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Stability of Interindividual Differences in Serotonin Function and Its Relationship to Severe Aggression and Competent Social Behavior in Rhesus Macaque Females

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*Few studies have investigated longitudinally interindividual stability of cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA) concentrations in adult nonhuman primates across time and between baseline and stressful conditions. Furthermore, whereas studies with male macaques consistently have reported a significant, negative correlation between CSF 5-HIAA and rates of spontaneous aggression, wounding, and severe aggression, very few studies have examined this relationship in adult female nonhuman primates. Even fewer studies have investigated correlations between CSF 5-HIAA and competent social behavior, such as social dominance, in female monkeys. In the present study, two social groups of adult rhesus monkeys (*Macaca mulatta*) were formed by placing 16 females (aged 42 to 180 months, mean age: 68 months) in one of two indoor-outdoor enclosures with one or two adult males. CSF norepinephrine (NE), monoamine metabolites, and behavioral data were collected systematically over a 24-week period. In week 5 of the study, one additional female, not familiar to any of the other subjects, was added to each social group. Thereafter the groups were left undisturbed, and data characterizing spontaneous aggressive wounding and severe wound injuries in the females were collected for an additional year. The results showed that both group introduction and the addition of a new subject into each group resulted in increased monoamine turnover in the animals within the social groups. Interindividual differences in CSF concentrations of each of the monoamine metabolites and NE were highly stable from the baseline period to the stress samplings, and between stress samplings. Females with low CSF 5-HIAA exhibited higher rates of spontaneous aggressive wounding, and they were more likely to be removed from their social groups for aggressive wounding and/or treatment of injuries. CSF NE concentrations also were negatively correlated with rates of spontaneous aggression. In contrast, competitive aggression, i.e. noninjurious aggression used to maintain social dominance ranking, was not correlated with CSF 5-HIAA or NE. Females with above average CSF 5-HIAA prior to and following group formation were more likely to attain and maintain a high social dominance ranking within their social group than females with below average CSF 5-HIAA. The present findings indicate that CNS monoamine functioning in adult female rhesus macaques is traitlike, showing a high degree of interindividual stability across time and setting. These findings also suggest a role for serotonin in controlling impulses that regulate aggression and that competent social behavior among nonhuman primates may require average or above average serotonin functioning. [**Neuropsychopharmacology 14:67–76, 1996**]*

KEY WORDS: *Serotonin; 5-Hydroxyindoleacetic acid; Aggression; Stress; Primate; Social competence*

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Numerous studies have shown that human males who engage in high levels of aggression or violence often have low central nervous system (CNS) serotonin (5HT) turnover rates, as indicated by low cerebrospinal fluid (CSF) concentrations of the major 5HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) (Linnoila et al. 1983b; Virkkunen et al. 1987; Virkkunen et al. 1994a; Virkkunen et al. 1994b) as well as unusually low or high CSF concentrations of the norepinephrine (NE) metabolite 3-methoxy-4-hydroxyl-phenylglycol (MHPG) (Brown et al. 1979; Linnoila et al. 1983b). CSF 5-HIAA concentrations are particularly low in boys who exhibit inappropriate or excessive aggression (Kruesi et al. 1990; Kruesi 1989; Kruesi et al. 1992) and men exhibiting unplanned violent or high lifetime rates of aggression (Brown et al. 1979; Brown et al. 1982; Lidberg et al. 1985; Limson et al. 1991; Linnoila et al. 1983b). The finding of a negative correlation between diminished central 5HT functioning and acts of excessive aggression and violence is not limited to humans. In adolescent male rhesus monkeys, decreased CSF 5-HIAA, and at times CSF norepinephrine (NE), are related to high levels of wounding and inappropriate aggression, but both are unrelated to milder forms of aggression, e.g., aggression used to maintain social status (Higley et al. 1992a; Mehlman et al. 1994; Mehlman et al. 1995). Studies by Botchin and colleagues (Botchin et al. 1993), have shown that in adult male cynomolgus monkeys, a closely related macaque species, males with high levels of physical aggression show a diminished prolactin response to a fenfluramine challenge. Similarly, in male vervet monkeys, another relatively closely related Old World species, chronic administration of fenfluramine decreases CSF 5-HIAA and increases the rate of aggression (Raleigh et al. 1986). In contrast to this emerging literature on males, few studies have investigated the relationship between aggression and CSF 5-HIAA in female primates. In a recent chapter, Raleigh and colleagues reported that when dominance ranking was controlled, CSF 5-HIAA was inversely correlated with an increased rate of prolonged, inappropriate aggression in both male and female vervet monkeys (Raleigh and McGuire 1994). These studies led us to postulate that among female rhesus monkeys, CSF 5-HIAA would be inversely correlated with rates of spontaneous aggression, as well as with severe wounding and inappropriate aggression.

Several nonhuman primate studies have suggested that interindividual differences in CSF monoamine metabolite concentrations are highly stable across time and experimental settings in both sexes of young animals. For example, in a study investigating infant rhesus monkeys, interindividual differences in baseline CSF monoamine metabolite concentrations were highly predictive of interindividual differences in stress-induced elevations of CSF monoamine metabolite concentrations when samples were taken 2 and 4 weeks apart (Higley et al. 1992b; Higley et al. 1993). Kraemer et al. (1989) also found interindividual stability in rhesus monkey infants across repeated sampling during the first year of life, particularly among infants reared by their mothers. Such interindividual differences also appear to be stable across longer periods, with the mean of CSF monoamine samples taken in late infancy (6 months of age) predicting mean concentrations in middle childhood, a year later (Higley et al. 1992b).

Because it appears to play a major role in regulating social behavior, we were particularly interested in the longitudinal stability of the 5HT system. In the only previously published study investigating individual stability of CSF 5-HIAA across repeated samples in adult nonhuman primates, Raleigh and colleagues reported a great degree of stability in adult male vervet monkeys (Raleigh et al. 1992); females, however, were not included in the study. Therefore, in the present study, we investigated the stability of CSF 5-HIAA and the other monoamine metabolites over time in adult female monkeys. Because other studies have demonstrated that CNS 5HT and catecholamine turnover rates are stress-responsive (Bayart et al. 1990; Bliss et al. 1968; Glavin 1985; Morgan et al. 1975; Thurmond and Brown 1984), we were particularly interested in the relationship between social stress and monoamine turnover rates in adult female rhesus monkeys. By simultaneously quantifying each of the major monoamine metabolites and norepinephrine, we were able to assess the global and selective nature of the social stressor of group formation and the introduction of novel social partners on monoamine functioning. Based on previous findings showing the stressful nature of group formation (Gust et al. 1991; Scallet et al. 1981), we hypothesized that group formation and introduction of a novel social partner would produce a global increase in monoamine turnover.

A third goal of the present study was to investigate the relationship between competent social behavior and 5HT functioning. Kruesi and colleagues found that in behaviorally disturbed and obsessive compulsive children, degree of social competence was positively correlated with CSF 5-HIAA (Kruesi et al. 1990), independent of psychiatric classification. Virkkunen and colleagues found that violent men exhibiting antisocial behaviors and impaired impulse control also had lower mean CSF 5-HIAA concentration than individuals who did not have personality disorders (Virkkunen et al. 1994a). One measure of competent social behavior in nonhuman primates is social dominance ranking. Although it is widely held that for nonhuman primates increased social dominance is based on high rates of aggression and fighting skills, recent studies have shown that social dominance is not related to fighting skills, size, or aggressiveness (Raleigh and McGuire 1991). Indeed, subordinate males are more likely to exhibit severe aggression, direct it at inappropriate targets, and show

decreased affiliative behaviors (Raleigh and McGuire 1991). Similarly, the rate at which a rhesus monkey acquires high social dominance ranking is correlated with rates of friendly interactions but not the frequency of aggression (de Waal 1993). The acquisition and maintenance of social dominance is largely dependent on the presence of other conspecifics and kin for social support (Chapais 1986; Chapais 1988; Higley and Suomi, in press; Raleigh et al. 1986; Raleigh et al. 1991). Concentrations of 5-HIAA are correlated positively with high social dominance rankings in adolescent male and female rhesus monkeys (Higley et al. 1994) and in adult male vervet monkeys (Raleigh et al. 1983). Moreover, in a series of pharmacologic studies performed on male vervet monkeys, Raleigh and colleagues (Raleigh and McGuire 1986; Raleigh et al. 1991) demonstrated that pharmacologic manipulations that reduced 5HT functioning also reduced social dominance rankings; conversely, pharmacologic manipulations that increased 5HT functioning increased social rank. It is noteworthy, that unlike 5HT turnover rate, turnover rates of the major catecholamines are not significantly correlated with social dominance ranking (Higley et al. 1994). These findings led us to postulate that increased 5HT functioning would facilitate social dominance acquisition in females placed together to form new social groups. Moreover, to the degree that CNS 5HT functioning represents a stable traitlike individual difference, it should remain positively correlated with social dominance ranking across time. Specifically, we hypothesized that increased CSF 5-HIAA, but not catecholamine metabolite concentrations, obtained prior to group formation would predict the acquisition of high social dominance ranking among adult females and that once a stable social dominance ranking emerged, CSF 5-HIAA would remain positively correlated with a social dominance ranking.

Longitudinal assessments are ideally suited to test hypotheses concerning interindividual differences in biochemistry and behavior, and they are necessary to demonstrate any changes over time. The present longitudinal assessment of two groups of adult female monkeys describes CSF monoamine data obtained prior to and following group formation, and correlates the monoamine metabolite data with social behaviors seen after group formation, including assessments of spontaneous aggression during a prolonged period when the groups were not subjected to any stress-producing experimental manipulations.

METHODS

Subjects and Data Collection

Two social groups of rhesus monkeys (*Macaca mulatta*) were formed by placing 16 adult females (aged 60 to 180 months, mean age: 68 months) in one of two indoor-outdoor enclosures with one or two adult males. One female became ill and could not be used in the study. The females were all premenopausal, and the two groups did not differ in age (M/SD in months: group A—100.0/32.9; group B—93.0/30.6; $t = 0.56$, $p > 65$). Subjects were selected and placed into groups to assure that each female subject knew one other subject in that group. All other females in each group were unfamiliar to each other. Systematic behavioral and biochemical data were collected over a 24-week period. To investigate the effect of the stress of the introduction of stranger on CSF 5-HIAA concentrations, following the CSF sample in week 5 of the study, one additional female, not familiar to any of the other subjects, was added to each social group to give a total sample of 17 adult female subjects, with eight females in one group and nine females in the other. To include these two additional females' data in the analyses, data were collected for an additional 5 weeks on the two females that were placed in the group during week 5. To assure that the stress of the CSF sampling was not provoking the aggression and to investigate the correlation between 5HT turnover and subsequent, spontaneous, severe aggression, documentation of aggressive wounding and wound injuries continued for an additional year after the CSF sampling was completed.

Design

After the group formation, during the following month, a CSF sample was obtained approximately each week; thereafter a sample was obtained every second or third week, for a total of 14 CSF samples from each female [sample number, and timing: (1) Baseline: At least one week prior to the formation of the two groups, a baseline sample was obtained. (2) Day 1: To form the groups, at 10:00 hours, the females were all placed in the indoor-outdoor run, and a CSF sample was obtained at 14:30 on the first day. (3) Day 4: At the end of the first week, another CSF sample was collected; the remaining 11 samples were obtained during the following periods: (4) Weeks 2–3; (5) Week 4; (6) Week 5; (7) Weeks 6–7; (8) Week 8; (9) Weeks 9–11; (10) Weeks 12–13; (11) Weeks 14–16; (12) Weeks 17–19; (13) Weeks 20–21; (14) Weeks 22–24.

CSF Sampling Procedure

To obtain the CSF samples, monkeys were captured from their homecages between 1130 and 1430 hours and administered general anesthesia (ketamine HCl 15.0 mg/kg). A 2-ml sample of CSF was removed from the cisterna magna of each female within 25 minutes of ketamine injection using a 5-cc syringe. To preclude food deprivation from becoming a conditioned stimulus signaling impending CSF sampling, normal feeding routines were maintained throughout the study, including

days when CSF samples were obtained, with the monkeys receiving their daily food rations at 0700 and 1500 hours each day. Previous studies have shown that there is no significant capture effect on CSF monoamine concentrations if samples are obtained within 15 to 25 minutes of ketamine injection (Bacopoulos et al. 1979; Brammer et al. 1987; Higley et al. 1991). As in our earlier study (Higley et al. 1991), preliminary analyses indicated that neither time to capture nor time from ketamine injection until the CSF sample was obtained was correlated with monoamine concentrations. Samples were immediately placed on dry ice and stored at −70°C. The CSF was analyzed for norepinephrine (NE), MHPG, homovanillic acid (HVA), and 5-HIAA concentrations using liquid chromatography with electrochemical detection (Scheinin et al. 1983; Seppala et al. 1984). Interassay and intraassay variability was less than 10%.

Behavioral Samples

Beginning 1 week after group formations, weekly behavioral samples were obtained using one of two behavioral scoring systems. First, once a week, an observational scoring system consisting of objectively defined behavioral categories was used to score spontaneous aggression. Each subject was scored for a 5-minute period. This system was designed to measure the frequency of unprovoked homecage aggression. An aggressive act was scored if an open mouth threat, aggressive chase, or contact aggression occurred—most of the aggression scores were typically chases and bites. A second behavioral scoring system was used to measure social dominance ranking. Competition among group members was elicited by throwing single pieces of fruit into the group pen and recording all displacements of one subject by another, as well as open mouth threats and aggressive chases. An animal was scored as a winner in an encounter if it displaced another animal or defeated the other subject in the aggressive exchange. It was scored as a loser if it was displaced by or lost the fruit to another animal. Three behaviors were scored: displacements, threats, and aggressive chases. In no case did this form of competition-directed aggression result in injuries to any other animal during the study. These two types of behavioral samples were collected by four trained observers who had used the scoring systems for over a year and demonstrated a reliability of >0.85 using Cohen's kappa. The observers were all blind to the CSF monamine metabolite concentrations of each subject. Social dominance rankings were obtained by assessing the directionality of outcomes for each subject when in direct competition with each of the other subjects, an established method to assess social dominance ranking in nonhuman primates (McGuire et al. 1986; Richards 1974). A subject was considered more dominant than another monkey when it won more encounters than it lost with that monkey.

Removal of Spontaneous Wounding or Excessive Aggression

Because severe aggression is a rarely occurring event in established social groups, an extended period of data collection was required to collect sufficient data to test our hypothesis of a negative correlation between CSF 5-HIAA and severe, unprovoked aggression. To assure that the aggression was not being induced by any stress associated with repeated capture and CSF removal, records were kept concerning the occurrence of spontaneous severe wounding for each subject during the 12-month period after the final CSF tap. A subject was scored as wounded if its injuries were clearly the result of aggression, sutures were necessary, and treatment required housing for more than 24 hours in the isolation ward. Only spontaneous wounds were scored; wounds that occurred following reintroduction to the social group after protracted removal, where fighting is typical, were not scored. Determination of the need to remove a subject from the social group and length of treatment was made by the facility veterinarian, who was blind to both the study's purposes and the subject's biochemical values. A subject was scored as excessively aggressive if it had repeatedly wounded another subject and the level of aggression by the aggressor precluded the return of the subject back into the social group. In these cases, an effective stragegy for returning and maintaining the victim in the social group was to remove the aggressor for 3 to 7 days and then to return the aggressor back into the group.

Data Analysis

Initial comparisons revealed no differences between the two groups of females on any of the dependent measures; therefore, the data were pooled to provide a total of 17 subjects for comparison of the monoamine metabolites and NE. Homecage spontaneous aggression occurred too infrequently to perform repeated measures analyses; thus, all analyses of homecage spontaneous aggression were performed using the overall mean for each subject collected over the first segment of the study. To assure that age and weight were not confounding our analyses, each behavioral and biochemical variable was first correlated with age and weight, and where necessary, age or weight was used as a covariate in subsequent analyses. Three subjects required treatment for minor injuries during the initial group formation. To assure that their brief removal from the group for injury treatment did not affect the acquisition of social dominance, a preliminary analysis of removal for injury treatment during group formation was per-

formed. These three subjects did not significantly differ from the means of the other 14 subjects on any of the dependent measures including eventual social dominance ranking. During subsequent phases of the experiment, whenever a subject required veterinary treatment, at least a week was allowed to pass before a CSF sample was obtained from that individual. In all cases, whenever a female was removed from her social group and treated for wounds or illness, her previous social dominance ranking was reestablished as soon as she was returned to her social group.

Mixed design two-way analyses of variance (ANOVA) were used to analyze each of the three metabolites and NE, with rank as the between group factor and week of the study as the within group factor. To assess the relationship between wounding and excessive aggression and each of the biochemicals, a second series of two-way mixed design ANOVAs was completed. Wounding data were scored as yes/no and used as a grouping factor to perform mixed design repeated measures ANOVAs on each of the biochemicals. One subject developed an illness that required her removal from the group before the end of the study period and could not be used to analyze the wounding rate data, and a second subject developed a pattern of self-biting that precluded the use of her data in the aggression and wounding analyses. Subjects removed for wounding or excessive aggression on more than two occasions were scored as yes ($n = 6$), and the others were scored as a no ($n = 9$). Greenhouse-Geiser corrections for repeated measures probabilities are reported for all ANOVAs. Where appropriate, further testing was performed by using univariate repeated measures analysis of variance, followed by Fisher's protected least significant difference. All comparisons are reported at the $p < .05$ level of significance unless otherwise noted. Two general comparisons were performed: baseline was first compared to each of the different weeks of the study. Second, week 6–7, which represented the introduction of a new subject into each group, was contrasted with the week prior, week 5, and each of the other weeks that followed week 6–7. Whenever subjects were not in their group at the time of the sample, or technical difficulties precluded the use of a subject's sample, the overall mean was used to predict a subject's missing value using univariate regression. Due to technical difficulties, samples for MHPG in weeks 12–13 could not be used in the analyses.

To assess interindividual stability of NE and each of the metabolites over time, Pearson product moment correlations were computed for NE and each metabolite by correlating values from each of the weeks that a sample was obtained. To provide an estimate of the sample-to-sample correlation, an overall mean correlation for NE and each metabolite was obtained by adding all of the correlation coefficients for each biochemical and dividing this total by the number of correlations. This average correlation coefficient for each biochemical was then tested for statistical significance. To assess the correlation between aggression and each of the biochemical measures, the overall mean value for each biochemical was correlated with mean scores for each of the categories of aggression: spontaneous homecage aggression, competition elicited threats, displacements, and chases.

RESULTS

Age and Weight Correlations

None of the biochemical measures were significantly correlated with age or weight. However, age was correlated with several of the behavioral variables: older animals were more likely to be removed from their social groups for wounding ($r = 0.48$, $p = .05$). On the other hand, younger subjects were more likely to receive aggressive chases from other subjects ($r = -0.54$, $p < .03$) and to be displaced by other subjects ($r = 0.48$, $p = .05$). Neither age nor weight was correlated with social dominance rank (p's $> .15$). Weight, but not age, was positively correlated with rates of spontaneous aggression ($r = 0.76$, $p < .005$). Neither weight nor age was correlated with removal from the group for wounds or severe aggression (p's $\geq .40$).

Rank and Aggressive Behavior

As expected, social dominance rank was positively correlated with the competitively elicited aggression used to assess high and low social dominance rank: initiate aggressive chases ($r = 0.62$, $p < .009$), displacements ($r = 0.57$, $p < .009$), and threats ($r = 0.57$, $p < .009$). Rank was not correlated with spontaneous aggression ($r = 0.14$, $p > .95$), nor with wounding and severe aggression ($r = 0.21$, $p > .95$), even when weight was statistically controlled.

Severe Aggression and Wounding and Other Forms of Aggression

With weight controlled, spontaneous homecage aggression was positively correlated with severe aggression and wounding ($r = 0.55$, $p < .03$). None of the competitively elicited aggressive measures were correlated with severe aggression and wounding, even when weight and age were statistically controlled ($p > .20$).

Description of Changes across Time

There were significant changes across the weeks of the study for each of the three metabolites and NE (5-HIAA: $F = 17.49$, $p < .0001$; HVA: $F = 9.09$, $p < .0001$; MHPG: $F = 9.67$, $p < .0001$; NE: $F = 2.47$, $p < .0001$; $df =$

13/195 for each of the ANOVAs except MHPG which had $df = 12/180$—see Figure 1 **A–D**).

Effect of Initial Placement into Group. Figure 1 illustrates the effect of group introduction, which increased each of the metabolites above baseline, with day 1 higher than baseline for all three of the metabolites. All three metabolites also showed a significant decline from day 1 to day 4 after group introduction. The percent change from baseline to day 1 of group introduction was greater for the catecholamines than for 5HT. Whereas the percent change from baseline to day 1 was less for 5-HIAA, across weeks of the study, it was the metabolite that was most consistently elevated above baseline throughout the sampling. For 5-HIAA, prior to week 20, all sample points except day 4 and week 4 were statistically higher than baseline, and even day 4 and week 4 nearly achieved statistical significance ($p < .10$). Both HVA and MHPG were higher than baseline on day 4 and week 2–3, but returned to baseline concentrations by week 4. NE was higher than baseline only on Day 4.

Effect of Additional Female Introductions. After the introduction of a new subject into each group late in week 5, only MHPG showed an immediate increase. It was significantly higher in week 6–7 than in week 5. Both 5-HIAA and HVA showed a delayed increase, with no initial change in week 6–7, but concentrations were higher than week 5 for both metabolites by week 8 and 9–11. HVA returned to week 5 levels, but 5-HIAA remained higher than week 5 through week 12–13. NE also exhibited a delayed but transitory increase. It was higher than week 5 in week 9–11 and 12–13. By week 14–16, both the catecholamine metabolites and NE had returned to baseline concentrations where their values remained throughout the rest of the study. Interestingly, for CSF 5-HIAA, the percent change from baseline to day 1 of new female introduction was greater than for the catecholamine metabolites. Indeed, for 5-HIAA,

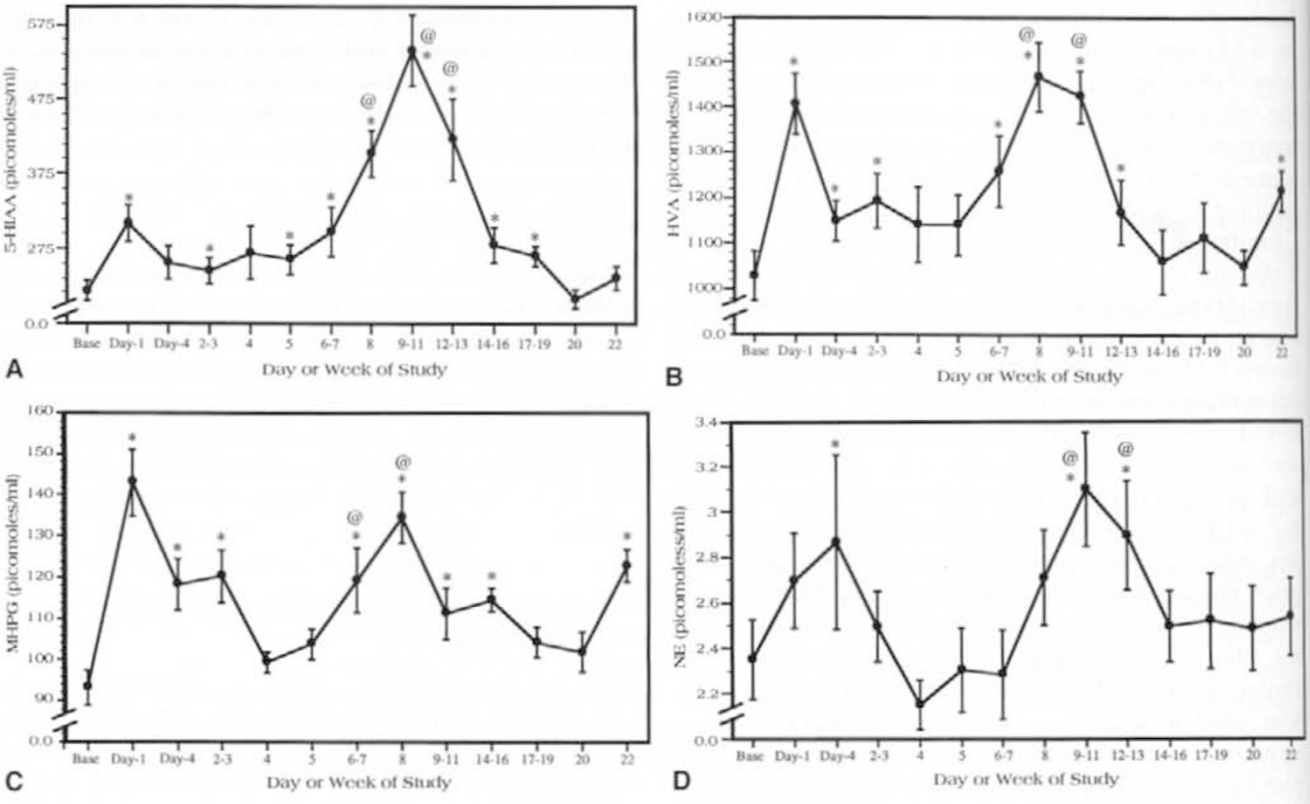

Figure 1. (**A**): 5-HIAA, (**B**): HVA, (**C**): MHPG, (**D**): NE shows the effect of group introduction and the addition a new subject into the group on mean CSF monoamine metabolites or NE. The x-axis for each of the biochemicals represents the period of time when the sample was obtained (baseline = a sample obtained prior to group introduction, day 1 = first day of group introduction, day 4 = the end of the first week, 4 days after initial group formation; the remaining numbers represent the week of the study when an additional sample was obtained: e.g., week 2–3 = a sample obtained between weeks 2 and 3 . . .). For Figure 1**C**, MHPG, assay errors precluded the use of the data obtained from weeks 12–13; thus the data are missing from the figure. The y-axis represents the concentrations of each biochemical in picomoles/ml. The range on the y-axis for each of the biochemicals is as follows: 5-HIAA: 175–600; HVA: 900–1600; MHPG: 80–160; NE: 2–3.4. Symbols: * = significantly higher than baseline at a significance level of $p < .05$ or less; @ = significantly higher than week 5 at a significance level of $p < .05$ or less.

weeks 8 and 9–11 were both statistically higher than all other weeks, including day 1.

Stability of Interindividual Differences

Despite the changes in setting and group composition, there was still a high degree of interindividual stability for NE and each of the monoamine metabolites across repeated samples. When the average correlation coefficient was obtained for NE and each of the monoamines, NE and MHPG demonstrated a nearly significant mean positive between sample correlation (NE: mean r = 0.45, $p < .08$; MHPG: r = 0.41, $p < .10$. 5-HIAA and HVA demonstrated a mean overall statistically significantly positive correlation between samples (5-HIAA: mean $r = .51$, $p < .04$; HVA: mean = 0.49, $p < .05$).

Social Dominance Rank and CSF 5-HIAA

High ranking animals exhibited significantly higher CSF 5-HIAA (4.09, $p < .04$, $df = 2/14$—see Figure 2) than low ranking females. The acquisition of social dominance rank was predicted by the baseline CSF 5-HIAA value (r = 0.61, $p < .009$). There were no significant week by rank interactions. None of the other metabolites or NE were significantly related to dominance ranking ($p > .40$).

Fight Wounds, Excessive Aggression, and CSF 5-HIAA

Weight-controlled spontaneous homecage aggression was negatively correlated with CSF 5-HIAA and NE (5-HIAA: r = −0.38, $p < .03$; NE: r = −0.35, $p < .05$). With age statistically controlled, mean CSF 5-HIAA taken prior to the wounding events was negatively correlated with whether a subject was removed from the group for severe aggression and wounding (r = −0.69, $p < .02$—see Figure 3). None of the other biochemical measures demonstrated significant correlations with severe aggression ($p > 2$).

Other Forms of Aggression and CSF 5-HIAA

With age statistically controlled, mean CSF 5-HIAA was positively correlated with threats (r = 0.52, $p < .05$, $df = 2/14$), although this was largely driven by one outlier, the most dominant subject of one group, and when this subject was removed from the analysis, the resulting correlation was no longer statistically significant (r = 0.19, $p > .50$, $df = 2/13$). None of the other competition-induced aggression categories was correlated with CSF 5-HIAA ($p > .50$).

DISCUSSION

Consistent with our hypothesis, CSF 5-HIAA concentrations were found to be stable over time. This was true during both baseline and stressful conditions, with the average sample-to-sample correlation coefficient accounting for approximately one-fourth of the variance in interindividual CSF 5-HIAA. There was also stability for HVA, and although not quite statistically significant, for NE and MHPG as well. Our findings in rhesus monkeys suggest that adult females exhibit a stable individual predisposition in the response of CNS 5HT and catecholamines, and that interindividual differences in monoamine functioning remain relatively stable across both baseline and stressful conditions, consistent with previous findings in young nonhuman

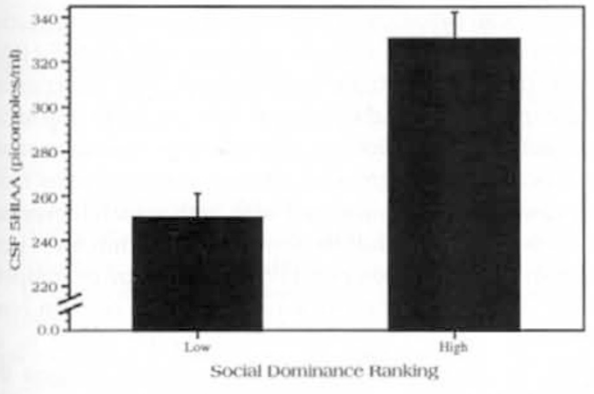

Figure 2. The mean CSF 5-HIAA concentrations in females high or low in social dominance ranking are shown. The x-axis shows a solid bar for females low (*left bar*) or high (*right*) in social dominance. The y-axis represents the concentrations of each biochemical in picomoles/ml, with a range of 200–345.

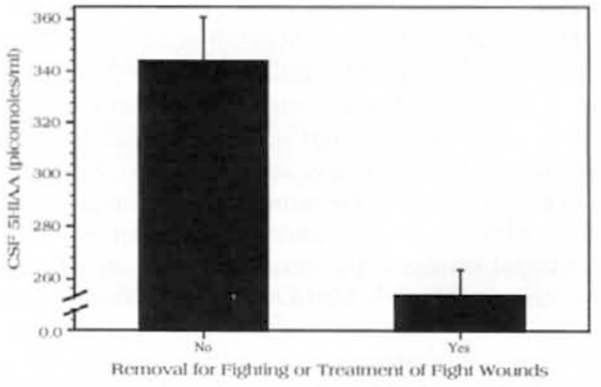

Figure 3. The mean CSF 5-HIAA concentrations in excessively aggressive females either removed or not removed from their social group for severe aggression or wound treatment are shown. The x-axis shows a solid bar for females who were not removed (*left bar*) or who were removed for excessive aggression or wound injuries (*right bar*). The y-axis represents the concentrations of each biochemical in picomoles/ml, with a range of 200–365.

primates. Although studies investigating individual stability of CSF 5-HIAA over time in humans are limited, one study of patients sampled during and following a depressive disorder demonstrated that over a short period of time, adult humans also show a high degree of stability of CSF 5-HIAA (Träskman-Bendz et al. 1984). However, not all studies in humans have shown this degree of interindividual stability of CSF 5-HIAA concentrations (Linnoila et al. 1983a).

Introduction to a novel social group has been shown to be a stressful experience for most nonhuman primates, producing an increase in glucocorticoid output (Scallet et al. 1981) and immune suppression (Gust et al. 1991). Historically, stress has been shown to increase CNS monoamine turnover in many mammals (Bliss et al. 1968; Dunn 1988; Glavin 1985; Morgan et al. 1975; Thurmond and Brown 1984). As shown by the present results, introduction to a social group increased concentrations of each of the monoamine metabolites and NE in the CSF, illustrating the stressful nature of introduction of a stranger to a group of female rhesus monkeys. It was surprising, however, that the introduction of an additional subject into an established social group, which occurred late in week 5, increased monoamine turnover essentially as much as did the initial group formation. All of the CSF monoamine metabolite concentrations were elevated by the introduction of a stranger into the social group, suggesting that the introduction of an unknown conspecific is stressful for the subjects in the established group, as well as for the individual that is introduced. This may be because the existing social structure of the group is disturbed, resulting in a challenge of individual subject's social status. In support of this interpretation, following the introduction of the new subjects, two subjects from the preexisting groups received minor veterinary treatment from aggressive interactions over the next 10 days.

Our study and others (Raleigh et al. 1986; Raleigh 1987; Raleigh et al. 1991; Raleigh et al. 1992) have demonstrated that 5HT functioning is related to social dominance ranking. Although somewhat speculative, the prolonged effect of a new animal on 5HT functioning may be a function of the reformation of the group hierarchy with the new coalitions and challenges that an additional subject imposes on the group structure. On the other hand, CSF 5-HIAA was not correlated with competitively elicited agonistic encounters used to maintain social dominance ranking, consistent with other findings showing that overall rates of aggression and the less severe, restrained aggression shown in typical day-to-day encounters between rhesus macaques are not correlated with 5HT functioning (Mehlman et al. 1994; Mehlman et al. 1995). .

CSF 5-HIAA was, however, negatively correlated with spontaneous homecage aggression that typically consisted of chases and bites. It was also correlated with and predictive of wounding and injuries that result from severe aggression, consistent with other studies of male nonhuman primates which show that unrestrained physical aggression and other forms of severe aggression are negatively correlated with CSF 5-HIAA (Higley et al. 1992a; Mehlman et al. 1994; Mehlman et al. 1995; Raleigh and McGuire 1994). The present findings are also consistent with human studies that have generally found a correlation between aggression and CSF 5-HIAA among men arrested for acts of severe aggression and violence (Brown et al. 1979; Brown et al. 1982; Lidberg et al. 1985; Linnoila et al. 1983b; Virkkunen et al. 1994a; Virkkunen et al. 1994b). Our findings on the stability of CSF 5-HIAA and its correlation with severe forms of aggression suggest that the stability of repeated aggressive behaviors in some individuals may have its basis in stable interindividual differences in 5HT functioning (Farrington 1991; Huesmann et al. 1984; Kruesi et al. 1992; Olweus 1979). These findings also suggest that the often replicated negative correlation between 5HT functioning and aggression found in males may generalize to females as well.

The present findings are also partially consistent with other studies in humans and nonhuman primates that have found correlations between the catecholamines and aggressive behavior (Brown et al. 1979; Virkkunen and Linnoila 1993) and wounding (Higley et al. 1992a). In these studies, however, aggression has been reported to be both negatively and positively correlated with MHPG and NE, whereas we found a negative correlation with NE and spontaneous acts of aggression. Differences in methodology and measurements of aggression preclude direct comparisons between studies. It is noteworthy, though, that correlations between aggression and the CSF catecholamines are less consistently found than those between aggression and CSF 5-HIAA.

To the degree that social dominance represents competent social behavior, our finding of a positive correlation between social dominance ranking and CSF 5-HIAA illustrates the relationship between 5HT functioning and competent social behavior seen in day-to-day social interactions. Our finding that threats, displacements, and occasional aggressive chases among rhesus monkeys are positively correlated with high social dominance rank serves to validate our social dominance rank assessment. In 5 years of recording this type of competitively elicited aggression, we have never seen an competitively elicited aggressive encounter result in an injury to another animal. These findings suggest the need for restrained aggression to maintain a social dominance rank. It is important to note that it was neither the most aggressive nor the oldest or largest females that acquired high social dominance. Indeed, the highest ranking females in both groups were not responsible for the wounds that the subjects who were

removed for treatment received, nor were they the females with the highest levels of spontaneous aggression, consistent with findings by Raleigh and colleges on male vervet monkeys showing that the most aggressive subjects rarely become the highest ranking (Raleigh and McGuire 1994). These findings suggest that high levels of aggression are a poor predictor of high dominance rank acquisition and that sociality and the capacity to form coalitions are better indices of a high social dominance rank. Nevertheless, our data showing a correlation between competitively elicited aggression and social dominance ranking suggest that assertiveness in response to a rank-related social challenge may play a role in maintaining social dominance rank.

In summary, we found that interindividual differences in CNS 5HT and catecholamine turnover are quite stable in adult female rhesus monkeys. Severe aggression, as measured by wounding and rates of spontaneous physical aggression, are negatively correlated with CSF 5-HIAA, but a measure of social competence in nonhuman primates, social dominance can be predicted by and is positively correlated with CSF 5-HIAA. These results suggest that CNS 5HT functioning is traitlike, showing a high degree of interindividual stability across time and setting, and also that competent social behavior may be related to proper 5HT functioning.

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