

Alteration Of Frontal EEG Asymmetry During Tryptophan Depletion Predicts Risk For Future Depression



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Abstract

Tryptophan depletion (TD) reduces brain serotonin and increases acute depressive symptomatology, especially among those with a history of Major Depression. Depressive response to TD among euthymic patients 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. Nine euthymic history-positive participants and nine controls were administered TD. Symptomatic and EEG data were collected for 6 hours following TD, and clinical status was followed for the next 12 months. 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. These 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.

Introduction

Frontal EEG Asymmetry: A Putative Endophenotype indexing Risk for Depression

- □ Frontal EEG asymmetry inferred from asymmetrical alpha power over homologous sites
 - □ relatively less left frontal activity, surmised by relatively greater left frontal alpha
- Differentiates depressed from nondepressed individuals
- Differentiates previously depressed but euthymic persons from never depressed individuals
- □ Predicts emotional responses to emotional provocation (e.g. films, separation)
- □ Is stable in clinical and nonclinical populations

Tryptophan Depletion (TD) and Depressive Risk

- Tryptophan (TRP) a precursor to serotonin (5-HT)
- □ Reductions of plasma TRP lead to significant reductions in brain 5-HT
- \Box TD produces a reversible depressive response in:
 - Antidepressant-treated persons in partial remission
 Never-depressed individuals considered "at-risk" due to a multi-generational history of Major Depression
 - Euthymic individuals with a personal history of depression
- □ These findings suggest that response to TD may index an underlying vulnerability to depression
 - □ TD response may also hold prognostic value in the prediction of future depressive episodes

Study Rationale

- Although a depressive symptomatic response to TD may be one indicator of serotonergically-mediated vulnerability to depression, there is considerable variability in response
- □ Therefore an endophenotype (i.e., frontal asymmetry) could possibly provide a more sensitive prognostic indicator than depressive response alone.

Hypotheses

- Participants with a history of depression (History +) would have a more pronounced symptomatic response to TD
- □ Depletion-related change in EEG asymmetry would predict subsequent depression more strongly than the symptomatic response to depletion
 - □ a larger shift towards relative right activity during TD should prognosticate an increased risk for future depression.

Method

Subjects

- □ Nine Euthymic subjects with history (History +) of Major Depressive Disorder (confirmed via SCID)
 - No Medication
 - Clinical Remission > 3 months
- $\hfill\square$ Nine Matched controls with no history of psychopathology (History -)

Procedure

- □ Tryptophan Depletion (TD)
 - Amino Acid Drink deficient in TRP decreases the rate-limiting step in the production of 5 HT: the hydroxylation of TRP into 5-hydroxy-TRP
 Two double blinds session:
 - Full strength reduced TRP levels to 16% of baseline
 - Quarter strength intended as control, but reduced TRP levels to 45% of baseline
 - Because the quarter-strength condition served as a weakened manipulation, results will focus only on the full-strength depletion.

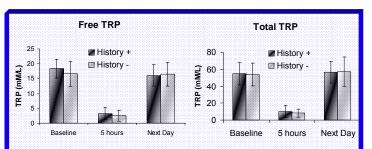
EEG Assessments

- Resting EEG assessed for 8 min
 - Baseline: Assessed one week prior to depletion
 - Depletion: Assessed 6 hours after ingestion of Amino Acid Drink
- Physiological Recording and Reduction
- 19-lead EEG
- Alpha Asymmetry scores computed using Ln(Right)-Ln(Left) for homologous leads

Symptom Assessment

- □ Hamilton Rating Scale for Depression (HRSD)
 - Pre-depletion, 6 hours after ingestion of Amino Acid drink, post depletion
 - Maximum change within 24 hour period used as measure of response to TRP depletion
- □ HRSD administered at 6 months and 12 months after TRP depletion
 - Depression during follow-up defined based on DSM-IV criteria for Major Depressive Episode, plus a doubling in HRSD score with a total score ≥ 16.

Results



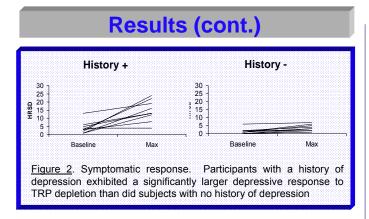
<u>Figure 1</u>. TRP levels were significantly lowered as a result of TRP depletion, but with no differential effect for History + or History – subjects, suggesting that any differences in symptomatic and EEG response cannot be attributed to differential depletion of plasma TRP between groups..



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PAGE 2



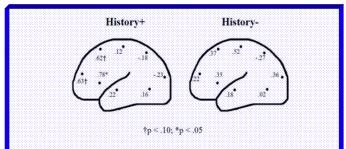
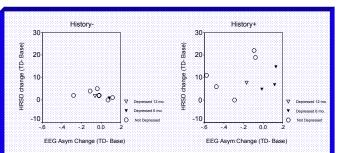


Figure 3. Correlations between TD-induced EEG alpha asymmetry change at 8 scalp regions under full-strength depletion and 6-month HRSD score by group. EEG asymmetry change is EEG asymmetry (Ln[Right]-Ln[Left]) during full strength depletion minus EEG asymmetry at baseline. Positive correlations reflect that a larger shift towards relative right activity during depletion is associated with lower depression scores six months later.

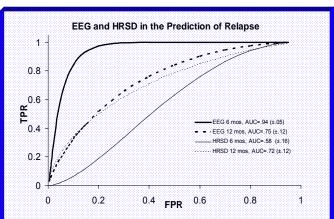


<u>Figure 4</u>. Relationship between TD-induced change in lateral frontal (Ln[F8]-Ln[F7]) alpha EEG asymmetry, TD-induced change in depression severity (HRSD), and depression status across 6 and 12 months. Filled triangles depict subjects who experienced depression within 6 months of the depletion, 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 \geq 16.

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Handout available at: http://www.psychofizz.org

Results (cont.)



<u>Figure 5</u>. 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 (Ln[F8]-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.

Discussion

- □ TD-induced change in frontal EEG asymmetry holds potential as a highly sensitive and specific marker of relatively imminent risk for depression
 - □ Although symptomatic response to TD predicted the subsequent development of depression over a 12-month period, TD-induced change in frontal EEG asymmetry was more strongly predictive of the development of depression over the ensuing 6 months
- □ The nature of the relationship of change in EEG asymmetry to TD and to the subsequent development of depression would not have been obviously predicted by prevailing theories of frontal brain asymmetry
 - Depression and negative affect associated with greater relative right frontal activity
 - Yet participants who responded to TD with a shift towards relatively greater right frontal activity were the *least* likely to develop subsequent depression
 - □ 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
 - □ Findings imply that a potential dysfunction in frontal brain systems dependent on 5-HT may play a role in the development or recurrence of depression
 - □ Consistent with the present findings, a presumed compensatory elevation of plasma brain-derived neurotrophic factor (BDNF) has been observed in healthy volunteers, but remitted patients were unable to mount such a response.
 - □ These findings suggest that depressive responses observed during TD may not reflect a primary dysfunction within the 5HT system per se, but a failure in compensatory systems potentially interacting with 5-HT