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Alteration of Frontal EEG Asymmetry during Tryptophan Depletion Predicts Future Depression

John J.B. Allen, Ph.D.¹, Katherine M. McKnight, Ph.D.¹, Francisco A. Moreno, M.D.², Heath A. Demaree, Ph.D.³, and Pedro L. Delgado, M.D.⁴

¹ Department of Psychology; University of Arizona; Tucson, AZ

² Department of Psychiatry; College of Medicine; The University of Arizona Health Sciences Center, Tucson, AZ

³ Department of Psychology; Case Western Reserve University; Cleveland, OH

⁴ Department of Psychiatry; University of Texas Health Science Center, San Antonio, TX

Abstract

Background—Tryptophan depletion (TD) reduces brain serotonin and may induce acute depressive symptomatology, especially among those with a history of Major Depression. Depressive response to TD among euthymic patients with a history of depression also predicts future depression. Better prediction might result by assessing a putative endophenotype for depressive risk, frontal electroencephalographic (EEG) asymmetry, in the context of TD.

Method—Nine euthymic history-positive participants and nine controls were administered TD. Symptomatic and EEG frontal asymmetry data were collected for 6 hours following TD, and clinical status was followed for the next 12 months.

Results—The magnitude of TD-induced change in frontal EEG asymmetry significantly predicted the development of depression during the ensuing six to twelve months, and with greater sensitivity than symptomatic response.

Limitations—The results are tempered by the small sample size.

Conclusions—Despite the limited sample size, these preliminary results suggest that TD-induced changes in frontal EEG asymmetry may provide a more sensitive indicator of risk for imminent depression than symptomatic response to TD.

Keywords

Serotonin; tryptophan depletion; brain asymmetry; mood; depression; risk; EEG

Because symptom-based diagnoses are heterogeneous (Buetler & Malik, 2002), identifying risk may be enhanced by utilizing endophenotypes (Gottesman & Gould, 2003; Iacono, 1998), measurable endogenous characteristics related to underlying mechanisms conferring risk (Hasler, Drevets, Manji, & Charney, 2004). The current study investigated risk for

Corresponding Author: John JB Allen, Ph.D., Department of Psychology, University of Arizona, Tucson, AZ 85721-0068, Email: E-mail: jallen@u.arizona.edu, Phone: (520) 621-4992, FAX: (520) 844-8270.

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depression in euthymic subjects with or without a history of depression, using a putative endophenotype for depressive risk, frontal electroencephalographic (EEG) asymmetry, in the context of manipulating serotonergic activity via tryptophan depletion (TD).

Frontal Functional Brain Asymmetry and Risk for Depression

Individuals with a history of depression, independent of current clinical status, demonstrate a pattern of asymmetrical resting EEG activity over the frontal cortex that distinguishes them from never-depressed persons (Allen, Iacono, Depue, & Arbisi, 1993; Gotlib, Ranganath, & Rosenfeld, 1998; Henriques & Davidson, 1990; Henriques & Davidson, 1991, but see Reid, Duke, & Allen, 1998). The EEG asymmetry is characterized by relatively greater left- versus right-frontal alpha-band (8–13Hz) power, which suggests decreased left-frontal activity since alpha is seen during periods of cortical quiescence (Allen, Coan, & Nazarian, 2004). In this paper, asymmetry will be discussed in terms of activity (cf. Coan & Allen, 2004), the inferred construct, rather than alpha, the putative inverse of activity. This pattern of relatively less left frontal EEG activity has been found among persons potentially at-risk for depression, such as infants with depressed mothers (Dawson, Frey, Panagiotides, Osterling, & Hessel, 1997; Jones, Field, Davalos, & Pickens, 1997) and adolescents of depressed mothers (Tomarken, Dichter, Garber, & Simien, 2004), raising the possibility that resting frontal EEG asymmetry may tap a diathesis towards risk for depression or other emotion-related psychopathology (Allen, Urry, Hitt, & Coan, 2004; Coan & Allen, 2004).

Tryptophan Depletion and Risk for Depression

Because it is reversible, tryptophan depletion (TD) has proven fruitful when examining the impact of serotonin (5-HT) on emotion in humans. TD is achieved by ingesting a 15 amino acid drink that does not contain tryptophan (TRP; Young, Smith, Pihl, & Ervin, 1985). In so doing, the rate-limiting step in the production of 5-HT – the hydroxylation of TRP into 5-hydroxy-TRP – is significantly decreased. TD has been found to decrease TRP levels to 10–50% of baseline levels, depending on the dose of amino acids utilized, within plasma (e.g., Delgado, Miller, Salomon, Licinio, Krystal, Moreno, Heninger, & Charney, 1999; Moreno, Gelenberg, Heninger, Potter, McKnight, Allen, Phillips, & Delgado, 1999; Neumeister, Nugent, Waldeck, Geraci, Schwarz, Bonne, Bain, Luckenbaugh, Herscovitch, Charney, & Drevets, 2004) and CSF (Carpenter, Anderson, Pelton, Gudín, Kirwin, Price, Heninger, & McDougle, 1998). TD led to significantly decreased brain 5-HT in rats (Moja, Stoff, Gessa, Castoldi, Assereto, & Tofanetti, 1988) and α -[^{11}C]methyl-L-tryptophan positron emission tomography (PET) in humans has found that TD causes a reduction of 5-HT synthesis to at least ten percent of baseline (Nishizawa, Benkelfat, Young, Leyton, Mzengeza, de Montigny, Blier, & Diksic, 1997).

TD produces a reversible depressive response in antidepressant-treated persons in partial remission (e.g., Delgado, Charney, Price, Aghajanian, Landis, & Heninger, 1990), and among never-depressed individuals considered “at-risk” due to a multi-generational history of Major Depression (Benkelfat, Ellenbogen, Dean, Palmour, & Young, 1994) or a personal history of depression (Moreno et al., 1999), but not among persons lacking a familial or a personal history (Barr, Heninger, Goodman, Charney, & Price, 1997; Danjou, Harmon, Lacambez, Warot, Kecskemeti, & Puech, 1990). Response to TD may thus index an underlying vulnerability to depression, and may hold prognostic value in the prediction of future depressive episodes (Moreno, Heninger, McGahuey, & Delgado, 2000). Although a depressive symptomatic response to TD may be one indicator of serotonergically-mediated vulnerability to depression, there is considerable variability in response (Van der Does, 2001) suggesting that an endophenotype (i.e., frontal asymmetry) might provide a more sensitive prognostic indicator than depressive response alone.

The Present Study

The present study evaluated the utility of TD-induced alteration of EEG asymmetry to predict the redevelopment of depression within a year among participants clinically remitted from a prior major depressive episode and matched controls without personal or family history of disorder. History positive participants were expected to exhibit a larger symptomatic response to TD, with TD-related change in EEG asymmetry predicting subsequent depression more strongly than the symptomatic response; a larger shift towards relative right activity during TD was predicted to portend an increased risk for future depression.

METHOD

Subjects

Participants recruited through newspaper advertisements were assessed with the Structured Clinical Interview for DSM-III-R (SCID). Previously-depressed subjects (History+) had at least one prior MDE, were not taking psychotropic medications, and had been in DSM-III-R defined clinical remission for at least 3 months. Exclusion criteria included any Axis I condition within the last three months, a Hamilton Rating Scale for Depression (HRSD) score greater than 10 on the 25-item version (Mazure et al 1986), history of serious medical or neurological illness, ongoing substance abuse, or current/planned pregnancy during the study. Age- and gender- matched participants were recruited who had no personal history (History-) of mental disorder or substance abuse/dependence, and no family history of mental disorder. Participants were free of medication for at least three months; three participants had no history of antidepressant medication use, with the others having received a variety of agents (Fluoxetine, Amitriptyline, Nefazodone, Sertraline, Alprazolam). No subjects were taken off medications for purposes of study participation. Inter-rater reliability for SCID and HRSD measures, calculated on a random sample of interviews for the trained raters from this and other contemporaneous studies, yielded an intraclass correlation of .90 for SCID diagnoses, and .96 for HRSD scores. After complete description of the study, and discussion of the possibility of experiencing depressive symptoms lasting from 6 to 24 hours during testing, written informed consent was obtained.

From among 14 History+ and 14 matched History- participants who completed TD, complete EEG data from right handed individuals were available for 9 History+ and 9 History- subjects, whose acute symptom data appear in other reports (Moreno et al., 1999; Moreno et al., 2000). Groups did not differ in demographic matching variables (Age Hx- = 48.3, Hx+ = 50.9; Sex, Hx- = 6F, Hx+ = 5F; handedness, Hx- = 38.1, Hx+ = 37.6, where 39 is right handed on all items). Patients averaged 2.3 MDEs.

Procedure

TRP depletion and mood rating—Two double-blind TD sessions were conducted one week apart (one full-strength 102.1g TRP-free amino acid drink, and one quarter-strength 25.5g proportionally identical TRP-free amino acid drink). The quarter-strength drink was intended to serve as a control for the full-strength drink, yet plasma TRP levels dropped to 45% of baseline during the quarter-strength depletion, compared to approximately 16% of baseline with full-strength, suggesting that the quarter-strength condition served as a weakened manipulation. Results thus focus only on the full-strength depletion.

For each TD session, participants arrived at 8 a.m. after an overnight fast, completed the HRSD, and provided blood for TRP level assessment. Interviews were conducted by trained raters blind to group status and depletion condition. Ingestion of the amino acid drink followed. Total and free plasma TRP were assayed by high performance liquid chromatography with

fluorometric detection (Anderson, Young, Cohen, Schlicht, & Patel, 1981). Six hours after amino acid drink ingestion, when TRP levels were expected to be lowest, blind HRSD ratings, EEG recordings, and blood samples were obtained. Eight hours after ingestion, blind HRSD ratings and blood samples were again obtained. Participants returned the next day for the HRSD and blood sample.

EEG recordings—EEG was recorded at baseline (pre-TD), and 6 hours after ingestion of the amino acid drink. Resting EEG was recorded for eight minutes (4 eyes open, 4 eyes closed), using tin electrodes in a stretch-lycra cap with all impedances < 5 Kohms. EEG was recorded from 19 scalp locations, referenced online to averaged mastoids (offline to Cz), with low-pass filters at 64 Hz, digitized at 256 Hz. Power spectra (derived via Fast Fourier Transform using a Hamming window) from overlapping 1 second epochs were averaged for each subject across 8 minutes to obtain alpha power (8–13 Hz).

Because asymmetrical activity was of interest, customary laterality indices (Allen et al 2004) were computed: $\ln(\text{Right}) - \ln(\text{Left})$; this score indexes the extent to which right or left alpha power is relatively greater, with larger numbers corresponding to greater relative left activity (less left-than-right alpha).

Follow-up—Subjects were monitored weekly for 1 month, monthly for 3 months, then retrospectively for depressive symptoms using the Depressive Disorder section of the SCID and the HRSD at 6 and 12 months after the lab visit. Depression during this phase was defined as a return of symptoms that met DSM-IV criteria for a MDE, plus a doubling in HRSD score with a total score ≥ 16 .

RESULTS

Tryptophan Level Changes

For each TRP measure (free and total TRP), a 2 (Group: History+ Versus History–) by 3 (Time: pre-TRP, 5 hours later, and next day) repeated measures ANOVA revealed a significant main effect of Time (all p s < .001). Post-hoc Tukey tests revealed that plasma TRP levels 5 hours after amino acid ingestion were significantly lower than measures taken at baseline or the following day. No significant Group $\times$ Time interactions were revealed (Table 1, all F s < 1.9), suggesting that any differences in symptomatic and EEG response cannot be attributed to differential depletion of plasma TRP between groups.

Symptom Changes

As in previous research, the maximum change in HRSD score within a 24 hour period was used as the measure of emotional response to TD. History+ and History– participants increased 10.3 points (s.d. = 7.1) and 2.1 points (s.d. = 1.5), respectively, a significant difference in response, $F(1,17) = 11.5$, $p < .01$.

EEG Changes

Alpha asymmetry change scores were calculated by subtracting baseline asymmetry from the asymmetry observed during depletion. Thus positive numbers reflect greater left hemisphere activity during depletion than at baseline.

TD-induced change in EEG asymmetry as a predictor of future depression

For History+ subjects, frontal EEG asymmetry changes during TD predicted depressive symptomatology 6 months following testing (HRSD score, Figure 1). Larger shifts towards relative right frontal activity during TD were associated with a *lower* chance of depression

recurrence 6 months later, opposite to the hypothesized direction of the effect. Among control subjects, similar but smaller magnitude correlations were observed.

To determine whether residual symptoms prior to depletion influenced this relationship, a hierarchical linear regression model predicting 6 month HRSD score was conducted entering subjects' pre-depletion HRSD scores as the first step, and then TD-induced change in lateral EEG asymmetry as the second step. In the absence of a significant effect for pre-depletion HRSD score ($F[1,16]=2.6$, ns) at step 1, TD-induced change in asymmetry significantly predicted 6-month depression severity ($F[1,16]=5.5$, $p<.05$). Thus TD-induced change in asymmetry was predictive of subsequent depressive symptom severity even after accounting for the potential impact of residual symptoms before depletion.

Symptomatic response and EEG asymmetry change as predictors of depression recurrence

Four of the nine History+ subjects experienced significant depression over the ensuing 12 months, 3 of them within the first 6 months. As shown in Figure 2, TD-induced change in EEG asymmetry had excellent sensitivity and specificity for predicting depression (defined by the joint DSM-IV and as HRSD score ≥ 16 criteria), even among the entire sample (History+ and History-). The results of a Receiver Operating Characteristic (ROC) analysis (Kraemer 1992; Swets et al 2000) are depicted in Figure 3, with the area under the curve AUC) summarizing how well change in EEG asymmetry discriminated those who developed depression from those who did not. Non-overlapping confidence intervals of AUC for symptomatic response and EEG response for predicting depression at 6 months indicated that TD-induced change in EEG asymmetry was a better predictor than was depressive response to TD. For predicting depression at any time during the ensuing 12 months, however, the symptomatic and EEG AUC values did not differ significantly.

DISCUSSION

TD-induced change in frontal EEG asymmetry holds potential as a sensitive and specific marker of relatively imminent risk for depression. History+ individuals experience a robust symptomatic response to TD, and TD-induced change in frontal asymmetry strongly predicted the likelihood of future depression among not only the history positive participants, but among the entire sample. These results are generally in agreement with Moreno et al. (2000), in that symptomatic response to TD predicted the subsequent development of depression over a 12-month period, yet TD-induced change in frontal EEG asymmetry was more predictive of developing depression in the ensuing 6 months than was depressive response to TD.

The nature of the relationship of change in EEG asymmetry and the subsequent development of depression would not have been obviously predicted by prevailing theories of frontal brain asymmetry (for review see Coan & Allen, 2004). The approach-withdrawal model of frontal EEG asymmetry posits that approach-related emotions such as joy and anger will be associated with relative left frontal activity, whereas withdrawal-related emotions such as sadness, fear, and disgust are associated with relatively greater right frontal activity (Coan & Allen, 2003; Coan, Allen, & Harmon-Jones, 2001; Harmon-Jones & Allen, 1997; Harmon-Jones & Allen, 1998). The model would thus suggest that, to the extent that TD increases sadness or decreases joy, a shift towards relative right frontal activity would be expected, and such a shift may predict future depression. In contrast, participants who responded to TD with a shift towards relatively greater right frontal activity were the *least* likely to develop subsequent depression. These data suggest that a robust response to provocation, in the direction predicted by the approach-withdrawal model of EEG asymmetry, appears to index *lower* risk for developing depression. A relative inflexibility of EEG asymmetry in response to TD, by contrast, portends increased risk (see Figure 2).

These data imply that potential dysfunction in frontal brain systems dependent on 5-HT may play a role in the development or recurrence of depression. Whereas subjects who remain depression-free show the predicted modulation of EEG asymmetry as a function of TD (i.e. a shift to relative right activity with TD), such modulation is largely absent in those subjects who subsequently develop depression. Altered modulation of frontal brain activity as a function of response to TD in remitted depressives has been observed using 11-fludeoxyglucose-F18 Positron Emission Tomography: Individuals showing a strong depressive response to TD had decreased metabolism in the middle frontal gyrus, thalamus, and orbitofrontal cortex relative to those who did not (Bremner, Innis, Salomon, Staib, Ng, Miller, Bronen, Krystal, Duncan, Rich, Price, Malison, Dey, Soufer, & Charney, 1997). The authors noted that deviations from expected patterns of prefrontal and limbic function may identify asymptomatic individuals at greater risk for the development of depression. Commenting specifically on lateralized frontal changes, George, Ketter, & Post, 1993) note that depression may be characterized by hypoactivity in left frontal systems normally activated by emotional challenge, an interpretation generally consistent with the present data.

Consistent with these findings, Neumeister et al (2005) observed a presumed compensatory elevation of plasma brain-derived neurotrophic factor (BDNF) during TD in healthy volunteers, but not in remitted patients. Thus depressive responses observed during TD may reflect not a primary dysfunction within 5HT systems, but a failure in compensatory systems interacting with 5-HT (Neumeister, Yuan, Young, Bonne, Luckenbaugh, Charney, & Manji, 2005). These results support using TD to challenge compensatory systems that may mediate the development of depressive symptoms or subsequent depression. One such system may involve compensatory modulation of frontal brain activity tapped by frontal EEG asymmetry.

The most notable limitation of this study is its small sample size; the results must be considered preliminary and thus warrant replication. The present small scale study, if replicated, would suggest that certain endophenotypes may be more sensitive, at least in the short term, to depression susceptibility than symptomatic response to TD. Such results would suggest that TD may prove to be an especially sensitive challenge, and frontal EEG asymmetry an especially sensitive measure, to tap serotonergic dysfunction within the frontal cortex that creates risk for the development of depression.

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Figure 1.

Correlations between TD-induced EEG alpha asymmetry change at 8 scalp regions under full-strength depletion and 6-month HRSD score by group. EEG asymmetry change is EEG asymmetry (Ln[Right]-Ln[Left]) during full strength depletion minus EEG asymmetry at baseline. Positive correlations reflect that a larger shift towards relative right activity during depletion is associated with lower depression scores six months later.

Figure 2.

Relationship between TD-induced change in lateral frontal (Ln[F8]-Ln[F7]) alpha EEG asymmetry, TD-induced change in depression severity (HRSD), and depression status across 6 and 12 months. Filled triangles depict subjects who experienced depression within 6 months of the depletion, and open triangles depict subjects who were not depressed within the first six months, but who had experienced depression by 12 months. Change in EEG asymmetry and HRSD reflect scores at tryptophan depletion minus those at baseline. Negative EEG scores reflect greater relative right cortical activity (less alpha) during depletion compared to baseline. Dichotomous classification of depressed versus nondepressed was based on meeting DSM-IV criteria for MDD and also a doubling of HRSD score and total ≥ 16 .

EEG and HRSD in the Prediction of Relapse

Figure 3.

ROC curves for predicting subsequent depression – over 6 and 12 months – on the basis of TD-induced change in lateral frontal EEG asymmetry or TD-induced depressive symptoms. HRSD = Maximum score on the Hamilton Rating Scale for Depression (HRSD) during the full strength depletion minus the baseline HRSD score. EEG = Lateral Frontal EEG alpha power asymmetry ($\text{Ln}[F8] - \text{Ln}[F7]$) during full strength depletion minus lateral frontal EEG alpha power asymmetry at baseline. AUC $\pm$ Standard Deviation of AUC is listed in the figure legend.

Table 1

Means (and standard deviations) for TRP plasma levels (mM/L) by time, and group.

Time	Free TRP		Total TRP	
	History+	History–	History+	History–
Baseline	18.4 (3.1)	16.6 (4.2)	54.6 (13.2)	53.8 (13.4)
5 hours	3.2 (2.1)	2.5 (1.8)	10.0 (7.2)	8.2 (4.6)
Next Day	16.1 (3.6)	16.5 (4.0)	56.3 (12.8)	57.2 (17.4)