, Kupfer, Frank, & Monk, 1993).

The importance of social zeitgebers may be ascending as society’s demands expand into the nighttime hours. For example, many modern humans choose to override the time cues offered by the natural light/dark cycle and remain awake in order to work, study, be entertained, or interact socially long after the sun goes down. Indeed, life in modern society affords us many reasons to remain active after dark (e.g. working a night shift) or to be inactive during the day (avoiding unpleasant events, catching up on sleep). Thus humans can choose to behave in ways that affect their circadian rhythms, and it is this interface of external social behavior and internal circadian physiology that may be an important factor in physical health outcomes.

Impact of circadian rhythms on health

Disrupted circadian rhythms have been associated with poorer health outcomes. Shift workers are employees who are assigned to work a shift other than the traditional 9AM to 5PM schedule. These shifts are sometimes known as the second or third shifts, and are increasingly common as companies seek to remain competitive in global markets. Shift workers must remain awake throughout much or all of the night, and sleep during
daylight hours. They report increased incidence of mental disorders such as depression and anxiety, as well as increased gastrointestinal complaints (Moore-Ede & Richardson, 1985). Several studies (reviewed by Costa, 1996) have found shift workers to be at greater risk of developing peptic ulcer disease compared to workers who work a daytime shift. Shift work has also been associated with increases in risk markers for cardiovascular disease (CVD), such as triglycerides and blood pressure, as well as an increased incidence in CVD the longer the workers were exposed to shift work (Scott, 2000).

Social processes shape the timing of biological rhythms

Although the light/dark cycle is the primary zeitgeber, social zeitgebers can have an influence on biological rhythms. Several studies provide evidence in support of a link between social zeitgebers and biological rhythms among healthy adults. McClintock and colleagues have described a phenomenon whereby a group of women living together will experience synchronization of their menstrual cycles, an effect mediated by chemosignals called pheromones (McClintock, 1971; Stern & McClintock, 1998). Group isolation studies conducted in the 1970's showed that when several subjects are housed in small groups but isolated from external time cues (e.g. clocks, windows), each group develops a unique circadian rhythm to which all members are entrained. When one group member is transplanted into a new group, his circadian rhythms lose their old timing from the original group and become re-entrained to the rhythms of the new group (Vernikos-Danellis & Winget, 1979).

Other researchers have capitalized on unique situations outside the lab to study the effects of social zeitgebers on circadian rhythms. During the month of Ramadan,
Muslims as a community alter their normal schedules and refrain from eating and drinking during daylight hours. A recent study (Bogdan, Bouchareb, & Touitou, 2001) found that these changes were associated with a change in the diurnal secretion patterns of several hormones, including cortisol. The morning rise was delayed and there was a distinct rise in the afternoon levels of serum cortisol measured during Ramadan. While a portion of these cortisol changes are due to changes in the timing of meals, it is possible that the altered pattern of social interactions played a role as well. Flying across multiple time zones typically produces a syndrome known as jet lag. Klein and Wegmann (1974) demonstrated that subjects who remained inside the hotel at their destination took much longer to resynchronize and had a much slower rate of recovery from jet lag than subjects who went outdoors and participated in social activities soon after arriving in the new environment. Again, the study's design does not allow us to determine whether the recovery was due to light exposure, participation in social activities, or both.

Nonetheless, changes in daily activity patterns and social contacts, whether natural or induced as part of an experiment, a religious observance, or long-distance travel, can have important effects on biological rhythms. On the whole, these findings suggest that social contacts can shape the timing of circadian rhythms. Given that proper circadian timing is critical for health and well-being, this may be one pathway by which social ties get inside the body to influence morbidity and mortality.

Social connections and biological rhythms in depression

One example of a condition where the influence of social zeitgebers may be important is depression, a disorder often characterized by poor-quality social relationships and an increase in social isolation. The fact that clinical depression is also
associated with disruptions in sleep, appetite, mood and hormones—systems with strong circadian rhythms—may not be coincidence. If social contacts do indeed work as cues to ensure proper circadian functioning, then deficits in social contacts during depression may play a role in the neurovegetative disruptions inherent to this condition. This potential connection, between the poor-quality social relationships and the circadian disturbances seen during depression, may represent an example of the larger link between the social environment and health.

Depressed individuals may lack social zeitgebers because they are more socially isolated and experience fewer social contacts than non-depressed individuals. Or the social contacts that they do have may be of poorer quality, perhaps more negative or more superficial and less intimate in nature. Thus social zeitgebers may still be present in the environment but lose their ability to influence the timing of biological processes during depression, just as someone with insomnia still experiences the setting of the sun and onset of darkness, but fails to become sleepy. These competing hypotheses—deficit versus loss of function—were examined in a previous study comparing individuals with clinical depression to healthy non-depressed individuals (Stetler, Dickerson, & Miller, 2004).

We found no significant difference in the amount of daily social contact between the depressed and non-depressed groups, suggesting that an absence of social zeitgebers is not responsible for any disruptions in biological rhythms experienced during depression. However, we did find support for the loss of function hypothesis. To the extent that they reported that more of their daily routine was done with other people, non-depressed individuals tended to show a steeper, more normative diurnal decline in
cortisol levels. Having a larger or more diverse social network would presumably increase the likelihood of having contact with others while going about a daily routine, and this may help to explain why social network size has been repeatedly associated with improved health outcomes. Among the depressed participants, this relationship was not present. Having other people around during their daily routine did not make a difference for depressed individuals’ diurnal cortisol levels, indicating that the normal programming influence of social contacts on biological rhythms is altered or absent during depression. This may be due to poor-quality social contacts that are unable to serve their proper regulatory function; this deficit may underlie some of the circadian disturbances seen during clinical depression.

The current line of research arose out of this previous study and the unanswered questions that remained. The objectives of the studies in this research program are: (1) to replicate and extend these cross-sectional findings to other samples as well as to other social and biological processes; (2) to determine the direction of the relationship between social contacts and cortisol rhythms; (3) to determine if depressive symptoms moderate the social contacts and cortisol association within a healthy, non-clinical sample; (4) to evaluate causality by developing and testing a manipulation of social contact; and (5) to investigate the specific types of relationships or specific nature of the social contact that is most able to influence cortisol rhythms. In the chapters that follow, three studies are described, and together they address these issues.
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Blunted Cortisol Response to Awakening in Mild to Moderate Depression:

Regulatory Influences of Sleep Patterns and Social Contacts

Alterations of the hypothalamic-pituitary-adrenal (HPA) axis, including corticotrophin-releasing hormone (CRH) and cortisol hypersecretion, disturbed negative feedback regulation, and alterations in circadian timing, are well documented during major depression (Halbreich, Asnis, Shindledecker, Zumoff, & Nathan, 1985a; Halbreich, Asnis, Shindledecker, Zumoff, & Nathan, 1985b; Hallonquist, Goldberg, & Brandes, 1986; Kocsis, Brockner, Butler, Fanelli, & Stokes, 1984; Linkowski et al., 1987; Mortola, Liu, Gillin, Rasmussen, & Yen, 1987; Pfohl, Sherman, Schlechte, & Stone, 1985; Souetre et al., 1989; Stokes et al., 1984; Yehuda, Teicher, Trestman, Leve, & Siever, 1996). HPA hyperactivity and/or disrupted circadian timing is most likely to be detected when hospitalized, severely depressed patients are compared to healthy, non-depressed controls (Maes, Calabrese, & Meltzer, 1994). When less severely depressed patients, or those who are not confined to a hospital are studied, evidence for HPA axis hyperactivity has been less consistent, with several reports finding comparable or reduced levels (Anisman, Ravindran, Griffiths, & Merali, 1999; Miller, Cohen, & Hebert, 1999; Ravindran, Griffiths, Merali, & Anisman, 1995; Stetler, Dickerson, Miller, 2004; Strickland et al., 2002; Watson et al., 2002; although see Bhagwagar, Hafizi, & Cowen, 2003; Cleare et al., 1995; and Young, Gallagher, & Porter, 2002, for evidence of elevated cortisol in non-hospitalized depressed patients).

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1 A version of this chapter has been published: Stetler, C., & Miller, G.E. (2005). Blunted cortisol response to waking in mild to moderate depression: Regulatory influences of sleep patterns and social contact. Journal of Abnormal Psychology, 14, 697-705.
The lack of consistent baseline differences in cortisol secretion does not preclude the possibility that more subtle disruptions in timing of HPA axis function exist among non-hospitalized depressed individuals. Few studies have examined diurnal parameters of cortisol secretion in cases of mild to moderate clinical depression drawn from a community population. Ahlberg and colleagues (2002) recently reported a negative association between depressive symptoms and morning cortisol levels (measured in serum at a single time point) within a non-clinical sample of middle-aged men. In a sample of participants from the general community Strickland and colleagues (2002) found a trend toward lower morning cortisol levels among women who met diagnostic criteria for depression versus healthy controls. This study measured salivary cortisol at one timepoint on each of two mornings. Another recent study also showed lower cortisol levels among depressed people sampled from the community at early but not later morning time points (Peeters, Nicolson, & Berkhof, 2004). Although these findings suggest that the morning cortisol response may be blunted in depression, at least one study has found the opposite, that the presence of depressive symptoms is associated with higher levels of cortisol shortly after awakening (Pruessner, Hellhammer, Pruessner, & Lupien, 2003). In addition, Bhagwagar, Hafizi, and Cowen (2003) reported evidence of morning cortisol hypersecretion in recovered depressed patients. To reconcile these disparate findings, a thorough assessment of psychiatric status and depressive symptoms, as well as morning cortisol response, is needed.

Researchers have examined the morning cortisol response to awakening as a potentially useful and easily accessible indicator of HPA axis function (Pruessner et al., 1997). Recent studies indicate that salivary measures of morning cortisol are sensitive to
known influences on HPA axis function such as chronic stress (Pruessner, Helhammer, & Kirschbaum, 1999) and are stable across time (Schmidt-Reinwald et al., 1999). In a majority of healthy people, cortisol levels peak shortly after waking up in the morning (30 – 45 minutes). Approximately an hour after awakening, cortisol levels begin to decrease and continue to decline throughout the day. Although the physiological reasons for this morning peak remain unclear, some have proposed metabolic or immunoregulatory functions (Hucklebridge, Clow, Abeyguneratne, Huezo-Diaz, & Evans, 1999; Pruessner et al., 1997). Among healthy samples, the magnitude of the cortisol response has been linked to the time of awakening, with later wake times associated with reduced peak cortisol levels (Edwards, Evans, Hucklebridge, & Clow, 2001; Kudielka & Kirschbaum, 2003). Other studies have failed to replicate this association (Hucklebridge et al., 1999; Wust et al., 2000). It makes theoretical sense that the timing of the sleep/wake cycle and cortisol secretion are linked, given that both processes are generated from the suprachiasmatic nucleus, a specialized part of the hypothalamus that controls circadian rhythms (Weitzman, Czeisler, Zimmerman, & Moore-Ede, 1981).

HPA axis function is also sensitive to input from the social environment. Earlier work in our lab demonstrated that the normal pattern of cortisol secretion across the day is associated with the presence of others. To the extent that daily activities were performed with other people involved, subjects tended to have steeper declines in their levels of cortisol secretion across the day (Stetler, Dickerson, & Miller, 2004). Steeper declines are indicative of a more normal diurnal pattern of cortisol secretion (Stone et al., 2001). However, this relationship between social contacts and the diurnal pattern of cortisol secretion was absent among clinically depressed participants. Of note, we did
not find differences in the absolute levels of social contact between depressed and non-depressed groups, a finding consistent with other research on depression (Nezlek, Hampton, & Shean, 2000). Thus, despite reporting levels of social contact equivalent to those of non-depressed persons, people with depression did not show the links between their social contacts and HPA axis function that the non-depressed people showed. This suggests that during depression, the HPA axis is unresponsive to events in the social environment that help to promote its proper function under normal conditions (Bogdan, Bouchareb, & Touitou, 2001; Klerman et al., 1998; Roy, Steptoe, & Kirschbaum, 1998).

The current study investigated the morning cortisol response to awakening among depressed and non-depressed participants. We tested the prediction that depressed participants would show an altered morning cortisol response compared to healthy control participants. We also examined the relationship between morning cortisol secretion and several potentially important regulatory factors, namely the sleep/wake cycle and social interactions. We hypothesized that characteristics of the sleep/wake cycle (e.g. hours slept, sleep quality, time of awakening) would be associated with morning cortisol response in healthy subjects, but not in depressed subjects. Similarly, we hypothesized that among control but not depressed participants, social contacts would be associated with morning cortisol levels. Such a pattern of results would suggest a loss of internal and external regulatory control over HPA axis functioning during depression.

Methods

Participants

Seventy-three women were recruited from the St. Louis metropolitan area as part of a study investigating the mechanisms linking depression and cardiac disease risk.
These women were recruited between June 2002 and June 2003. Although this study was similar in design to our previous research (Stetler, Dickerson, & Miller, 2004), the two samples had no overlap in terms of composition. Thirty-seven of the participants met criteria for clinical depression, and thirty-six healthy non-depressed participants served as a control group. Participants were recruited by advertisements placed in mass transit stations, local newspapers and around the university. Exclusion criteria for all participants were the presence of a chronic medical illness, acute infectious disease, current or recent (past year) pregnancy, use of anti-depressant medications, or any standing medication regimens other than oral contraceptives during the previous month.

Diagnoses of depression were made by two trained interviewers using the Depression Interview and Structured Hamilton (DISH; Freedland et al., 2002). This interview is a semi-structured interview that yields information regarding the presence, frequency, duration, history and severity of symptoms of clinical depression. The DISH’s structure enables interviewers to integrate the probes needed to make clinical diagnoses according to DSM-IV (American Psychiatric Association, 1994) with those needed to make symptom severity ratings according to the 17-item Hamilton Rating Scale (Hamilton, 1960). The DISH was developed for use in clinical research and its reliability and validity have been established across multiple studies (Freedland et al., 2002; Miller, Stetler, Carney, Freedland, & Banks, 2002). To assess the presence of other Axis I psychiatric disorders, the interviewer also administered modified versions of the Diagnostic Interview Schedule (DIS; Robins, Helzer, Coughan, & Ratcliff, 1981) and the Primary Care Evaluation of Mental Disorders (PRIME-MD; Spitzer et al., 1994).
To be included in the study, volunteers had to meet DSM-IV criteria for either major or minor depression, and be free of co-morbid Axis I disorders other than generalized anxiety disorder (GAD). These criteria yielded a sample of 37 participants in the depressed group, the majority of whom (N=33) met criteria for major depression and four who met criteria for minor depression (Diagnostic and Statistical Manual of Mental Disorders-IV; American Psychiatric Association, 1994).

For each depressed participant enrolled, a healthy control participant, matched on race and age (within 3 years) was enrolled. Participants in the control group were also given the DISH, DIS, and PRIME-MD and were excluded if they reported any history of Axis I psychiatric disorders. This yielded a sample of 36 participants in the control group.

The interviewers received extensive training on the DISH before the study began. To assess the extent of their diagnostic agreement, both interviewers rated a series of 20 participants. Across the 11 symptom dimensions of the DISH, the interviewers showed an average kappa of .79, a value indicating good to excellent diagnostic agreement (Landis & Koch, 1977).

Procedure

During an initial lab session, participants were introduced to the lab setting and underwent diagnostic interviewing. Once the participants were determined to be eligible for the study, they were given instructions regarding the ambulatory collection of data. Ambulatory data collection took place each morning for three days, over no greater than a 7-day span. In order to maximize generalizability, the days on which data were collected were always non-consecutive. Participants were asked to collect data on days
that included a "typical schedule for them", which would include workdays if participants were employed. Data were not collected on days when participants anticipated deviations from their usual routine, such as vacations, travel or exams.

Participants were given a handheld computer (Palm Pilot M100, Palm Inc., New York) that prompted collection of saliva samples and administered questionnaires about their social interactions and sleep patterns (see below). The Palm Pilot was programmed to beep at a set schedule: 0 minutes, 30 minutes, 1 hour after the participant's pre-reported waking time. For example, if the participant reported their usual wake-up time as 7AM, they would be prompted by the computer to collect saliva at 7AM, 7:30AM, 8AM. This sampling frequency immediately post-awakening was chosen in order to capture the early morning peak that is part of the diurnal pattern of cortisol secretion (Pruessner et al., 1997).

At each of these pre-set times, the participants were instructed to collect a saliva sample by placing a small roll of cotton in the mouth for at least one minute and saturating it with saliva before depositing the cotton into a sterile collection tube (Salivette, Sartstedt Inc.). Participants were asked not to eat or brush their teeth immediately prior to collecting the saliva in order to prevent sample contamination with food or blood. Participants were told to keep their used Salivettes in the refrigerator or at room temperature before returning them to the lab, usually 2-3 days after collection was completed. It has been established that salivary cortisol concentrations are stable at room temperature (Clements & Parker, 1998). To ensure compliance, the Palm Pilot briefly displayed a unique 3-digit code that the participants were to record on the Salivette at each collection time. Compliance rate was excellent; 637 of 657 possible saliva samples
generated usable cortisol values (i.e. correct code and sufficient saliva), a 97% success rate.

Measures

Participants completed measures of sleep patterns and social interactions on their Palm Pilots one hour after they awoke each day, immediately following their third saliva collection. The Palm Pilots provided a check on compliance via their automatic time and date stamp feature. Data that were collected more than 60 minutes beyond its scheduled time was not included in the analyses; 93% of Palm Pilot entries were completed within 60 minutes of their target time.

Sleep. At 60-minutes post-awakening, sleep parameters concerning the previous night were assessed using four items derived from the Pittsburgh Sleep Quality Index (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). The items were: What time did you go to bed last night? What time did you finally wake up this morning? How many minutes after the lights went out did you fall asleep? How would you rate your sleep quality overall last night? (1 = very poor to 4 = very good). We used these data to create sleep onset, sleep duration, sleep lost, and sleep quality variables, respectively.

Social contacts. At 60 minutes after awakening, participants were asked to record the number of social interactions they had had in the past hour. A social interaction was defined as “communication with one or more persons that lasted at least 5 minutes and that you would describe as significant”. The interactions need not have been in person; they could have been over the phone or via Internet. If the participant reported having any social interactions, they were then asked to think about the interaction that had the most effect on them or that they considered to be the most significant. Regarding that
interaction, they were then asked a series of questions taken from the Diary of Ambulatory Behavioral States (Kamarck et al., 1998) and the Rochester Interaction Record (Reis & Wheeler, 1991). These items queried the overall quality of the interaction, and were summed into separate positive and negative scales. Participants were asked to rate the interaction on a 0-4 scale, with higher scores indicating greater levels of that quality. The positive scale consisted of 14 items, including the extent to which the interaction was friendly, intimate, helpful or included positive feedback. The negative scale consisted of three items: the extent to which there was conflict in the interaction, someone treated the participant badly, and interfered with their efforts. Participants answered these items again regarding a second significant social interaction, if one had occurred.

**Cortisol Assays**

After the saliva containers were returned to the lab, they were spun in a centrifuge for five minutes at 3000 rpm until a clear, low-viscosity supernatant emerged. The supernatants were then collected and frozen at -70°C until the completion of the study. At that time the samples were shipped to the Institute of Experimental Psychology II at the University of Duesseldorf, Germany. Cortisol assays were performed in duplicate using a commercially available chemiluminescence assay (IBL, Hamburg, Germany). This assay has a sensitivity of 0.16 ng/ml. The intra-assay coefficient of variation was less than 10 percent; the inter-assay coefficient of variation was less than 12 percent.

**Statistical Analyses**

Participants who did not return any days of usable saliva samples or Palm Pilot data were dropped from the sample. This meant excluding four participants, three in the
depressed group and one in the control group, from the final analyses. After these participants were dropped, 597 data points remained out of a possible 609, a 98% compliance rate. Morning cortisol response was represented by the area under the curve (calculated with reference to zero) for the 0, 30 and 1 hour post-awakening data points. In order to take advantage of the nested structure of our data (i.e. days nested within participants nested within diagnostic groups) we utilized hierarchical linear modeling (HLM) techniques (Bryk & Raudenbush, 1992). All analyses were done using HLM v5.04 software (Raudenbush, Bryk, & Congdon, 2001), specifying a first-order autoregressive covariance matrix and robust standard errors (Schwartz & Stone, 1998). Where appropriate, we also present means (± SD) aggregated across the three days.

In order to determine whether depression was associated with a dysregulated morning cortisol response, we constructed a two-level model. On the first level, we modeled each participant’s morning cortisol response as a function of day of sampling (which was participant-centered). At the second level, we modeled the level-1 intercept, which corresponds to cortisol response on the average sampling day, as a function of diagnostic group. This analysis examines whether depressed and non-depressed participants differ in their average morning cortisol response across the sampling period. In subsequent analyses we included sleep parameters or social interactions on the first level of our model, in order to determine whether these factors were accounting for any disparities in cortisol response. We considered these variables to be potential mediators if their presence attenuated the relationship between diagnostic status and morning cortisol response.
Given that biological rhythms often become dysregulated in depression, we also examined whether events that normally promote cortisol release were operating properly. Our focus was on both internal (sleep parameters) and external (social contacts) factors. To answer this question we tested whether the relationship between sleep parameters or social contacts and morning cortisol response varied by diagnostic group. We modeled the association between sleep patterns or social contacts and cortisol AUC for each participant at level one. At level two, we examined whether the association varied by diagnostic group. If so, we then analyzed the groups separately in order to characterize the nature of the relationship between morning cortisol response and sleep parameters or social interactions within each diagnostic group.

Results

Sample characteristics

Table 2.1 displays demographic, psychiatric, and health behavior information for the depressed and control participants. The groups were successfully matched on age and race. The groups did not differ significantly on marital status; the vast majority in each group (86%) had never been married. Control participants were more likely to report taking oral contraceptives ($\chi^2 = 5.16, p < .02$) and less likely to report daily tobacco use ($\chi^2 = 6.49, p < .01$) compared to depressed participants. None of these variables were significantly associated with morning cortisol response, and statistically controlling for them did not attenuate any of the associations between depression and cortisol that we report below (all $p$'s < .001). Control participants averaged more years of education ($t(71) = 2.4, p < .02$) than depressed participants. Although participants with more education had larger morning cortisol responses, ($r = .49, p < .01$), statistically
controlling for this variable also did not attenuate the differences in morning cortisol response reported below.

As expected, the groups showed marked differences on BDI and HRSD-17 scores. These scores indicate a mild to moderate level of symptom severity among the depressed participants. Nearly one quarter (22%) of the depressed participants reported receiving some type of therapy or counseling at the time of the study. Almost a third (32%) of depressed participants also met diagnostic criteria for GAD. These participants did not display significantly different morning cortisol responses compared to depressed participants without GAD. Similarly, the four participants who met criteria for minor depression did not differ significantly from those who met criteria for major depression on morning cortisol response.

**Morning Cortisol Response**

The two groups of participants showed markedly different early morning cortisol profiles. As Figure 2.1 shows, depressed and control participants had similar salivary cortisol values immediately after awakening; controls had an average of 11.57 (±4.98) nmol/L, while depressed participants averaged 10.51 (±4.4) nmol/L at this timepoint. Thirty minutes later, the groups diverged: the controls exhibited the expected rise in cortisol that occurs following morning awakening (cortisol_{30min} = 18.3 (±7.3)), while the depressed participants showed very little increase in cortisol (cortisol_{30min} = 12.4 (±5.4)). The groups continued to differ at 1 hour post awakening (control cortisol_{60min} = 18.0 (±7.2), depressed cortisol_{60min} = 10.7 (±5.3)). According to data from Wust and colleagues (2000), normal adults show cortisol levels of 15.12, 22.95, and 20.23 nmol/L at 0, 30, and 60 minutes after waking, respectively. These data suggest that control
participants in our study are showing morning salivary cortisol levels that fall within normal ranges, while the depressed participants are displaying a blunted morning cortisol response.

Table 2.2 displays the results of the HLM analysis of group differences in cortisol levels at each of these timepoints. As we noted above the depressed and control groups had similar cortisol levels at awakening ($p = .15$), but diverged significantly 30 minutes later ($p = .001$) and remained this way at 60 minutes post-awakening ($p = .003$).

To summarize the morning cortisol response, we calculated the area under the curve (AUC). Hierarchical linear models also revealed a marked group difference in area under the curve, $\beta = 5.07$, SE = 1.15, t(67) = 4.4, $p < .001$, such that on an average day, controls had greater morning cortisol AUC compared to depressed participants. Average AUC across all three days was 16.36 ($\pm5.7$) for controls compared to 11.27 ($\pm4.4$) for depressed participants. This disparity translates into an effect size of $d = -1.00$; the depressed group had a morning cortisol response one standard deviation unit smaller than that of the control group. The AUC variable served as the dependent variable for all subsequent HLM analyses.

We used HRSD or BDI scores to examine whether a dose-response relationship existed between depression severity and morning cortisol response among the depressed group. HRSD scores were negatively associated with morning cortisol response ($\gamma = -.31$, SE = .14, $p < .03$) but BDI scores were not ($\gamma = -.06$, SE = .08, $p = .47$). These results provide mixed evidence for a dose-response effect within the depressed group.

It may be that the group differences in morning cortisol response are a product of unstable/random cortisol levels across days for depressed participants. To test this
hypothesis, we looked at stability across the three days using Cronbach's alpha and found that morning cortisol levels were stable across the three days of data collection for each group. Reliability for the AUC among the controls (α = .63) was comparable to that among the depressed group (α = .68), suggesting that group differences are not reflecting unstable cortisol levels among the depressed participants.

**Sleep**

Given that mild to moderate levels of clinical depression seem to be accompanied by a blunted morning cortisol response, we now turn our focus to identifying mechanisms that might underlie this phenomenon. As we noted earlier in the paper, sleep can be an important regulator of cortisol secretion. We assessed sleep onset, duration, quality and hours lost for each night prior to morning cortisol collection. Depressed and control groups did not differ on average time of sleep onset (γ = -1.87, SE = 1.83, t(67) = -1.02, p = .31) or on number of hours slept (γ = .37, SE = .34, t(67) = 1.09, p = .27). Depressed participants did report poorer sleep quality (γ = .66, SE = .14, t(67) = 4.73, p < .001), and more hours of sleep lost (γ = -7.94, SE = 3.08, t(67) = -2.58, p < .01) than controls. When each of these variables was included as a covariate, diagnostic group continued to predict morning cortisol, with all p values < 001. These findings suggest that sleep parameters are not responsible for the blunted morning cortisol response seen among the depressed participants.

The process of awakening has been shown to drive the morning cortisol response, implying a link between timing of the sleep/wake cycle and timing of HPA axis function (Hucklebridge, Clow, Rahman, & Evans, 2000; Pruessner et al., 1997). Depressed participants may be waking up earlier or sleeping later than their non-depressed
counterparts, thus affecting their cortisol responses. In order to address this question, we calculated the time of awakening for each participant in terms of number of hours past midnight. The two groups showed no significant differences on average waketime (γ = .44, SE = .48, t(57) = .92, p = .36); controls awoke an average of 7.87 (±1.7) hours after midnight, while depressed participants awoke an average of 7.51 (±2.0) hours after midnight. When average waketime was included in the model, the group differences in morning cortisol AUC remained significant.

Although the groups do not differ on time of awakening, the relationship between time of awakening and cortisol secretion could vary by group. It may be that awakening normally promotes activity in the HPA axis, but has lost its ability to function in this way during depression. Indeed, the relationship between time of awakening and morning cortisol AUC differed by group (β = 2.69, SE = 1.07, t(67) = 2.52, p < .02). Among the control group, waketime was negatively correlated with morning cortisol AUC (β = -2.03, SE = .64, t(34) = -3.18, p < .01); later wake times were associated with lower morning cortisol levels. Among depressed participants, waketime was not associated with cortisol AUC (β = .26, SE = .33, t(33) = .79, ns). In fact, time of awakening accounted for 27.4% of the cortisol variance among controls and 3.1% of the variance among depressed participants. Thus, time of awakening is associated with the magnitude of the morning cortisol response among control participants, but not among depressed participants. These findings suggest that during depression, the HPA axis is not responding to an important internal event, the timing of the sleep/wake cycle.
Social Interactions

Another factor that has been shown to influence cortisol production is social interaction. It may be that depressed participants lack the social contacts in their environment that may contribute to morning cortisol production. However, the groups did not differ in the number of morning social interactions they reported ($\gamma = -.01$, $SE = .15$, $t(57) = -.08$, $p = .93$). Controls reported an average of 2.00 (±1.64) interactions while depressed participants reported on average 2.24 (±1.86) interactions across the three days. When we controlled for the number of social interactions, the group differences on morning cortisol AUC remained significant ($p < .001$). Therefore, the blunted morning cortisol responses seen among the depressed group cannot be explained by a lack of social interactions in the morning.

The next series of analyses concern the valence of these social interactions. The groups did not differ significantly on how positive they reported their morning interactions to be ($\gamma = 1.67$, $SE = 4.03$, $t(57) = .42$, $p = .68$), but there were significant differences in reported negativity ($\gamma = -1.06$, $SE = .34$, $t(57) = -3.15$, $p = .003$). Overall positivity or negativity of the social interactions did not account for group differences in morning cortisol. Thus, depressed participants did not report fewer social contacts than controls, and although the contacts they did have were more negative, this did not explain their blunted morning cortisol response.

Social contacts can help to promote activity within the HPA axis, helping to set its normal diurnal rhythm. As with the time of awakening, social interactions may lose this function during periods of depression. In fact, the relationship between social interactions and morning cortisol did differ significantly by group ($\beta = 2.97$, $SE = 1.05$, ...
Among the control participants, social interactions were significantly associated with morning cortisol levels ($\beta = 2.25$, SE $= .81$, $t(34) = 2.79$, $p < .01$) while no significant association emerged among the depressed participants ($\beta = -0.46$, SE $= .74$, $t(33) = -0.64$, ns). The number of morning social interactions accounted for 7% of the variance in morning cortisol response among the control participants, but only 2% of the variance among the depressed participants. Having more social interactions during the hour after awakening was linked to increased cortisol responses, but only among non-depressed persons (Figure 2). This figure displays the average morning cortisol response for depressed and control participants who had high or low numbers of morning social interactions (as defined by a median split on this variable). These results suggest that for depressed participants, the HPA axis is not responding to daily external events (social contacts) that are thought to promote diurnal rhythms.

Given that social interactions seem to help promote a robust morning cortisol response for non-depressed people, what qualities of social interactions might be important? Among controls, greater positivity was associated with a larger cortisol AUC ($\beta = 0.733$, SE $= .17$, $t(29) = 4.31$, $p < .001$), indicating that the more positive they reported their morning social interactions to be, the higher their morning cortisol response. Among the depressed group, there was no association ($\beta = -0.85$, SE $= .055$, $t(28) = 1.54$, ns). Positivity accounted for 51% of the variance in morning cortisol levels among the control group, but only 2% of the variance among the depressed group. Neither group's cortisol levels were associated with the negativity of their social interactions ($p's > 0.5$). Positive social interactions during the hour after awakening seem to be fostering a more normative pattern of cortisol secretion among healthy controls, but
among depressed participants the same levels of positive social contacts are not influencing cortisol.

Discussion

Our analyses showed a blunted morning cortisol response among depressed women compared to non-depressed controls. Although the two groups showed similar cortisol levels immediately after awakening, cortisol levels within the depressed group failed to increase over the next 30 minutes and remained significantly lower than controls at 60 minutes post-awakening. These differences were large in magnitude. When the morning cortisol response data were summarized using an AUC statistic, depressed women showed a one standard deviation reduction in cortisol response compared to healthy controls. This translates into a 31% difference. To ensure that these findings reflect a “blunted” response in depressed women, rather than an elevated response in healthy controls, we compared our data to published norms for morning cortisol levels (Wust et al., 2000). This disparity persisted even though the groups were equivalent on age, race and gender, and even after controlling for tobacco use, medication use, quantity and quality of sleep.

These findings are at odds with a large body of research showing that depressed persons experience elevated levels of cortisol, particularly during the normally quiescent late evening hours. In addition, the HPA axis is often less sensitive to the negative feedback effects of cortisol, as evidenced by a failure to suppress cortisol production following dexamethasone administration. However, few of these studies have examined the cortisol response to awakening, and most have focused exclusively on hospitalized participants with severe depression. HPA axis function is likely to be quite different in a
community-based sample that has milder symptoms and is not undergoing antidepressant treatment. Thus, because clinical depression is such a heterogeneous condition, there may be a multitude of HPA axis abnormalities that depend on severity, course, history, and treatment. In outpatient samples like our own, HPA function may be best characterized as dysregulated (Peeters et al., 2004), and not hyperactive as in severely depressed patients. Consistent with this argument, lower morning cortisol levels have been found among a community sample of depressed adults by Strickland et al. (2002) and among a sample with depression co-morbid with PTSD (Oquendo et al., 2003). The presence of atypical symptoms, something not assessed in the current study, is also more common in community compared to clinic-based samples (Quitkin, 2002). Because atypical symptoms are associated with reduced cortisol levels, this may be important for future studies to assess (Anisman et al., 1999; Gold & Chrousos; 2002).

One alternative explanation for these findings grows out of research suggesting that depressed patients’ cortisol rhythms are phase-advanced compared to their sleep-wake cycle. To the extent that this is true, depressed patients cortisol peak would have occurred earlier in the morning, and would not have been captured with our sampling protocol. Although we do not have the data to rule out this explanation definitively, there are several reasons to believe that it is not a plausible mechanism underlying our findings. First, although the circadian phase advance hypothesis of depression has received some empirical support (Halbreich, Asnis, Shindledeker, Zumoff, & Nathan, 1985c; Linkowski et al., 1985; Sherman, Pfohl, & Winokur, 1984), the evidence is drawn from depressed inpatients. A recent study that compared 24-hour cortisol secretion among inpatients with psychotic depression, outpatients with non-psychotic depression,
and non-depressed controls found no evidence of a phase advance among the depressed outpatients (Posener et al., 2000). Second, the participants did continue to collect salivary cortisol samples throughout the rest of the day (data not shown). Examination of these diurnal slopes revealed that cortisol levels in the depressed group continued to decline across the day at the same rate as those of the control group. If the depressed group were indeed phase advanced, they would show a flatter slope across the day as their cortisol levels reached the evening trough earlier. This did not occur. Finally, Hucklebridge and colleagues (2000) have reported that cortisol levels increase in response to awakening independent of basal values. So even if the depressed participants were phase advanced, they should have shown a cortisol increase, and they did not. Given these considerations, we are inclined to believe that our findings reflect a true blunting of cortisol response to awakening, and are not simply an artifact of phase advance.

We also sought to identify mechanisms that might underlie the blunted morning cortisol response in depression. Although the depressed and control participants reported similar patterns of social contacts and wake times, these processes exhibited different regulatory capacities within each group. Among the controls, a greater amount of morning social contact was associated with higher morning cortisol levels. Positive social contacts, rather than negative ones, seemed to be most important for promoting cortisol secretion. This association was not present among depressed participants, perhaps reflecting an inability to biologically respond to positive stimuli. This state may parallel the psychological anhedonia or insensitivity to reward that is a central feature of clinical depression (Davidson, Pizzagalli, Nitschke & Putnam, 2002).
A similar pattern of results was found for time of awakening. This variable was negatively correlated with cortisol levels among the control group, but was not associated with morning cortisol response among the depressed group. It appears that both internal (timing of awakening) and external (social contact) events are linked with the magnitude of the morning cortisol response in non-depressed individuals. The lack of association during depression suggests a loss of regulatory control over the morning cortisol response. The HPA axis is not responding to either internal or external events, even though these events are still present. This loss of regulatory control may be one facet of a more general pattern of HPA axis dysregulation during mild to moderate depression (Siever & Davis, 1985).

One potential limitation of the current study is that the data were collected as the participants went about their daily activities outside of the laboratory. Although this increases the external validity of the findings, it adds a source of variability that may influence our interpretation of the results. We did our best to ensure that both depressed and non-depressed participants were compliant with data collection procedures, but our system was not fool-proof. Systematic group differences in compliance may have influenced our results, although we do not believe this to be the case. If depressed participants were less compliant and late taking their saliva samples, that would not explain why the groups are equal at the first cortisol assessment immediately after waking, and diverge only at the second and third assessments. Furthermore, there were no large systematic differences in compliance between the two groups, either on rate of usable cortisol samples or on timing of diary entries. Among the depressed group, 12 saliva samples (3.6% of total samples) were discarded as unusable, while 8 samples
(2.4% of total samples) were discarded among the control group. Regarding diary entries, depressed participants answered their questions an average of 1 hour and 11 minutes after awakening, while control participants completed their questions an average of 1 hour and 13 minutes after awakening (target time was one hour). These data suggest that group differences in compliance do not account for our results. Nonetheless, future studies should use as sophisticated a means as possible to ensure participant compliance. The naturalistic design also prevents us from ruling out the existence of other unmeasured factors in the daily environment that may influence cortisol response to awakening and may differ systematically between depressed and non-depressed individuals. These factors include food intake, physical exertion, the presence of a bed partner, and physical contact with other people. Future studies should assess these variables in order to better understand how they might influence the morning cortisol response.

Our sample of depressed persons included young, physically healthy, unmedicated women who had few Axis-I co-morbidities. A sample such as this closely mirrors the phenomenon of clinical depression in the community, which includes a mild to moderate level of symptoms and a low likelihood of receiving psychiatric treatment (Wang, Berglund & Kessler, 2000). Our study included women who were from urban neighborhoods, low SES (approximately half of the sample reported that their annual income was below $15,000), and a member of a minority group (mostly African-American). Samples such as this are seldom represented in clinic-based studies that frequently appear in the literature. The sample's lack of mental and physical co-morbidities allows us to reduce error variance and rule out confounds. However, this does
create some problems with generalizability, as community depression has high rates of co-morbidity. This aspect will need to be explored in future research.

Another important limitation is the cross-sectional design of our study, which precludes inferences about the direction of causality. This is less of an issue with regard to time of awakening, which occurs temporally earlier than the associated increase in cortisol. However, we assume that social contacts are influencing cortisol levels, and the reverse relationship may exist as well. Future studies could employ a design that permits lagged analyses in order to explore this possibility. This study cannot speak to whether cortisol disturbances are a cause or consequence of depression, as a longitudinal designed would be required to address this issue.

The current study demonstrated a blunted morning cortisol response to awakening among a community sample of women with clinical depression. This effect was large and independent of age, smoking, medication use, and sleep duration. Among non-depressed women, social contacts in the hour after awakening were associated with a more normative morning cortisol response. This relationship was not present among depressed women, suggesting dysregulation of the HPA axis. The current line of research establishes a link between interpersonal and neuro-biological models of clinical depression and suggests a pathway by which psychosocial factors influence biological processes that may be involved in the pathophysiology of affective disorders.
Table 2.1 Demographic information by group.

<table>
<thead>
<tr>
<th></th>
<th>Depressed</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size of sample</td>
<td>37</td>
<td>36</td>
</tr>
<tr>
<td>Average age in years (SD)</td>
<td>26.5 (6.6)</td>
<td>26.6 (6.8)</td>
</tr>
<tr>
<td>Race (% White/ % Black)</td>
<td>49/43</td>
<td>47/44</td>
</tr>
<tr>
<td>Education in years (SD)</td>
<td>14 (2)</td>
<td>15 (1.9)</td>
</tr>
<tr>
<td>Employed (% full time)</td>
<td>24</td>
<td>28</td>
</tr>
<tr>
<td>% Married</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Oral contraceptive use (% yes)</td>
<td>24</td>
<td>50</td>
</tr>
<tr>
<td>Daily smoker (% yes)</td>
<td>32</td>
<td>8</td>
</tr>
<tr>
<td>Over the counter med use (% yes)</td>
<td>70</td>
<td>80</td>
</tr>
<tr>
<td>Average BDI score (SD)</td>
<td>25.2 (8.8)</td>
<td>1.2 (1.5)</td>
</tr>
<tr>
<td>Average HRSD-17 score</td>
<td>19.6 (5.7)</td>
<td>-</td>
</tr>
<tr>
<td>History of depression (% yes)</td>
<td>67</td>
<td>0</td>
</tr>
<tr>
<td>Avg. # of previous episodes (SD)</td>
<td>3.1 (3.82)</td>
<td>-</td>
</tr>
<tr>
<td>Average age (yrs) at 1st episode</td>
<td>16.8 (5.8)</td>
<td>-</td>
</tr>
<tr>
<td>% in psychotherapy</td>
<td>22%</td>
<td>-</td>
</tr>
<tr>
<td>% with co-morbid GAD</td>
<td>32%</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 2.2.

Results of HLM Analysis for Group Differences on each Salivary Cortisol Measurement.

<table>
<thead>
<tr>
<th>Time Post Wake-up</th>
<th>$\gamma_0$</th>
<th>SE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 minutes</td>
<td>1.57</td>
<td>1.1</td>
<td>.15</td>
</tr>
<tr>
<td>30 minutes</td>
<td>5.82</td>
<td>1.4</td>
<td>.001</td>
</tr>
<tr>
<td>60 minutes</td>
<td>2.73</td>
<td>0.9</td>
<td>.003</td>
</tr>
</tbody>
</table>
Figure 2.1. Cortisol response to awakening in depressed and non-depressed control groups. Bars represent SEM.
Figure 2.2. Cortisol response to awakening is associated with number of morning social interactions among non-depressed controls but not among depressed participants. High and low social interactions groups were determined by a median split on this variable. Bars represent SEM.
References


psychotic and nonpsychotic major depression. *Archives of General Psychiatry, 57,* 755-760.


Daily Social Contact Predicts Diurnal Cortisol Secretion:
Evidence from a Prospective Daily Diary Study

Social relationships have important benefits for health. This is true whether social relationships are viewed functionally, as supportive resources that buffer the negative impact of stress, or structurally, as networks of enduring social connections that provide a sense of community (Berkman & Syme, 1979; House, Landis, & Umberson, 1988; Cohen, Gottlieb, & Underwood, 2000). With regard to the biological mechanisms underlying this effect, several well-characterized pathways have been elucidated, including the cardiovascular system, and the sympathetic-adrenal and hypothalamic-pituitary-adrenal axes. When social relationships are viewed functionally, the presence or perception of social support is associated with a reduced activity in one or more of these systems in the face of a stressor (Uchino, Cacioppo, & Kiecolt-Glaser, 1996). Less well-understood are the mechanisms through which social relationships, viewed structurally as social networks or social connections, act to influence risk for morbidity and mortality. Social networks may influence health through behavior, by shaping patterns of smoking, drinking, and activity (Cohen, 1988). Social networks may also exert non-behaviorally mediated effects through the same biological systems as social support does, yet the parameters of these effects have been the subject of relatively few research investigations up to this point.

We propose that social contacts have direct regulatory influences on the rhythms of hormonal systems that are important for health. The extent to which one’s social network can provide direct social contact may be an important determinant of its health.

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1 A version of this chapter has been submitted for publication: Stetler, C., & Miller, G.E. (submitted). Daily social contact predicts diurnal cortisol secretion: Evidence from a prospective daily diary study.
effects via these regulatory effects on hormones. Although Hofer (1984) made the case that maternal social contacts have a profound influence on the infant’s ability to regulate physical functioning based on animal studies, few studies have specifically examined the influence of social contact on physiological rhythms in humans. In 1971, Aschoff and colleagues found that social contacts were sufficient to maintain circadian rhythms (including hormone production) in a group of participants housed together in a lab without light/dark cues. While this result supports the idea that social contacts regulate hormonal rhythms in a highly controlled lab environment, little is known about whether this is also the case in the real world. Given what is known about the health consequences of disrupted circadian rhythms (e.g. Moore-Ede & Richardson, 1985), the ability of social contacts to influence the rhythms of hormone production may represent an important but unexplored pathway for the effect of social relationships on health outcomes.

Our previous research provides support for the idea that daily social contact regulates diurnal cortisol secretion (Stetler, Dickerson, & Miller, 2004). Participants completed daily diary measures of their social contacts as well as provided saliva samples throughout the day in order to assess cortisol levels, which peak in the morning shortly after waking and then decline steadily. Our results revealed a significant within-person association between social contacts and cortisol slope, or rate of decline in cortisol across the day. Days during which participants performed more of their routine daily activities with other people were associated with steeper cortisol slopes compared to days on which they performed more of their daily activities alone. Steeper cortisol slopes indicate better circadian regulation of HPA axis function and may predict better health outcomes (Lundberg, 2005). We replicated these findings in a second study that examined morning
social contacts and the peak in cortisol that occurs shortly after waking (Stetler & Miller, 2005). Similar to the first study, high levels of social contact were associated with higher morning cortisol levels, another result suggesting social regulation of the diurnal pattern of cortisol secretion.

Although these studies support the hypothesis that social contact has the ability to program patterns of cortisol output in a manner that is beneficial for health, their cross-sectional design prevents us from drawing valid conclusions about directionality. In order to test the hypothesis that social contacts are influencing cortisol secretion in the absence of any influence of cortisol on social contact, the current study will employ a prospective design. This design will allow us not only to replicate the cross-sectional association in a different population, but will allow for the testing of directional hypotheses as well. We will examine whether social contacts predict the next day’s cortisol slope. To examine whether the relationship is bi-directional, we will also test the association between cortisol slope and the next day’s social contacts. Such analyses will extend previous research by enhancing our understanding of the directional nature of the social contacts-cortisol association.

Our previous research has also examined the regulatory influence of social contact on cortisol secretion among individuals with clinical depression. Given the disruptions in cortisol secretion that are often present in depression, we wondered if those disruptions could be explained by a reduction in social contacts compared to non-depressed controls. Surprisingly, we did not find evidence of such a pattern - depressed individuals had comparable levels of daily social contacts compared to healthy controls. However, unlike healthy controls, depressed patients did not exhibit a coupling of social
contacts and cortisol secretion. These results suggest that cortisol disruptions during depression stem not from a lack of social contacts, but in a loss of the social contact’s ability to regulate cortisol secretion. This is analogous to the insomniac who still experiences darkness and the setting of the sun, but is no longer made sleepy by these cues. However, it is unclear at what point this loss of regulatory ability occurs. In the current study, we attempted to shed light on this question by measuring depressive symptoms among healthy individuals who do not meet criteria for clinical diagnosis. We then explored whether increased depressive symptoms are associated with a weaker association between social contacts and cortisol secretion. Examining this relationship in a non-clinical sample allowed us to determine whether this loss of regulatory function existed as depressive symptoms developed but had not reached clinical threshold, or if this loss of regulatory function was unique to clinical depression.

We predicted that days with greater levels of social contact would be associated with steeper diurnal cortisol slopes compared to days with fewer social contacts. We also predicted that days with greater levels of social contact would predict steeper cortisol slopes on the subsequent day, but that diurnal cortisol secretion would not be associated with level of social contact on the subsequent day, consistent with the idea that social contacts have a uni-directional regulatory influence on cortisol secretion. Finally, parallel to our previous findings among clinically depressed individuals, we predicted that increased depressive symptoms would be associated with a smaller association between social contacts and cortisol levels.
Methods

Participants

Fifty-seven female participants were recruited from the student population at the University of British Columbia through flyers placed on campus. This study’s protocol was approved by the University of British Columbia’s Behavioural Research Ethics Board. All participants gave written informed consent prior to participating in the study. Next, participants completed a modified version of the Patient Health Questionnaire module of the PRIME-MD (Spitzer, Kroenke, & Williams, 1999). This questionnaire was used as a screening tool to determine study eligibility. Potential participants were excluded from the study if they endorsed the presence of a chronic illness, acute infection, recent or current pregnancy, or use of medications that affect the HPA axis (not including oral contraceptives). Participants were also referred to counseling services and excluded from the study if they met diagnostic criteria for major depression, panic disorder, drug or alcohol abuse, generalized anxiety disorder, anorexia or bulimia based on the PRIME-MD screening. One potential participant was excluded due to these reasons. All participants were required to speak, write and understand English. Participants received $5 at the initial visit and $20 after completing the study.

Protocol

Eligible participants then completed baseline questionnaires (demographics and depressive symptom measures) and were trained on ambulatory data collection methods.

Depressive symptoms. The Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977) is a 20-item self-report scale designed to measure depressive symptoms in non-clinical populations. The CES-D has been used extensively in
depression research and has demonstrated good internal reliability ($\alpha = .87$) in college student populations (Radloff, 1991). Higher scores indicate greater levels of depressive symptoms. Cronbach’s alpha in the current sample was $\alpha = .82$.

**Ambulatory data collection.** Each participant was lent a Palm Pilot that served not only as an alarm to prompt saliva collections, but also as a device for data collection (Palm M100; Palm Inc., New York). Participants collected data on four consecutive days following their initial lab appointment. On day 1, participants reported information on their social interactions only, while on days 2, 3 and 4, they did this and collected saliva samples throughout the day. Saliva collection was limited to three days in order to minimize participant burden while still achieving a reliable assessment of salivary cortisol.

Each day, participants set the alarm on the computer to act as their morning alarm. They were told to maintain their normal wake-up time. Palm Pilots were programmed to sound an alarm when the participant awoke, and at 1 hour, 4 hours, 9 hours and 14 hours later. This procedure has been used in previous studies and has been shown to capture the diurnal pattern of cortisol production without placing undue burden on the participants (MacArthur Research Network on SES and Health, 2000). For example, if a participant woke up at 7AM, then the Palm Pilot was programmed to go off at 7AM, 8AM, 11AM, 4PM and 9PM.

Once the computer alarm went off, it instructed participants to collect a saliva sample using a Salivette (Sartstedt Inc, Germany), a cotton dental roll within a sterile plastic tube. Participants placed the cotton roll in their mouths for approximately one minute in order to saturate it with saliva. The cotton roll was then returned to the plastic
tube. The tube was capped tightly and placed in a refrigerator until returned to the lab. The handheld computer also briefly displayed a unique 3-digit code that the participant was instructed to record. Proper recording of this code indicated that the saliva collection was done at the correct time. Saliva samples with missing or inaccurate codes or samples with insufficient amounts of saliva for assay were excluded from analysis, resulting in a loss of 110 samples (12.9% of 855 possible saliva samples). The PalmPilot also stored the time that participants responded to each code. This time was used to determine the actual number of minutes since awakening that the saliva sample was obtained and thus served as a useful way to evaluate participant compliance with the sampling protocol and to accurately model the pattern of cortisol secretion throughout a day.

Cortisol samples. After they were returned to the laboratory, saliva collection containers were centrifuged for five minutes at 750 x g until a clear, low-viscosity supernatant emerged. The supernatants were then collected and frozen at −30°C until the end of the data collection sequence. Cortisol assays were performed in duplicate using a commercially available chemiluminescence assay (IBL, Hamburg, Germany). This assay has a sensitivity of 0.16 ng/ml. In previous research done in our lab the intra-assay coefficient of variation was less than 10 percent; the inter-assay coefficient of variation was less than 12 percent. Levels of cortisol in saliva have been shown to be highly correlated with levels in plasma (Kirschbaum & Hellhammer, 1994).

Assessing HPA axis function. Each day’s data were used to create an index that represents the change in cortisol secretion across the day. The diurnal pattern of cortisol secretion was computed as a linear slope measure, with salivary cortisol values at each timepoint regressed on the number of hours since awakening. In order to better model the
curvilinear diurnal rhythm as a linear slope, we computed slopes based on log-transformed cortisol values. Five (log-transformed) cortisol values per day were regressed on the actual time since waking (in hours) that the sample was collected according to the Palm Pilot codes. Higher (less negative) values indicate a flatter diurnal cortisol slope, while lower (more negative) values indicate a steeper diurnal cortisol slope.

**Daily social interactions.** On each of the four days, at one hour, 4 hours, 9 hours and 14 hours after waking up, participants were asked to report whether or not they had a social interaction (defined as an important social exchange usually lasting at least 5 minutes) in the previous hour or since last responding to the PalmPilot, and if so, how many interactions occurred. This information was used to calculate the total number of social interactions that occurred each day.

Because the number of social contacts each day may not capture the level of social integration present in participants' daily lives, they were also asked to complete a measure of social contact that is linked to common daily activities at the final time point (14 hours after waking) each day (Social Rhythm Metric; Monk, Flaherty, Frank Hoskinson, & Kupfer, 1990). Participants were asked to record whether or not each of 14 given activities occurred for them that day (e.g. going to school, eating lunch, exercising, watching TV), and whether or not other people were present or involved when the activity occurred (See Appendix A, pg. 109). For each day, a measure of social integration of daily activities was calculated based on the ratio of activities done with other people to total activities done each day. We refer to this measure as Other Person...
Involvement (OPI). Scores on this index could range from 0 to 1, with higher scores indicating more socially integrated daily activities.

Data analysis. Estimates of the within-person association between each measure of daily social contacts and cortisol slope were generated using hierarchical linear modeling (HLM; Bryk & Raudenbush, 1992). HLM is appropriate for handling nested data such as ours and is able to deal with repeated-measures designs and to efficiently model missing data. Because measurements collected from the same individual at different points in time are often correlated and have correlated error terms (thus violating the assumption of independence), we took advantage of HLM’s ability to model dependence in the data. We tested our models for an autoregressive error structure (meaning that data on day 1 were correlated most highly with data from day 2, less strongly with data from day 3, even less from day 4, and so forth) against the standard assumption of homogenous error structure (meaning that data are correlated consistently across days). This test was non-significant ($p = 0.07$), allowing us to use the simpler homogenous error structure throughout our analyses. We performed the analyses using both types of error structures, and received identical results for our variables of interest.

Diurnal cortisol slope was modeled as a function of social contact in order to determine whether cortisol slope differed on days when a person had higher versus lower amounts of social contact. The HLM equations appear below:

$$
Y_{ij}(\text{CORTISOL SLOPE}) = \beta_{0j} + \beta_{1j}(\text{Social Contact}) + \epsilon_{ij}
$$

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2 The author chose to use a two-level model to predict daily cortisol slope rather than to use a three-level model to predict momentary cortisol levels because the pattern of diurnal decline, rather than specific cortisol levels at any individual timepoint, was the outcome variable of interest. Furthermore, although very little has been published detailing the sample size requirements for a three-level model to have sufficient statistical power, a three-level model involves the estimation of more parameters than a two-level model. Such a model would presumably require more datapoints to achieve reliable estimates of more model parameters, while generating similar results (Snijders, 2005).
Level Two: $\beta_{0j} = \phi_{00} + \nu_{0j}$

$$\beta_{1j} = \phi_{10} + \nu_{1j}$$

Here $\beta_{1j}$ is the relationship between cortisol and social contact on day 1 for participant $j$. Meanwhile, $\epsilon_{ij}$ represents the within-person residual parameter (i.e., the difference between an individual’s own mean across all days and their cortisol slope on that particular day). We predicted that $\beta_1$ would be negative, indicating that days with higher social contact also tend to be days with steeper (more negative) cortisol slopes.

In order to assess the directionality of the social contact-cortisol relationship, HLM equations were constructed that were similar to those for the cross-sectional analyses, but cortisol was modeled as a function of the previous day’s social contacts, controlling for cortisol on the previous day. We expected this coefficient to be significant and negative, such that the greater one’s level of social contacts on day one, the more negative the cortisol slope on day two. Uni-directionality was tested by modeling cortisol as a function of the next day’s level of social contacts, an association that should prove to be non-significant.

Assessing moderating effect of depressive symptoms. Depressive symptoms (mean CES-D score) were entered as a between-subjects variable on level 2 in order to determine whether the relationship between social contacts and cortisol slope changes as a function of depressive symptoms.

Level One: $Y_{ij}(\text{CORTISOL SLOPE}) = \beta_{0j} + \beta_{1j}(\text{Social Contacts}) + \epsilon_{ij}$

Level Two: $\beta_{0j} = \phi_{00} + \phi_{01}(\text{CES-D SCORE}) + \nu_{0j}$

$$\beta_{1j} = \phi_{10} + \phi_{11}(\text{CES-D SCORE}) + \nu_{1j}$$
We expected that $\phi_{11}$ would be negative, meaning that the relationship between cortisol slope and social contacts becomes weaker (association will get smaller) as depressive symptoms (CES-D score) increase.

Results

Fifty-seven women were enrolled in the study, and the mean age was 20.4 years (SD = 2.6, range: 18-29). Approximately two-thirds (64.9%) of the sample described their ethnic background as Asian, while the remaining participants described their ethnic background as Caucasian (35.1%). All participants were students at the University of British Columbia.

Other potential influences on cortisol

Because of the potential impact on cortisol secretion, we assessed whether participants were smokers and whether they took oral contraceptive medications. Only one participant reported smoking cigarettes on a daily basis. Forty-four (77.2%) participants reported using oral contraceptive medication at the time of the study. There were no differences in the average cortisol slopes between participants who were taking oral contraceptives and those who were not ($p's > 0.2$). Because none of these potential confounds were associated with our cortisol outcomes of interest in the current sample and because we wished to maximize power by conserving degrees of freedom in our statistical models, we did not include these variables in the analyses reported below.

Daily social contacts and cortisol secretion rhythms

Daily social contacts were measured two ways: the number of social interactions reported each day and the level of other person involvement in daily activities (OPI). Across all four days, participants reported an average of 12.1 (SE = 0.49, 0-20) social
interactions per days. The average percentage of their daily activities done with other people involved (OPI ratio) was 57% (SE = 0.03, 0%-100%).

**Cross-sectional analyses.** The average slope value across all days and all participants was −0.10 (SE = 0.007). We hypothesized that days with more social contact would be associated with steeper cortisol slopes compared to days with fewer social contacts. Number of daily social interactions was not associated with cortisol slope ($\beta_{1j} = -0.006$, SE = 0.005, $t(53) = -1.25, p = 0.22$). However, OPI score was associated cross-sectionally with diurnal cortisol, such that days with more activities done with other people were associated with steeper cortisol slopes compared to days with fewer activities done with others ($\beta_{1j} = -0.06$, SE = 0.03, $t(55) = -2.09, p < 0.04$). A rapid decline in cortisol across the day is thought to indicate healthier, better regulated HPA axis function.

When we entered both measures of social contact into the model, OPI score remained a strong predictor of cortisol slope ($\beta_{1j} = -0.06$, SE = 0.03, $t(56) = -2.12, p = .04$). Number of daily social interactions was not significantly associated with cortisol slope ($\beta_{2j} = -0.0008$, SE = 0.003, $t(56) = -0.29, p = .77$). OPI ratio accounted for 7.9% of the within-subjects variance in cortisol slope, while number of daily social interactions accounted for less than 1% of this variance. Thus, having a larger percentage of daily activities involving other people was linked to a more rapid decline in diurnal cortisol secretion above and beyond absolute number of daily social interactions. These findings replicate those of our previous study (Stetler et al., 2004).

**Day-lagged analyses.** We were interested in the direction of the social interactions and cortisol slope association, something the above cross-sectional analyses could not
determine. In order to examine this question, we constructed a model that predicted (within-person) cortisol slope from the previous day’s social interactions and the previous day’s cortisol slope. Number of social interactions the previous day was not associated with cortisol slope ($\beta_{ij} = -0.004$, $SE = 0.003$, $t(56) = -1.40$, $p = 0.17$). However, the previous day’s OPI score did predict cortisol slope ($\beta_{ij} = -0.06$, $SE = 0.03$, $t(56) = -2.04$, $p = 0.05$) such that having more activities involved with others yesterday was associated with a steeper diurnal cortisol slope today, controlling for yesterday’s cortisol slope. When we tested the opposite relationship, that yesterday’s cortisol slope predicts today’s OPI ratio (controlling for yesterday’s OPI ratio), we found no evidence to support the reverse relationship ($\beta_{ij} = 0.26$, $SE = 0.21$, $t(56) = 1.11$, $p = 0.27$). This set of within-person results shows two things: that having other people involved in one’s routine daily activities (not just having a lot of social interactions) is important for daily cortisol production, and that doing routine activities with others temporally precedes changes in cortisol and not vice versa, suggesting a uni-directional relationship between these two variables.

**Depression symptoms as moderator**

We hypothesized that depressive symptoms would moderate the association between daily social contacts and cortisol. The average CESD score in the sample was 11.1 ($SE = 0.87$, 0-27). This hypothesis was supported for the relationship between OPI and cortisol slope ($\gamma_{ij} = -0.008$, $SE = 0.003$, $t(53) = -2.34$, $p = 0.02$). For participants with higher levels of depressive symptoms, the association between OPI and cortisol slope was smaller compared to participants with fewer depressive symptoms. Depression symptoms accounted for 19.8% of the between-subjects difference in social contacts-
cortisol association. Thus, increasing depressive symptoms may interfere with the ability of social contacts to influence cortisol secretion. Depression symptoms did not moderate the effects of the number of daily social interactions on cortisol slope ($p's > 0.3$).

Depression symptoms did not moderate the effects of either OPI score or number of social interactions on next day's cortisol slope (all $p's > .19$).

**Discussion**

The current study demonstrated that daily social contacts predict future cortisol secretion patterns. This establishes temporal precedence and, together with lack of evidence for an association in the reverse direction (i.e. cortisol secretion didn't predict future social contacts) is an important step toward demonstrating a causal relationship between daily social contacts and HPA axis function. Given that the HPA axis is a well-established neuroendocrine intermediary of disease, these results have important implications for the pathways by which social relationships influence health. According to the current study, simply being around or involved with other people during one's daily routine can support a healthier pattern of HPA axis activity. A better-regulated pattern of HPA axis function may in turn reduce risk for future negative health outcomes.

A daily routine involving other people predicted cortisol levels above and beyond the total number of daily social interactions. These findings support the idea that there is something unique about doing activities such as eating meals, watching TV, going to and from home, and exercising with other people compared to social contact not based on routine daily activities. Having companionship during part or all of one's daily routine may impart feelings of belongingness or reduce loneliness in a way that simple social exchanges do not, analogous to the way that people often experience feelings of
loneliness among a crowd of people. Therefore, companionship during daily activities may be a better indicator of social integration or social imbeddedness compared to a simple tally of daily social interactions. Sharing a routine activity such as watching TV or eating a meal with another person suggests that a substantial relationship exists between two people. Social interaction apart from a routine activity, however, may be more likely to occur between strangers or acquaintances. Close relationships may shape biology in a way that more distant or superficial relationships do not. Furthermore, the lack of a relationship that is able to provide companionship during some portion of one's daily routine may not make up for a day filled with quick hellos and interactions that do not further the establishment or maintenance of a deeper connection.

We also found that individuals with higher levels of depressive symptoms were less sensitive to the regulatory influences of social companionship on their HPA axis compared to individuals with fewer depression symptoms. The current study extends the literature by suggesting that disruptions to the daily social environment and HPA axis do not occur abruptly among individuals with major depression, but these disruptions begin during periods of low to moderate levels of depressive symptoms. This diminution of a potentially important regulatory influence on the HPA axis may contribute to the perturbations in cortisol secretion that are common to, and perhaps a trigger for, an episode of major depression. With the control of social contacts waning, the HPA axis may be more vulnerable to the dysregulating effects of stressful events or changes in the social environment. A dysregulated HPA axis may also contribute to the increased risk of medical illnesses like coronary heart disease and diabetes mellitus that exists for depressed individuals (Wulsin & Singal, 2003; Anderson et al., 2003).
Several important limitations of the study need to be addressed. Cigarette smoking, eating and exercising can all have acute effects on cortisol levels, and it is possible that these activities could have altered the overall diurnal slope. Although these health behaviors were not assessed in participants immediately prior to each saliva sample, they were measured at the beginning of ambulatory data collection. Only one participant reported smoking cigarettes on a regular basis, and excluding her data from the analyses did not change the results. Participants were asked about eating meals and exercising during the last set of questions each day. Cortisol slope did not differ on days when participants ate either breakfast, lunch or dinner compared to days when they did not eat one of those meals (data not shown). However, days on which participants exercised showed a non-significant trend toward steeper cortisol slopes compared with days participants did not exercise. Days that included exercise were not associated with either measure of social contact (OPI ratio or total social interactions; data not shown). Because none of these three health behaviors were associated with both predictor and dependent variables, we can reasonably conclude that they do not account for the observed relationship between social contact and cortisol slope.

Another limitation is that the current study included only women; it is unknown whether the results would generalize to men. One pathway by which social contact is thought to convey its effects on physiology is via the hormone oxytocin (Uvnas-Moberg, 1997). Oxytocin may offset or counteract the effects of cortisol in the body (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003). The effects of oxytocin, which is produced in response to affiliative social contact, are potentiated by estrogen. Although we did not access oxytocin production in the current study, the literature in this area suggests that
social contact may have a greater influence on women’s cortisol levels compared to men’s due to the enhancing effects of estrogen. Further studies are necessary to test this idea empirically and to determine if daily social contacts influence diurnal cortisol levels in men as well.

In summary, we were able to accomplish many of our goals in the current study. In addition to replicating our previous cross-sectional findings in a new sample, we also gained new information about the temporal ordering of the social contact-cortisol relationship which suggests that a causal relationship from the social environment to biology (but not the other direction) may exist. The findings from this study provide initial support for a novel hypothesis about the mechanisms underlying social integration’s benefits for longevity— that social contacts themselves have direct regulatory influences on the rhythms of important biological systems.
Table 3.1 Descriptive statistics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol slope</td>
<td>-0.10</td>
<td>0.007</td>
</tr>
<tr>
<td>Number of daily social contacts</td>
<td>12.1</td>
<td>0.49</td>
</tr>
<tr>
<td>OPI</td>
<td>0.57</td>
<td>0.03</td>
</tr>
<tr>
<td>Age</td>
<td>20.3</td>
<td>0.33</td>
</tr>
<tr>
<td>CESD score</td>
<td>11.1</td>
<td>0.87</td>
</tr>
</tbody>
</table>
References


Social integration of daily activities and cortisol secretion: A laboratory based manipulation

Social integration is an important predictor of well-being and health status, such that more diverse social networks have been associated with reduced disease and increased longevity (Berkman and Syme 1979; House and others 1988). Several explanations for this phenomenon have been explored (Uchino and others 1996; Cohen and others 2000). The presence of social relationships has been linked to improved health behaviors such as diet and exercise that have known implications for health. Second, social support has been shown to reduce the body’s response to stressful events, and this reduced reactivity may lead to better health outcomes. However, the idea that social relationships may have a direct effect on physiology has been relatively unaddressed, despite the theoretical support that exists for such an effect. In the early days of life, maternal proximity and behavior regulates the activity of multiple bodily systems such as the nervous, cardiovascular and digestive systems (Polan and Hofer 1999). Just as the nature of and expectations formed from early social contacts are thought to remain throughout development as templates for future social relationships, the regulatory function of these early contacts may also be maintained as the organism develops, allowing it to be physiologically responsive to its social environment. A high level of responsiveness may benefit the organism by maximizing adaptation to social conditions.

We have proposed that social contacts have direct regulatory influences on the rhythms of hormonal systems that are important for health. The extent to which one’s social network can provide direct social contact may be an important determinant of its

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1 A version of this chapter has been submitted for publication: Stetler, C., & Miller, G.E. (submitted). Social integration of daily activities and cortisol secretion: A laboratory based manipulation.
health effects via these regulatory effects on hormones. Although Hofer (1984) made the case that maternal social contacts have a profound influence on the infant's ability to regulate physical functioning based on animal studies, few studies have specifically examined the influence of social contact on physiological rhythms in humans. In 1971, Aschoff and colleagues found that social contacts were sufficient to maintain circadian rhythms (including hormone production) in a group of participants housed together in a lab without light/dark cues. While this result supports the idea that social contacts regulate hormonal rhythms in a highly controlled lab environment, little is known about whether this is also the case in the real world. Given what is known about the health consequences of disrupted circadian rhythms (e.g. Moore-Ede & Richardson 1985), the ability of social contacts to influence the rhythms of hormone production may represent an important but unexplored pathway for the effect of social relationships on health outcomes.

Our previous research provides support for the idea that social contacts regulate hormone secretion across the day (Stetler et al., 2004; Stetler & Miller 2005). In two studies we found that having higher levels of social contact was associated with either a steeper decline in cortisol production across the day (Stetler et al., 2004) or a higher morning peak in cortisol (Stetler & Miller 2005). This pattern of high morning cortisol levels with a rapid decline throughout the day reflects more normative HPA axis function and has been associated with lower disease risk factors (Matthews et al., 2006; Rosmond and Bjorntorp, 2000). Most recently, we were able to refine our understanding of the relationship between daily social contacts and cortisol (Stetler and Miller, submitted) by addressing the issue of directionality. Social contacts predicted cortisol secretion not only
on the same (concurrent) day, but on the subsequent day as well. Cortisol slope did not predict future social contact, indicating that the direction of the relationship went from social contact to cortisol and not in the opposite direction. Results of this study support the idea that social contacts regulate cortisol secretion in a way that is likely to be health-promoting. Of interest, social contact during routine daily activities predicted cortisol where total number of daily social interactions did not. This suggests that cortisol is responsive to having others involved in one’s daily activities, and not simply having large numbers of social contacts over the day.

Although the direction of the effect is consistent with our model of how social contact affects health, an experimental manipulation is necessary to convincingly eliminate alternative explanations involving third variables. For example, it is possible that dispositions such as loneliness influence both the amount of daily social contact a person has and his/her rhythm of cortisol output (Cacioppo et al., 2000). The primary goal of the current study was to develop a manipulation of daily social contacts that was informed by the results of previous research. Because our previous research demonstrated that social interaction during daily activities was the better predictor of daily cortisol secretion (above and beyond the absolute number of daily social interactions), we chose to manipulate whether a specific daily activity was done with another person or alone. The current study varied the social contact involved in eating lunch, from one day to the next. Lunch was selected as the focus of the manipulation for two reasons: Data from previous research with the sample (Stetler and Miller, submitted) suggested that the majority of participants ate lunch as a part of their daily routine, and lunch was an
activity whose social context could reasonably be altered in a controlled laboratory setting.

We reasoned that if social contact regulates hormonal output in a causal fashion, days that included eating lunch with another person should be accompanied by steeper diurnal cortisol slopes, compared to days that included eating lunch alone. Finally, the current study assessed whether characteristics of the lunch partner influenced the effect of the manipulation. These characteristics included the relational identity of the lunch partner (close friend, family member, or romantic partner vs. roommate or classmate/acquaintance), relationship length, frequency of contact, and level of intimacy or closeness. We reasoned that lunch partners with whom participants had longer or more intimate relationships or who saw the participants more frequently would have a greater influence on diurnal cortisol secretion compared to lunch partners that had shorter, less frequent, or less intimate relationships to the participants.

Methods

Participants

Fifty-three female participants were recruited from the student population at the University of British Columbia through flyers placed on campus. After the details of the study were explained, interested participants were scheduled for an initial lab appointment. This study’s protocol was approved by the University of British Columbia’s Behavioral Research Ethics Board. All participants gave written informed consent prior to participating in the study. Next, participants completed a screening tool to determine study eligibility (modified version of the Patient Health Questionnaire module of the PRIME-MD; Spitzer and others 1999). Potential participants were excluded from the
study if they endorsed the presence of a chronic illness, acute infection, recent or current pregnancy, or use of medications that affect the HPA axis (not including oral contraceptives). Participants were also excluded from the study if they met diagnostic criteria for major depression, panic disorder, drug or alcohol abuse, generalized anxiety disorder, anorexia or bulimia based on the PRIME-MD screening. One potential participant was excluded due to these reasons. All participants were required to speak, write and understand English. Participants received monetary compensation for participating in the study.

Protocol

Eligible participants then completed baseline questionnaires (demographics and depressive symptom measures) and were trained on ambulatory data collection methods. Participants then completed a baseline phase: 4 days of ambulatory data collection during which they recorded information about their daily social contacts and collected saliva samples using the measures and methods described below. Data from this phase of the study have been reported elsewhere (Stetler and Miller, submitted). No manipulation was employed during this phase, and the data are referred to here for comparison purposes.

Ambulatory data collection. Each participant was lent a Palm Pilot that served not only as an alarm to prompt saliva collections, but also as a device for data collection (Palm M100; Palm Inc., New York). Participants collected data on six days following their initial lab appointment. Each day, participants set the alarm on the computer to act as their morning alarm. They were told to maintain their normal wake-up time. Palm Pilots were programmed to sound an alarm when the participant awoke, and at 1 hour, 4 hours, 9 hours and 14 hours later. This procedure has been used in previous studies and
has been shown to capture the diurnal pattern of cortisol production without placing undue burden on the participants (MacArthur Research Network on SES and Health 2000). For example, if a participant woke up at 7AM, then the Palm Pilot was programmed to go off at 7AM, 8AM, 11AM, 4PM and 9PM.

The computer alarm prompted participants to collect a saliva sample using a Salivette (Sartstedt Inc, Germany), a cotton dental roll within a sterile plastic tube. Participants placed the cotton roll in their mouths for approximately one minute in order to saturate it with saliva. The cotton roll was then returned to the plastic tube. The tube was capped tightly until returned to the lab. One tube was used at each saliva collection. It has been established that salivary cortisol concentrations are stable at room temperature (Clements & Parker, 1998). The handheld computer also briefly displayed a unique 3-digit code that the participant was instructed to record. Proper recording of this code indicated that the saliva collection was done at the correct time. The Palm Pilot also stored the time that participants responded to each code. This time was used to determine the actual number of minutes since awakening that the saliva sample was obtained and thus served as a useful way to evaluate participant compliance with the sampling protocol.

Total daily social contact. On each of the six study days, at one hour, 4 hours, 9 hours and 14 hours after waking up, participants were asked to report whether or not they had a social interaction (defined as an important social exchange usually lasting at least several minutes) in the previous hour or since responding to the Palm Pilot, and if so, how many interactions occurred. This information was used to calculate the total number of social interactions that occurred each day.
Social integration of daily activities. In order to assess the level of social integration in each participant's daily activities, participants completed the Social Rhythm Metric (SRM; (Monk et al., 1990) at the final time point (14 hours after waking) each day. The SRM assesses whether or not each of 14 given activities occurred for them that day (e.g. eating lunch, going to work/school, exercising, watching TV), and whether or not other people were present or involved when the activity occurred. For each day's activities, the level of social integration was calculated based on the ratio of activities done with other people to total activities done each day. Scores on this index could range from 0 to 1, with higher scores indicating more socially integrated daily activities.

Experimental manipulation of daily social contacts. Participants were asked to eat lunch in the lab, either by themselves (2 consecutive days) or with another person (2 consecutive days). Participants continued to collect saliva samples and information about their social interactions and daily activities as described above. Conditions were separated by a minimum of 5 days. Lunches were generally scheduled between 10AM and 3PM each day; the exact time varied according to participants' availability. Ambulatory data collection occurred on all four “lunch in the lab” days, and on the one day immediately following each condition, for a total of 6 days.

During one condition (labeled friend condition), participants were asked to bring someone in to the lab to eat lunch with them (a friend, romantic partner, roommate or relative). Participants could bring anyone they chose but were asked to bring the same person each day. Under the other condition (labeled alone condition), participants were asked to eat lunch in the lab alone. Conditions were scheduled in counterbalanced order across participants. At each appointment, participants (and their lunch partners, where
applicable) were seated in a lab room and offered something to eat and drink. Meal contents were not identical across participants or across days; low-protein meals such as vegetable soup and crackers or pastries stuffed with vegetables were offered at each visit. Meals high in protein have been shown to cause an acute increase in cortisol levels (Slag et al., 1981) which could have been inadvertently captured by one of the daily salivary cortisol samples. Participants were then left undisturbed in a private room for one hour.

**Lunch partner characteristics.** At the end of the hour on one of the friend condition days, participants completed a brief questionnaire about their lunch partner. This questionnaire asked how long the participant had known the person accompanying her, how many times during an average week the participant had contact with this person, and how long the average contact lasted. Participants were also asked to classify the person accompanying them as one of the following: friend, best friend, roommate, romantic partner, sibling, classmate/coworker, or acquaintance. Finally, participants answered five items regarding the level of closeness/intimacy in the relationship. An example of an item is “How much do you confide in this person?” Items were answered on a 1 to 7 scale, with higher scores indicating more intimacy/closeness in the relationship. Cronbach’s alpha for these 5 items in the current sample was $\alpha = 0.80$.

**Cortisol samples.** After they were returned to the laboratory, saliva collection containers were centrifuged for five minutes at 750 x g until a clear, low-viscosity supernatant emerged. The supernatants were then collected and frozen at $-30^\circ$ C until the end of the data collection sequence. Cortisol assays were performed in duplicate using a commercially available chemiluminescence assay (IBL, Hamburg, Germany). This assay has a sensitivity of 0.16 ng/ml. In previous research done in our lab the intra-assay
coefficient of variation was less than 10 percent; the inter-assay coefficient of variation was less than 12 percent. Levels of cortisol in saliva have been shown to be highly correlated with levels in plasma (Kirschbaum & Hellhammer 1989).

**Assessing HPA axis function.** Each day’s data were used to create an index that represents the change in cortisol secretion across the day. The diurnal pattern of cortisol secretion was computed as a linear slope measure, with salivary cortisol values at each timepoint regressed on the number of hours since awakening. In order to better model the curvilinear diurnal rhythm as a linear slope, we computed slopes based on log transformed cortisol values. Five (log-transformed) cortisol values per day were regressed on the actual time since waking (in hours) that the sample was collected according to the Palm Pilot codes. Higher (less negative) values indicate a flatter diurnal cortisol slope, while lower (more negative) values indicate a steeper diurnal cortisol slope.

**Data Analysis.** Estimates of the within-person association between each manipulation condition and cortisol slope were generated using hierarchical linear modeling (HLM; [Bryk & Raudenbush 1992]). HLM is appropriate for handling nested data such as ours and is able to deal with repeated-measures designs and to efficiently model missing data. Because measurements collected from the same individual at different points in time are often correlated and have correlated error terms (thus violating the assumption of independence), we took advantage of HLM’s ability to model dependence in the data. We conducted our analyses two ways: using an autoregressive error structure (meaning that data on day 1 were correlated most highly with data from day 2, less strongly with data from day 3, even less from day 4, and so forth) and using
the standard homogenous error structure (meaning that data are correlated consistently across days). We performed the analyses using both types of error structures, and obtained identical results for the variables of interest. Thus, we report below outcomes with the simpler homogenous structure.

Assessing effect of social rhythm manipulation

Manipulation check. Each measure of social contacts (number of social interactions or social integration of daily activities) was modeled as a function of manipulation condition using planned contrasts (see below). Social contact scores should be higher during ‘high social contact’ condition compared to ‘low social contact’ condition. Social contact scores during each of these conditions were also compared to the social contact scores during the pre-manipulation baseline phase in order to determine which condition represented a change for the participant. That is, either the high social contact condition represented an increase from baseline for a given participant, or the low social contact represented a decrease from baseline. Validity of the manipulation was supported if social contact scores are greater during the high social contact condition compared to the low social contact condition, and if either of those conditions represents a change from social contact scores across the baseline phase.

Level One: \[ Y_{ij}(Social \ Contacts) = \beta_{0j} + \beta_{1j}(Condition \ Contrast \ Code) + \epsilon_{ij} \]

Level Two: \[ \beta_{0j} = \gamma_{00} + \nu_{0j} \]

\[ \beta_{1j} = \gamma_{10} + \nu_{1j} \]

Effect on cortisol rhythms. These models are similar to those for the manipulation check except that now cortisol slope is the dependent variable. Cortisol slope was modeled as a function of social contact condition (a within-subjects variable) using
planned contrasts. Two sets of contrasts were made. First, cortisol during the high social contact condition was compared to cortisol during the low social contact condition. We expected that during the high social contact condition, cortisol slopes will be steeper (more negative) compared to the low social contact condition. Second, we also compared cortisol levels during a pre-manipulation baseline phase to cortisol levels during each experimental condition.

Level One: $Y_{ij}(\text{Cortisol Slope}) = \beta_{0j} + \beta_{1j}(\text{Condition Contrast Code}) + \epsilon_{ij}$

Level Two: $\beta_{0j} = \gamma_{00} + \nu_{0j}$

$\beta_{1j} = \gamma_{10} + \nu_{1j}$

Here $\beta_{1j}$ is the difference in cortisol slope between manipulation conditions for participant $j$. Each of the three days of each condition are coded the same and thus averaged within participant. Meanwhile, $\epsilon_{ij}$ represents the within-person residual parameter (i.e., the difference between an individual’s own mean slope across all other days and their cortisol slope during that condition). A significant $\beta_1$ term indicates that the difference in cortisol slope between manipulation conditions is non-zero. Subsequent models using dummy codes are then run to examine the cortisol slope means for each condition. We predicted that cortisol slope should be significantly steeper (more negative) during the high social contact condition compared to the low social contact condition.

We also conducted lagged analyses, where we modeled the relationship between social contact condition and the following day’s cortisol slope. We expected that on the day following the high social contact condition, cortisol slope would be steeper (more negative) compared to the day following the low social contact condition.
Characteristics of the lunch partner. Participants were free to bring in whomever they liked in to the lab during the high social rhythm condition. We modeled whether differences in lunch partners across participants moderates the effect of the manipulation by including type of relationship, duration, frequency of contact or level of closeness in Level 2 of the model.

Level One: $Y_{ij}(\text{Cortisol Slope}) = \beta_{0j} + \beta_{1j}(\text{Condition Contrast}) + \varepsilon_{ij}$

Level Two: $\beta_{0j} = \gamma_{00} + \gamma_{01}(\text{Duration}) + \upsilon_{0j}$

$\beta_{1j} = \gamma_{10} + \gamma_{11}(\text{Duration}) + \upsilon_{1j}$

Results

Manipulation Check

Given the results of previous studies (Stetler & Miller, submitted), we intended the manipulation to alter social integration of daily activities, but not necessarily the total number of social interactions each day. We hypothesized that daily social integration scores would be higher during the friend condition compared to the alone condition, confirming that the manipulation of social involvement in daily activities did indeed work. Social integration scores did vary by condition. Participants reported an average daily social integration score of .50 (SE = 0.03) during the alone condition and .59 (0.03) during the friend condition. Contrast analyses indicate that the average difference in social integration between alone and friend condition days was 4% (SE = 0.009, $t(513) = 4.56, p < 0.001$). This small but significant difference is consistent with a manipulation that attempted to alter social integration during one (lunch) of many possible daily activities. The manipulation did not significantly influence the total number of daily social interactions that participants reported ($p > 0.17$).
We were interested in exactly how the manipulation altered social integration, i.e. whether having lunch with a friend was an increase relative to usual baseline or if having lunch alone was a decrease relative to usual baseline. Comparing social integration scores during the friend and alone conditions to social integration scores across baseline days allowed us to examine this question. Across all baseline days of data collection prior to the manipulation phase, the average social integration score was 0.57 (0.03), which is not significantly different from social integration during the friend condition (0.59, p > 0.6). However, social integration during baseline was significantly different compared to the alone condition (average difference 3% (SE = 0.01, t(513) = 2.67, p < 0.01). Thus, asking participants to eat lunch alone seemed to take away a social interaction that would usually occur, while asking them to eat lunch with a friend maintained their usual pattern of social contact.

Influence of manipulation on cortisol secretion

We next asked whether cortisol slope would vary by manipulation condition. The hypothesis was that there would be a significant difference in cortisol slope between the friend and alone conditions, such that cortisol slope would be steeper (more negative) during the friend condition compared to the alone condition. The average cortisol slope during the friend condition was –0.11 (0.01), while the average slope during the alone condition was also –0.11 (0.01). This was not a significant difference (p > 0.7). The average slope during baseline phase was –0.10 (0.01), which was not significantly different from either the friend or alone condition’s average slope\(^2\). Thus, although the

\(^2\) Although less consistent with our overall hypothesis about the regulatory effect of social contacts on the diurnal rhythm of cortisol secretion, we also examined the effect of the
manipulation successfully altered social integration, it did not have an effect on that day's cortisol secretion. Furthermore, the manipulation did not predict the following day's cortisol slope after controlling for current day's cortisol ($\beta_{ij} = -0.002$, SE = 0.01, $t(52) = -0.20$, $p = 0.84$). Another possibility is that the effect of the manipulation may not be fully realized for a while, so including the first day's cortisol slope as an outcome may be diluting the social contact effect. Even when this day was removed from analyses, however, there were still no differences in cortisol slope between the friend and alone conditions ($\gamma_{ij} = -0.005$, SE = 0.01, $t(52) = -0.61$, $p = .55$).

**Lunch partner characteristics**

Participants were free to choose their lunch partner during the friend condition. Because we were interested in whether one's choice of lunch partner during the friend condition influenced cortisol production, we assessed whether differences in the type of relationship that the participants had with their lunch partners moderated the effect of the manipulation on cortisol secretion.

The majority of participants ($n = 28$) brought someone they classified as a friend in to the lab for lunch. Eight participants brought a sibling, 6 participants brought a best friend, 4 brought a roommate, 4 brought a romantic partner, and 1 brought a classmate/coworker. Because there were insufficient numbers in each category to manipulation on total daily cortisol production and daily area under the curve. Those analyses did not yield any significant effects.

$^3$ Because previous studies have shown that daily social contact and cortisol output rhythms become uncoupled in episodes of clinical depression (Stetler, Dickerson, & Miller, 2004; Stetler & Miller, 2005), we wondered if high levels of depressive symptoms may have muted the effect of our manipulation. The data did not support this explanation: the severity of depression symptoms (CESD score) did not predict cortisol responses to the manipulation ($\gamma_{ij} = -0.001$, SE = 0.001, $t(50) = -1.00$, $p = 0.32$).
perform specific contrasts, we grouped the participants into 2 groups based on their lunch partner; participants who brought in lunch partners that were closer relationships such as best friends, siblings or romantic partners (n = 18) were compared to participants who brought in partners who were perhaps more distant such as friends, roommates or classmates (n = 33). When the difference in diurnal cortisol slopes between the alone and friend conditions were compared for each group, no significant differences were found ($y_{ij} = -0.011$, $SE = 0.015$, $t(48) = -0.72$, $p = 0.48$). The type of relationship that participants had with their lunch partners did not influence cortisol slope, based on this crude grouping of relationship categories.

Participants varied widely in the number of months they had known their lunch partners. The average participant had known her lunch partner for 40.9 (SE = 8.35) months, but relationships ranged from 1 to 252 months old. Because this variable was not normally distributed, it was natural log-transformed prior to analysis. The length of relationship was not a significant moderator of the manipulation’s effect on cortisol slope ($y_{ij} = 0.003$, $SE = 0.005$, $t(48) = 0.69$, $p = .50$).

Participants were also asked how often they saw their lunch partners in an average week. Answers ranged from 0 to 30 times per week, with an average rate of 6.12 (SE = 0.71) times per week. Because this variable was not normally distributed, it was natural log-transformed prior to analysis. Although the amount of weekly contact was not a significant moderator of the manipulation’s influence on cortisol slope ($y_{ij} = -0.001$, $SE = 0.0009$, $t(47) = -1.57$, $p = 0.12$), whether or not the participant reported daily contact with the lunch partner was ($y_{ij} = -0.027$, $SE = 0.014$, $t(48) = -1.95$, $p = 0.05$). That is, participants who had daily contact with their lunch partners had steeper slopes in the
friend condition (-0.13) compared to the alone condition (-0.10), while participants who did not see their lunch partners on a daily basis had steeper slopes during the alone condition (-0.12) compared to the friend condition (-0.09). See Figure 4.1.

Participants also rated the level of closeness or intimacy present in their relationship with their lunch partner. The average score on this five-item measure was 27.2 (SD = 4.8; range: 16-34). Level of closeness was not a significant predictor of the manipulation's effect on cortisol ($\gamma_{11} = -0.001$, SE = 0.002, $t(47) = -0.57, p = 0.57$). Thus, participants who reported a higher-than-average degree of closeness with their lunch partners did not have any greater change in their cortisol slopes during the friend condition compared to participants who reported lower-than-average levels of closeness. Including level of closeness in the model with relationship length and daily contact did not change this result. It appears that quantitative aspects of the relationship such as frequency of contact were more predictive of changes in cortisol slope than qualitative aspects of the relationship, such as level of closeness or intimacy.

Discussion

The goal of the current study was to develop and evaluate a manipulation of daily social contact, so we could determine whether it has a causal influence on the rhythms of cortisol secretion. Although the manipulation was not associated with a change in the diurnal pattern of cortisol secretion, we did learn potentially important information about what types of social contact might have the greatest capacity to act in such a regulatory fashion. Lunch partners whom the participants had known for a long time or with whom they typically have daily contact were associated with the biggest changes in cortisol slope across manipulation conditions.
Manipulation of social contact

In designing the manipulation of social contact, we attempted to balance the need for control over the manipulation with the desire to make the manipulation mimic participants' daily lives as much as possible. Thus, we continued to use ambulatory methods of data collection while asking participants to take part in a lab-based manipulation. We wanted to make the manipulation as minimally disruptive as possible, in order to maximize subject participation, while maintaining as powerful a manipulation as we could. Thus we chose to manipulate the social environment in which participants consumed their lunches. Of all the daily activities assessed with the daily diary measures, lunch seemed the most feasible to re-create in a laboratory setting given our sample of university students.

The results suggest that we were successful in altering the level of social integration of our participants' daily activities. Social integration scores were significantly greater on days when participants ate lunch in the lab with another person compared to days when they ate lunch alone. The small but statistically significant change in social integration score is consistent with the fact that the manipulation changed only 1 out of 14 daily activities assessed by our inventory. Notably, the total amount of daily social contact was not altered by the manipulation. The fact that this variable was not affected by the manipulation may indicate that when participants ate lunch by themselves, they moved their usual lunch-time social interactions to other times during the day. As there were no significant differences in the number of daily social contacts on usual baseline days and days when participants ate lunch in the lab by
themselves, we suspect that participants were able to maintain their normal levels of social contact despite eating lunch alone in a lab.

Effect of laboratory manipulation on cortisol production

Because we were able to show that the manipulation altered at least one measure of social contact (social integration score), we then tested whether the manipulation influenced cortisol secretion. We hypothesized that diurnal cortisol slopes would be steeper on days when participants ate lunch with a friend and flatter on days when they ate lunch by themselves. However, we found no significant differences in cortisol slope between manipulation conditions. Neither did we find differences when we looked at cortisol slope on the days after each manipulation condition.

We do not believe that these null findings reflect a lack of statistical power, as associations between similar variables were detected with data from the baseline phase, which included approximately the same number of participants and fewer total days of data collection (Stetler & Miller, submitted). Measurement unreliability is not a likely cause of the null findings here. Associations among these variables measured in the same manner have been shown in previous studies as well as in the baseline phase of the study (Stetler & Miller, submitted). Although previous research (Stetler et al., 2004; Stetler & Miller 2005) showed that higher levels of depressive symptoms reduced the association between social contacts and cortisol production, including participants with some amount of depressive symptoms does not appear to be the reason why our manipulation of social contacts had no significant effect on cortisol slope.

The manipulation’s effect on cortisol was strongest when participants chose a lunch partner with whom they had daily contact. When a participant chose an individual
whom they see on a daily basis as a lunch partner, their cortisol slopes were steeper during friend condition and flatter during alone condition. Given our conceptualization of steeper cortisol slopes as indicating better HPA axis function compared to flatter cortisol slopes, this finding lends support to the hypothesis that daily social contacts to some extent drive daily cortisol secretion. When an individual whom a participant normally sees every day is removed (during the alone condition), cortisol slope flattens, suggesting weaker HPA axis regulation. These findings suggest that contact with the same person every day stabilizes biological rhythms; that is, regular social contacts act as zeitgebers that entrain healthy patterns of cortisol output. Future studies could control whom participants chose as lunch partners in order to maximize the power of a similar manipulation.

Another way to increase the potency of the manipulation would be to extend its duration. One limitation of the study’s manipulation was that participants were only exposed to each condition for one hour a day for two days. This may not have been long enough to produce immediate changes in cortisol slope. In addition, when participants ate lunch by themselves in the lab, they may have compensated for that missed social interaction by seeking social involvement in other daily activities. A manipulation of social contact involving more if not all of one’s daily activities would be more likely to produce an effect on cortisol. This would be easily accomplished by isolating participants in a lab during the day, but that would reduce the ecological validity of the manipulation. Future studies should continue to undertake the challenge of designing a well-controlled manipulation that is representative of normal daily experiences yet powerful enough to affect physiology.
In order to conclusively examine the issue of causality and extend previous research, we conducted a manipulation of daily social environment that proved to be of some success. We were able to produce changes in social integration of daily activities. Although these changes in social integration were not associated with changes in diurnal cortisol slope for all participants, we did succeed in altering cortisol production in some people. These people were those who brought in a lunch partner that they had regular daily contact with. This finding gives us some insight into what relationships are most important for cortisol production and offers some exciting ideas for future studies.
Table 4.1 Descriptive statistics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SE) unless otherwise noted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol slope during alone condition</td>
<td>-0.11 (0.01)</td>
</tr>
<tr>
<td>Cortisol slope during friend condition</td>
<td>-0.11 (0.01)</td>
</tr>
<tr>
<td>Length of relationship with lunch partner</td>
<td>40.9 months (8.35)</td>
</tr>
<tr>
<td>Frequency of contact with lunch partner (times per week)</td>
<td>6.12 (0.71)</td>
</tr>
<tr>
<td>Percent of sample reporting daily contact with lunch partner</td>
<td>45.1% (n = 23)</td>
</tr>
<tr>
<td>Level of closeness in relationship with lunch partner</td>
<td>27.2 (0.67)</td>
</tr>
</tbody>
</table>
Figure 4.1. Mean diurnal cortisol slope (with SEM) during each manipulation condition is moderated by daily contact with lunch partner (yes/no).
References


Conclusions

Several important conclusions arise from the studies that comprise this program of research. Foremost, social contacts were associated with cortisol secretion among the non-depressed participants in the first two studies. The first study found a link between morning social contacts and the morning cortisol peak, such that more social contact was associated with higher level of cortisol in response to awakening. The second study found not only a cross-sectional association but also a prospective link between social contacts and cortisol slope on the subsequent day. Higher levels of social contact during daily activities predicted faster declines in cortisol levels over the following day. Taken together, the results are consistent with the idea that social contacts help to regulate the HPA axis by promoting the normative pattern of diurnal cortisol secretion. However, the third study's experimental manipulation of social contacts failed to produce the expected changes in cortisol secretion, precluding definitive conclusions regarding causality.

Effect of laboratory manipulation on cortisol production

The failure of the social contact manipulation to produce changes in cortisol slope leaves open the possibility that a common third variable underlies the link between social contacts and cortisol secretion. We examined three such potential third variables: exercise, meals, and smoking. None of these behaviors could explain the relationship between social contacts and cortisol slope. Caffeine consumption was not assessed in this research, and its association to baseline cortisol production during the day is unclear (Lane, Peiper, Phillips-Bute, Bryant & Kuhn, 2002). However, this would be an important behavior to assess in future studies, since it has potential links to social contact.
as well as HPA axis activity. Beyond behaviors, trait differences such as extraversion or loneliness are unable to account for within-person effects.

We do not believe that the third study’s null findings reflect a lack of statistical power, as associations between similar variables were detected with data from the second study, which included approximately the same number of participants and fewer total days of data collection. Measurement unreliability is not a likely cause of the null findings here. Associations among these variables measured in the same manner have been shown in previous studies as well as in the second study. Instead we think the manipulation may not have been powerful enough to alter cortisol production.

The data on lunch partners suggest one way to improve the potency of the social contacts manipulation: use a person whom the participant sees on a daily basis. Participants who brought in someone whom they normally saw each day had a significant difference in cortisol slope between friend and alone conditions: steeper slopes on days they had lunch with their partner and flatter slopes on days they had lunch alone. A similar effect, but in the opposite direction was found for lunch partners that the participants had known a long time. Although having a long-standing relationship with the lunch partner predicted a significant difference in cortisol slope between manipulation conditions, slopes were flatter during the friend condition and steeper during the alone condition. Given that we conceptualize steeper slopes as indicating better HPA axis regulation, the influence of relationship length is opposite of what we would predict. One potential explanation for these findings is that participants took the lunches during the friend condition as an opportunity to catch up with a good friend that they had not seen in a while. The novelty and stimulation of that social interaction may have counteracted any
regulating effects of social contact. In a future study, the laboratory manipulation should replicate the usual social environment as much as possible. Requiring participants to eat lunch in the laboratory with someone whom they would typically have contact with may improve the potency of the manipulation and produce a higher likelihood of significant results.

**Implications of cortisol levels for health**

HPA axis regulation and diurnal decline in cortisol levels from a high morning peak have implications for future health. Recent research has shown that patterns of cortisol secretion similar to the ones promoted by social contacts in the current research are associated with lower disease risk. In a study of HPA axis activity and disease risk factors, Rosmond and Bjorntorp (2000) demonstrated that having a lower morning cortisol peak or a flatter diurnal cortisol slope was associated with an increased risk for Type 2 diabetes, cardiovascular disease and stroke. Matthews, Schwartz, Cohen & Seeman (2006) also found evidence suggesting that flatter cortisol slopes were associated with risk of atherosclerosis, as measured by coronary artery calcification. A third study (Sephton et al., 2000) has demonstrated that flattened cortisol slopes predict earlier mortality in a sample of women with metastatic breast cancer, even after controlling for other factors related to cancer progression. Thus, the pattern of cortisol secretion (higher morning values, steeper decline across the day) associated with greater social contacts in the current research is also the pattern linked to reduced risk for or progression during several major diseases.

Several mechanisms have been proposed for cortisol’s influence on medical outcomes. Metabolically, chronic exposure to elevated cortisol levels has been linked to
increased central fat deposition, a marker of coronary heart disease risk (Andrew, Phillips & Walker, 1998). There is also evidence for facilitative effects on tumor growth by cortisol and other stress hormones via metabolic pathways. For example, cortisol may differentially affect glucose uptake in tumor cells compared to healthy cells, producing energy deficits for the latter and energy surpluses for the former (Turner-Cobb, Sephton, & Spiegel, 2001). Angiogenesis, the formation of new blood vessels in bodily tissues, has important implications for a variety of disease. Glucocorticoids like cortisol have been shown to inhibit production of vascular endothelial growth factor (VEGF), a protein that plays an essential role in angiogenesis (Koedam, Smink, & van Bull-Offers, 2002). This may have important implications for normal somatic growth and wound healing, as well as tissue repair following myocardial infarction or stroke.

Regarding the immune system, growing evidence also links disturbances in HPA axis function with increases in systemic inflammation, which has been implicated in a variety of medical conditions including heart disease, asthma, and dementia (Mrak & Griffin, 2005). A flatter cortisol slope during the day may be a marker of decreased sensitivity of the negative-feedback loop within the HPA axis, such that activation of this axis is not reduced despite inhibitory signals. When the HPA axis is continually activated, cortisol receptors in bodily tissues are downregulated, reducing sensitivity to cortisol signals in these tissues as well (Miller, Cohen, & Ritchey, 2002). The result is an inflammatory response that endures despite inhibitory signals from cortisol. Furthermore, cortisol has been shown to modulate other aspects of immune function, including T and B cell function, cytokine and adhesion molecule expression, cell trafficking and cell proliferation (Webster, Tonelli, & Sternberg, 2002). Such immune effects may be
mediated by the transcription factor nuclear factor κB (NF-κB), which is well recognized as a regulator of genes encoding cytokines and cell adhesion molecules as well as genes controlling cellular proliferation and apoptosis (Perkins, 2007). Recent work has demonstrated that NF-κB levels rise in parallel with cortisol in response to acute stress (Bierhaus, Wolf, Andrassy, Rohleder, Humpert, Petrov, et al., 2003).

To the extent that social contacts promote a healthier pattern of HPA axis activity, which in turn is associated with reduced risk of disease, this may represent an important but relatively unexplored pathway by which social relationships predict morbidity and mortality. Contact with other people during one’s daily routine may function as a zeitgeber that helps maintain proper circadian timing of physiological processes such as HPA axis function. Given the important role of proper circadian rhythms for health (Moore-Ede & Richardson, 1985; Costa, 1996), daily social routines may impact health to the extent that they impact circadian rhythms. In addition to acting as buffers during stress and influencing health behaviors, daily social contacts may serve as stabilizing influences on physiology that reduce fluctuation and help maintain the circadian pattern. The direct effects of daily social contacts are likely to be small influences that accumulate over time to have a significant impact on health.

Another important conclusion derived from this research is that social contacts lose their capacity to regulate HPA axis function during clinical depression, and this loss of regulatory function can be seen in individuals with sub-clinical levels of depressive symptoms. Thus, one factor that may contribute to the HPA axis disturbances often present during depression (Young, Haskett, Grunhaus, Pande, Weinberg, Watson et al., 1994) is the loss of the normal regulatory influences. Social contacts are still present, but
they do not influence cortisol production in the same way they do for non-depressed individuals. The current research extends the literature by suggesting that disruptions to the daily social environment and HPA axis do not occur abruptly among individuals with major depression, but these disruptions begin during periods of low to moderate levels of depressive symptoms. To definitely evaluate this hypothesis, however, we would need a prospective design, in which the role of social contacts was examined as euthymic individuals transitioned from mild affective symptoms into episodes of clinical depression.

Researchers have proposed that the HPA axis abnormalities often present during depression may help to explain why lifetime prevalence of depression is a risk factor for several leading causes of death, including coronary artery disease and diabetes (Brown, Varghese, & McEwen, 2004). Indeed, numerous studies have demonstrated a positive association between number of depressive episodes and risk for future cardiovascular disease (Wulsin & Singal, 2003). Additionally, depression has been associated with increased risk of developing Type 2 diabetes (Anderson, Freedland, Clouse, & Lustman, 2001), as well as osteoporosis (Cizza, Ravn, Chrousos, & Gold, 2001), hypertension (Davidson, Jonas, Dixon and Markovitz, 2000), dementia (Jorm, 2000), as well as overall earlier mortality (Takeshita, Masaki, Ahmed, Foley, Li, Chen, et al., 2002). To the extent that HPA axis dysfunction is promoted or maintained during depression due to a failure of regulatory influences like social contacts, the current research may help to elucidate a psychosocial mechanism involved in the depression-medical illness link.
Limitations and future studies

Although the ambulatory assessment of salivary cortisol and daily diary methodology gives the research a high degree of ecological validity, such methods also have inherent limitations. Given that our main findings have been with cross-sectional and prospective data collected outside of the laboratory, unmeasured variables could explain the observed associations between social contacts and cortisol slope. For example, known zeitgebers such as exposure to sunlight or activity level could have fluctuated from day to day and may be underlying third variables, predicting both social contacts and HPA axis activity. In the second study, the percent of daily activities done with other people remained a significant predictor of cortisol slope even after controlling for the total number of activities reported each day (data not reported). However, we did not obtain an objective (i.e. not self-report) measure of daily activity, such as steps taken, calories expended, or average heart rate. The existence of an unmeasured third variable such as this could explain the failure of the social contact manipulation to alter cortisol slope.

Apart from the existence of an underlying third variable, the manipulation also may have failed to yield significant changes in cortisol slope because it did not represent a large enough change in social contacts. Participants were only exposed to each condition for one hour a day for two days. This may not have been long enough to produce immediate changes in cortisol slope. A manipulation of social contact involving more if not all of one’s daily activities would be more likely to produce an effect on cortisol. This would be easily accomplished by isolating participants in a lab during the day and exposing them to controlled amounts of their usual daily contacts, but that would
reduce the ecological validity of the manipulation, and be difficult to feasibly conduct. In addition to involving the cooperation of the participants, such a study would require the participation of their friends, family, classmates, co-workers, etc., since the current research suggests that the biggest effects on cortisol come from people whom the participant normally sees every day. Future studies should undertake the challenge of designing a well-controlled manipulation that is representative of normal daily experiences yet powerful enough to affect physiology. Such a manipulation might examine whether some representation of daily interpersonal contact, such as looking at photographs, listening to voice recordings, or watching a videotape of a friend, partner, etc. instead of actually having contact with that person would be enough to produce changes in cortisol secretion (Gardner, Pickett, & Knowles, 2005). Additionally, emails or instant messaging might replace in-person social contact in a laboratory-based manipulation. Not only would this improve the feasibility of the manipulation, it may yield important insights into the mechanism for the effect; if looking at pictures or having email contact can produce changes in cortisol levels in the same way that person-to-person contact can outside the lab, then social contacts must not be having their effects via any physical pathways (e.g. touch). Designing and implementing a more powerful manipulation of daily social contacts will offer the best test of whether the relationship between social contacts and cortisol secretion is causal, or if a common underlying third variable needs to be explored.

Although reducing ecological validity, bringing participants into the laboratory for several days while their entire set of daily social contacts are altered offers some advantages as well. Collecting data in the laboratory, instead of in the field, would allow
blood samples to be drawn at regular intervals in order to measure other components of the HPA axis. While cortisol slope is a widely used and reliable indicator of HPA axis function, it does not capture other aspects of HPA axis function such as adrenocorticotropic hormone (ACTH) production (only measurable via blood) or feedback sensitivity. Thus the current research’s limited ability to make claims about how social contacts influence overall HPA axis function could be overcome. Although useful in ambulatory data collection protocols such as this, diurnal cortisol slope inherently does not capture nighttime cortisol values. To make true inferences about circadian rhythms, cortisol production over a 24-hour (minimum) period would need to be assessed. Overnight assessment of cortisol might be informative given the finding that the effect of social contacts carries over into the next day. Furthermore, cortisol secretion is only one of many diurnal processes that occur in the body. Asking participants to spend several days in the laboratory would permit us to measure a range of diurnal and/or circadian processes, such as patterns of oxytocin or melatonin production. Finally, such a study would also enable us to control and/or measure potential third variables previously mentioned: exposure to sunlight and activity/sleep patterns. However, such a study would require considerable resources and represent a significant departure from the variable of primary interest: the participant’s normal daily routine.

Although a causal relationship has not been demonstrated conclusively, results of the current line of research suggest that one way that social relationships may influence health is via social contact during daily activities. Contact with other people during one’s daily routine may function as a zeitgeber that helps maintain proper circadian timing of physiological processes such as HPA axis function. Given cortisol’s crucial role in a
variety of physiological systems and its pervasive links to the leading causes of morbidity and mortality, as well as the importance of proper circadian rhythms for health, daily social routines may impact health to the extent that they impact the circadian pattern of the HPA axis function. In addition to acting as buffers during stress and influencing health behaviors, social relationships may provide daily social contacts that serve as stabilizing influences on physiology, reducing fluctuation and helping maintain the circadian pattern. The direct effects of daily social contacts are likely to be small influences that accumulate over time to have a significant impact on health.
References


Appendix 1: Social Rhythm Metric

This questionnaire (Monk, Flaherty, Frank, Hoskinson, & Kupfer, 1990) was completed by participants at the end of each day. For each of the following activities, participants were asked:

1. Did you do X today? (e.g. did you eat breakfast today?)
2. Were you alone when you did X? (yes/no)

Activities:
1. Get out of bed
2. First have contact with another person
3. Have morning beverage
4. Have breakfast
5. Go outside for first time
6. Start work/school/childecare activities
7. Have lunch
8. Take nap
9. Exercise
10. Watch television
11. Have snack/drink
12. Eat dinner
13. Return home for the last time
14. Go to bed