

BIPOLAR DISORDER AS FAILURE OF INTERHEMISPHERIC INHIBITION

TRASTORNO BIPOLAR COMO FALLA DE LA INHIBICIÓN INTERHEMISFÉRICA

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RESUMEN

Este artículo tiene tres partes. En la primera parte presentamos la hipótesis de G. Munévar sobre la neurociencia del trastorno bipolar. Según esta hipótesis, el trastorno bipolar es un fallo de la inhibición interhemisférica en el lóbulo frontal. Cuando la activación eléctrica del lado izquierdo supera a la del derecho, el lóbulo frontal izquierdo domina, lo que lleva a estados exagerados de euforia (u otros que también constituyen manía). La dominación en la activación del lado derecho, a su vez, conduce a estados de depresión. La literatura de neurociencia ya ofrece una gran cantidad de apoyo para esta hipótesis, como explicamos. La segunda parte describe nuestro propio estudio que utiliza la estimulación de corriente continua transcraneal (tDCS) para disminuir con éxito los estados de ánimo positivos en 25 individuos sanos. Este resultado se obtuvo al conectar los electrodos tDCS al hemisferio derecho del lóbulo frontal de los participantes mientras observaban imágenes en movimiento (de la Escala Internacional de Imágenes Afectivas), lo que concuerda con la hipótesis. La tercera parte proporciona un esquema de trabajo para un nuevo estudio potencial para establecer la hipótesis de falla de inhibición interhemisférica del lóbulo frontal en el trastorno bipolar. Este estudio usaría una nueva tecnología de imágenes cerebrales funcionales basada en qEEG: tomografía electromagnética ponderada estandarizada de baja resolución (swLORETA). Si tiene éxito, este estudio puede conducir a una terapia de estimulación eléctrica para pacientes con trastorno bipolar.

Palabras Clave: Neurociencia, trastorno bipolar, estimulación de corriente continua transcraneal, tomografía electromagnética ponderada estandarizada de baja resolución.

ABSTRACT

This paper has three parts. In the first part we introduce G. Munévar's hypothesis about the neuroscience of bipolar disorder. According to this hypothesis, bipolar disorder is a failure of interhemispheric inhibition in the frontal lobe. When the electrical activation of the left side overwhelms that of the right, the left frontal lobe dominates, thus leading to exaggerated states of elation (or others that also constitute mania). Dominance in activation by the right side, in turn, leads to states of depression. The neuroscience literature already offers a large amount of support for this hypothesis, as we explain. The second part describes our own study using transcranial direct current stimulation (tDCS) to successfully decrease positive moods in 25 healthy individuals. This result was obtained by connecting the tDCS electrodes to the right hemisphere of the frontal lobe of participants while they viewed arousing pictures (from the International Affective Picture Scale), which accords with the hypothesis. The third part

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gives a working outline for a potential new study to establish the hypothesis of frontal lobe interhemispheric inhibition failure in bipolar disorder. This study would use a new functional brain imaging technology based on qEEG: standardized weighted low-resolution electromagnetic tomography (swLORETA). If successful, this study may lead to electrical-stimulation therapy for bipolar disorder patients.

Key Words: Neuroscience, Bipolar Disorder, Transcranial Direct Current Stimulation, Standardized Weighted Low-Resolution Electromagnetic Tomography.

1. Background and Hypothesis

By the 1990s it had been noticed that lesions to the right frontal lobe lead to manic episodes and lesions to the left frontal lobe lead to depression (Davidson, 1995). This provided a clue to one of us, Munevar, about the nature of Bipolar Disorder. Of course, bipolar patients do not have such lesions to the frontal lobes. What brain states, however, could be temporary equivalents to such lesions? They must be temporary, since in Bipolar Disorder we have alternations between manic and depressive phases, with “neutral” periods called “euthymic”. His tentative answer: a failure of interhemispheric inhibition in the frontal lobes. Also important to the genesis and plausibility of this paper’s hypothesis is an analogy to attention. In mechanisms of attention the right and left hemispheres inhibit each other but tend to reach an equilibrium between them. Otherwise, if the left side, say, overwhelms the right, a person would be unable to experience consciously objects presented to his or her left visual field (which is handled by the right hemisphere) when similar objects are presented to the right visual field. This is the disturbing phenomenon called “extinction,” caused by lesions to the right parietal lobe (Gazzaniga, 2009). Our hypothesis is, then, that a similar failure of interhemispheric inhibition takes place in the frontal lobes of bipolar patients. This means that when the electrical activation of the left side overwhelms that of the right, the left frontal lobe dominates, thus leading to exaggerated states of elation (mania). Dominance in activation by the right side, in turn, lead to states of depression.

In addition to extinction, another interesting case of possible interhemispheric inhibition occurs in binocular rivalry, a phenomenon that occurs when incompatible inputs are received by the left and right visual fields. Since the brain is unable to combine them (unlike depth perception, for example), it perceives first one of the two and, a few seconds later, the other. In studies with subjects suffering from mental disorders, Pettigrew and Miller (1998, 2003) found that those subjects had the same time responses as normal subjects, with

one exception: bipolar patients. Their “switching time” between visual fields was as much as three times longer! Influenced by this research, Dodson (2003) decided to try one of its aspects on a patient in severe manic state that did not respond to any of the available treatments. Applying cold water to the right ear during binocular rivalry forces a switch to the other visual field. When Dodson applied cold water to the right ear of his patient, the manic symptoms subsided (after a short period of vertigo). The manic episode was gone for 24 hours but began to return and was in full swing within 72 hours. Dodson repeated the procedure with the same results. The explanation in the case of binocular rivalry is that the cold water in the ear disturbs the mechanism of attention. Dodson’s experiment suggests an overlap with such mechanism also in the case of bipolar disorder, beyond the analogy offered previously.

It should be mentioned that the neuroscience literature already offers a good amount of support for this hypothesis. For example, higher electrical activity in the left frontal lobe leads to better control of negative emotions, which are associated with depression (Jackson, 2003). There is greater relative right prefrontal activation in depression (Imaging: Bench, 1995; Martinot, 1990. EEG: Henriques & Davidson, 1991). Likewise, there are larger left activation asymmetries in mania (Migliorelli, 1993). And an fMRI study showed hemispheric asymmetry for affective stimuli (Beraha, 2012). Moreover, activation of the left hemisphere with transcranial magnetic stimulation (TMS) (George, Wassermann, Kimbrell, Little, Williams, Danielson, Greenberg, Hallett, & Post, 1997) and transcranial direct current stimulation (tDCS) (Brunoni, Valiengo, Baccaro, Zanao, de Oliveira, Goulart, & Fregni, 2013) helps reduce depression, as should be expected from the hypothesis. Indeed, TMS is approved in the USA for treating depression.

Pettigrew and Miller have tried to explain bipolar disorder as a failure of an interhemispheric mechanism based on Circadian rhythms, although both manic and depressive phases may last not just

days but even weeks in some patients. It seems to us that an explanation free of such difficulties, and consistent with our hypothesis, is provided by the work with stem cells done in K.S. O'Shea's lab (2014), which is supported by findings in F. Gage's lab (2017). O'Shea observed that cultures of neurons developed from skin cells of bipolar patients exhibited electrical hyper-activity, likely because neurons coming from bipolar patients had more calcium ion channels. This unusual hyperactivity may explain why the frontal lobe inter-hemispheric inhibition mechanism gets stuck in a manic or a depressive phase, instead of remaining at near equilibrium most of the time.

Some early attempts to use TMS on bipolar disorder were "preliminary but intriguing" (Agarkar, Mahgoub, & Young, 2011). It seemed to us that a first fruitful step, in accordance with our hypothesis, would be to alter high positive emotions (such as elation) in normal subjects by using electrical stimulation on the right frontal lobe, before moving on to the far more difficult task of electrically stimulating bipolar disorder patients in a manic phase. In this paper we will present a study in which we took precisely such a first step, and then propose more elaborate experiments that may offer very strong evidence for (or against) our hypothesis.

Brunoni *et al.* (2013) used tDCS on patients with major depressive disorder. They placed the anodal electrode on the left side of the prefrontal lobe and the cathodal electrode on the right side of the prefrontal lobe. The anodal electrode increased cortex excitability on the left side of the prefrontal lobe while the cathodal electrode decreased excitability on the right side. It was found that participants who received tDCS alone and tDCS mixed with sertraline hydrochloride had a higher decrease in the scores for the Montgomery-Asburg Depression Rating Scale.

Our own tDCS study's principal investigator was Alyssa Shaver, with supervision by Gonzalo Munevar on the design and by Matthew Cole in the data analysis. We changed the anodal and cathodal electrodes, relative to the Brunoni *et al.* study to see whether we could provide evidence that tDCS can be used for a treatment for mania in people with bipolar disorder. By placing the anodal electrode on the right side of the prefrontal lobe and the cathodal electrode on the left side of the prefrontal lobe we hoped to decrease the emotions

associated with mania (such as elation) in healthy individuals. As suggested earlier, if stimulation can decrease these feelings in healthy individuals, then this would give us an incentive to develop a tDCS therapy for patients with bipolar disorder who are experiencing a manic episode.

Using a transcranial direct current stimulator (tDCS) we tried to reduce positive feelings by activating the right side of the prefrontal lobe and deactivating the left side of the prefrontal lobe while participants viewed arousing pictures from the International Affective Picture Scale (IAPS). Participants rated the pictures and then we gauged their mood during electrical stimulation and compared it to the picture ratings and the mood during sham stimulation. We hypothesized that by stimulating the right hemisphere we would reduce positive moods. By conducting this study, we hoped to open up an opportunity to further the investigation of the mechanisms that cause bipolar disorder and create a way to develop alternative therapies for bipolar disorder.

Methods

Participants

In this study there were twenty four participants, five male and nineteen female. They consisted of individuals aged nineteen to sixty-four. Individuals were not allowed to participate in the study if the individual or any immediate family member has a known history of a mental disorder (ie. depression, bipolar disorder, autism, etc). All participants were provided with an informed consent form (in accordance with Lawrence Technological University Institute Review Board) that was completed prior to the experiment in order to participate in the study.

Apparatus

To perform this experiment we used the following materials:

- Transcranial Direct Current 1 ch Stimulator (tDCS)
- 5 x 5 centimeter electrodes
- Neoprene head harness
- Dual wire electrode cable
- Survey Monkey
- Microsoft Excel 2013
- Lenovo Yoga Laptop
- International Affective Picture Scale (IAPS)

- Positive and Negative Affect Schedule (PANAS)

Design and Procedure

Participants in this study first underwent a control session (Session 1) and then an experimental session (Session 2). Half of the participants were shown Picture Set 1 during Session 1 and Picture Set 2 during Session 2. The other half of the participants were shown Picture Set 2 during Session 1 and Picture Set 1 during Session 2. The valence mean and the arousal mean were similar for both picture sets (see Table 1). Each of these sessions happened during the same meeting. In Session 1 participants were hooked up to the tDCS but stimulation was turned on for only two minutes in order to create “sham” stimulation. During the sham stimulation, the participant believed that he or she was receiving the stimulation but did not actually receive any stimulation beyond the first two minutes. The electrodes were placed in the same positions during the control session as during the experimental session. While hooked up to sham stimulation they viewed 34 arousing pictures selected from the International Affective Picture Scale (IAPS) and 12 neutral pictures. The pictures were shown using Survey Monkey. Participants were asked to rate the pictures on a scale from 1 to 5, 1 being not at all excited and 5 being extremely excited, to express how the picture made them feel. At the end of the sham session participants were also asked to complete a Positive and Negative Affect Schedule (PANAS) (see Figure 1).

The second part of the meeting was the experimental session. During this session the active electrode was placed in a way that covered both the Fp2 and AF4 positions. The reference electrode was placed in a way that covered both the Fp1 and AF3 positions (See Figure 2). After the electrodes were placed the participants were stimulated for five minutes as described above, for a total of 25 minutes. After five minutes the participants were shown a different set of 34 arousing pictures and 12 neutral pictures that were similar to the pictures that were shown during the control session while still receiving stimulation. They were asked to rate the pictures on the same scale they were given during the control session. At the end of the experimental session the participants were asked to complete a PANAS again.

Data Analysis

Data were entered into Microsoft excel for descriptive and inferential statistics. Descriptive statistics were comprised of mean, standard deviation, and standard error of the mean for scores on Session 1 and Session 2. Inferential statistics were comprised of paired samples t test to test the null hypothesis that the difference between scores on sessions 1 and 2 was zero. Specifically, H_0 : Mean session 1 - mean session 2 = 0. Statistical significance was evaluated at the 95% level of significance (i.e., $\alpha = 0.05$, two-tail test of significance).

Results

We ran a paired samples t-test on the results of the study in order to see if the independent variable (the stimulation) was effective. The results are significant at the 95% level of significance: $t = 2.61$, $df = 23$, $p = 0.016$. Specifically, the mean (SD) score of session 1, 2.50 (0.80), is significantly higher than the mean (SD) score of session 2, 2.34 (0.75). These results suggest that the intervention was effective. Figure 3 shows the mean (+/- SEM) score on session 1 and session 2. As shown, the mean score on session 1 was higher than the mean score on session 2 ($p < 0.05$). We initially presented these results to the Michigan Academy of Sciences (2017).

Discussion

The results from the study support our hypothesis that by placing the anodal electrode on the right side of the prefrontal lobe and the cathodal electrode on the left side of the prefrontal lobe we would decrease in healthy individuals some emotions normally associated with mania in bipolar patients. This indicates that areas in the prefrontal lobe are associated with emotion and gives support for the interhemispheric switch theory in which individuals with bipolar disorder may have a dysfunction in the mechanism that allows the two hemispheres to switch.

The evidence provided by this study lends plausibility to the attempt to use tDCS for treating mania in patients with bipolar disorder. Since we were able to decrease in healthy subjects moods associated with mania in patients with bipolar disorder, it may be possible to decrease these same elevated moods in bipolar patients when they are experiencing mania. A potential study would be the

mania counterpart to the tDCS study by Brunoni *et al.* (2013) on patients with major depressive disorder.

Potential Future Experiment

G. Munevar is collaborating with Douglas MacDonald and Adnan Jaber to design an experiment that would establish the hypothesis of this paper. The actual study would require a larger team. What follows is a working outline for it. This study of Frontal Lobe Interhemispheric Inhibition Failure in Bipolar Disorder would use a new functional brain imaging technology based on qEEG, standardized weighted low-resolution electromagnetic tomography (swLORETA). The spatial resolution is good, while the temporal resolution is excellent, down to perhaps 2 milliseconds. The latter is a great advantage over fMRI, which has a temporal resolution of seconds. Another great advantage of swLORETA is the cost, which is in the thousands of dollars, as compared to the millions of dollars that need to be invested in an fMRI lab. It is also highly portable and flexible, which should be advantageous in experiments with bipolar disorder patients. As examples of the use of swLORETA in neuroscience research the reader may consult Soler (2007) and Cebolla (2017). For a very accessible introduction to this rather new technology we have included a reference to a video by Robert Thatcher.

This experiment would have two phases.

Phase I Experiment

Using the swLORETA equipment, we will carry out a Within Subject study on 40 bipolar participants. We will determine the electrical activation in each patient's frontal lobes during euthymic, depressive and manic phases. We will look both at the power but also, importantly, at the neuroimaging, so as to determine the extent of the activation, as well as the connectivity to other brain regions (which will help us explain this brain disorder better). We will make two measurements in each type of phase per participant. Given the research referenced above, and some additional considerations mentioned below, we predict relatively higher electrical activation of the left frontal lobe in manic phases, and relatively higher electrical activation of the right frontal lobe in depressive phases.

Phase II Experiment

In this phase we will test whether it is possible to restore equilibrium of inhibition between the two frontal lobes of bipolar patients by the use of electrical stimulation: transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). TMS uses a magnetic coil which, when applied to a section of the scalp, induces an electrical current in the brain area underneath. tDCS applies a small direct current (less than 2 milliamps) to an electrode placed on the scalp. We will compare the effectiveness of the two devices.

We want to determine whether electrical stimulation can change the temporary imbalance present in manic and depressive phases. We will divide the participants between two groups of 20 each. We will first examine mania. One group will receive sham TMS and then regular TMS on the right frontal lobe, with determination of activation by swLORETA before and after sham and regular stimulation. The other group will do likewise with tDCS.

The same procedure cannot be followed in measuring activation during depressive episodes. The reason is that the sham setting can be easily recognized by subjects as such once they have experienced regular activation (Mennemeier, 2009). Thus, we will add an additional group of 20 bipolar participants in a depressive phase. They will receive a sham-regular activation of TMS in the left frontal lobe, mirroring the procedure of the mania group. Again, in all groups we will determine the prior and subsequent electrical lobe activation, both power and neuroimaging, using swLORETA.

Eventual Application of the Research Based on the Hypothesis

Success in this potential study would lead to a follow-up clinical study in which bipolar patients would receive electrical activation with TMS or tDCS, depending on their individual activation characteristics in the two sides of the frontal lobe, in order to control their elevated moods of mania or depression. This new approach might work in conjunction with lower doses of medication than those hitherto required to control their moods, and in some cases might do away with the need for medication altogether.

Table 1. Valence and Arousal Mean for Picture Sets (IAPS)

<i>Picture Set 1</i>				<i>Picture Set 2</i>			
Description	Slide No.	Valence Mean	Arousal Mean	Description	Slide No.	Valence Mean	Arousal Mean
Skydivers	8185	7.57	7.27	Erotic Female	4220	8.02	7.17
Skier	8030	7.33	7.35	Erotic Female	4290	7.61	7.2
Rollercoaster	8492	7.21	7.31	Sky Divers	5621	7.57	6.99
Sailing	8080	7.73	6.65	Rafting	8370	7.77	6.73
Money	8501	7.91	6.44	Skier	8190	8.1	6.28
Water Skier	8200	7.54	6.35	Erotic Couple	4660	7.4	6.58
Roller Coaster	8490	7.2	6.68	Gymnast	8470	7.74	6.14
Erotic Couple	4659	6.87	6.93	Sky surfer	8186	7.01	6.84
Sailboat	8170	7.63	6.12	Erotic Couple	4668	6.67	7.13
Cliff Divers	8180	7.12	6.59	Erotic Couple	4670	6.99	6.74
Rafters	8400	7.09	6.61	Rollercoaster	8499	7.63	6.07
Cupcakes	7405	7.38	6.28	Parachute	8163	7.14	6.53
Erotic Couple	4608	7.07	6.47	Hiker	5629	7.03	6.55
Bungee	8179	6.48	6.99	Erotic Couple	4800	6.44	7.07
Erotic Couple	4652	6.79	6.62	Erotic Couple	4695	6.84	6.61
Erotic Couple	4607	7.03	6.34	Erotic Couple	4687	6.87	6.51
Astronaut	5470	7.35	6.02	Erotic Couple	4681	6.69	6.68
Erotic Female	4311	6.66	6.67	Skier	8034	7.06	6.3
Cliff diver	8178	6.5	6.82	Erotic Couple	4664	6.61	6.72
Erotic Couple	4810	6.56	6.66	Erotic Couple	4680	7.25	6.02
Pilot	8300	7.02	6.14	Erotic Couple	4698	6.5	6.72
Erotic Couple	4689	6.9	6.21	Erotic Couple	4656	6.73	6.41
Erotic Couple	4658	6.62	6.47	Erotic Couple	4694	6.69	6.42
Erotic Couple	4690	6.83	6.06	Hiker	8158	6.53	6.49
Erotic Couple	4676	6.81	6.07	Jaguar	1650	6.65	6.23
Surfers	8206	6.43	6.41	Erotic Couple	4643	6.84	6.01
Hang Glider	5626	6.71	6.1	Erotic Couple	4697	6.22	6.62
Erotic Couple	4683	6.17	6.62	Hang Glider	8161	6.71	6.09
City	7650	6.62	6.15	Erotic Couple	4677	6.58	6.19
Erotic Couple	4693	6.16	6.57	Skier	8193	6.73	6.04
Erotic Couple	4651	6.32	6.34	Erotic Couple	4611	6.62	6.04
Erotic Couple	4666	6.24	6.1	Wing walker	8341	6.25	6.4
Erotic Couple	4672	6	6.29	Erotic Male	4490	6.27	6.06
Motorcycle	8251	6.16	6.05	Ice Climber	8191	6.07	6.19
Grand Mean		6.88	6.49	Grand Mean		6.93	6.49

Figure 1. The Positive and Negative Affect Schedule (PANAS) and rating scale

1	2	3	4	5
Very slightly or not at all	A Little	Moderately	Quite a Bit	Extremely
_____ 1. Interested		_____ 11. Irritable		
_____ 2. Distressed		_____ 12. Alert		
_____ 3. Excited		_____ 13. Ashamed		
_____ 4. Upset		_____ 14. Inspired		
_____ 5. Strong		_____ 15. Nervous		
_____ 6. Guilty		_____ 16. Determined		
_____ 7. Scared		_____ 17. Attentive		
_____ 8. Hostile		_____ 18. Jittery		
_____ 9. Enthusiastic		_____ 19. Active		
_____ 10. Proud		_____ 20. Afraid		

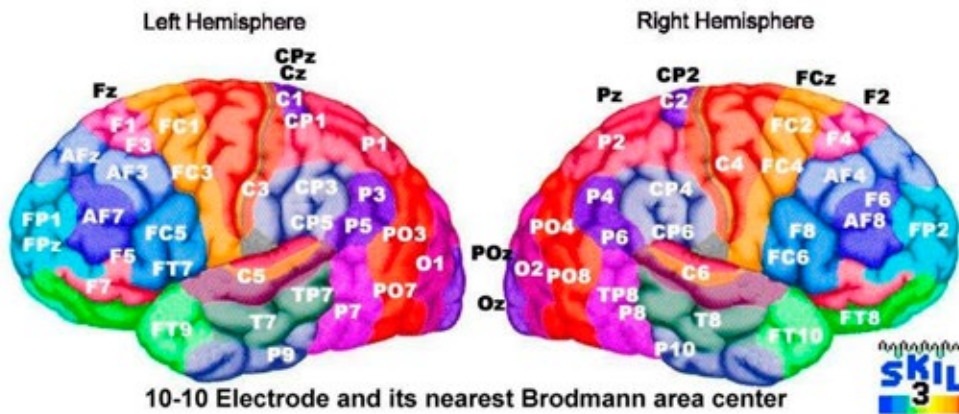
Scoring Instructions:

Positive Affect Score: Add the scores on items 1, 3, 5, 9, 10, 12, 14, 16, 17, and 19. Scores can range from 10 – 50, with higher scores representing higher levels of positive affect. Mean Scores: Momentary = 29.7 (SD = 7.9); Weekly = 33.3 (SD = 7.2).

Negative Affect Score: Add the scores on items 2, 4, 6, 7, 8, 11, 13, 15, 18, and 20. Scores can range from 10 – 50, with lower scores representing lower levels of negative affect. Mean Score: Momentary = 14.8 (SD = 5.4); Weekly = 17.4 (SD = 6.2)

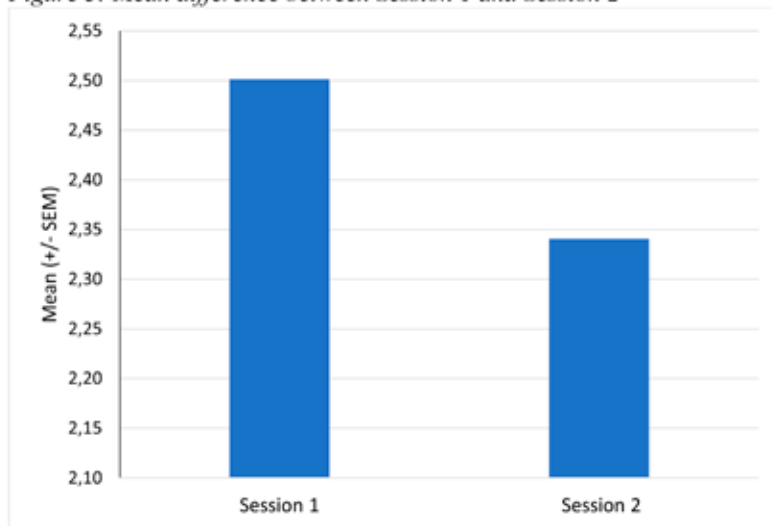
Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: The PANAS scales. *Journal of Personality and Social Psychology*, 54(6), 1063-1070.

Figure 2: Electrode Placement



Electrode and Its Nearest Brodmann Area Center [Digital image]. (n.d.). Retrieved June 22, 2016, from http://www.brainm.com/software/pubs/dg/BA_1020_ROI_Talairach/nearestteeg.htm.

Figure 3: Mean difference between Session 1 and Session 2



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