

UCLA

UCLA Previously Published Works

Title

Neurophysiologic effects of repeated exposure to antidepressant medication: Are brain functional changes during antidepressant administration influenced by learning processes?

Permalink

<https://escholarship.org/uc/item/9q17v6pt>

Journal

Medical Hypotheses, 81(6)

ISSN

0306-9877

Authors

Hunter, Aimee M
Cook, Ian A
Abrams, Michelle
et al.

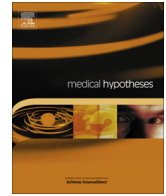
Publication Date

2013-12-01

DOI

10.1016/j.mehy.2013.09.016

Peer reviewed



Neurophysiologic effects of repeated exposure to antidepressant medication: Are brain functional changes during antidepressant administration influenced by learning processes?



Aimee M. Hunter^{*}, Ian A. Cook, Michelle Abrams, Andrew F. Leuchter

Laboratory of Brain, Behavior, and Pharmacology, and the UCLA Depression Research & Clinic Program, Semel Institute for Neuroscience and Human Behavior at UCLA, Los Angeles, CA, USA

Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

ARTICLE INFO

Article history:

Received 6 June 2013

Accepted 8 September 2013

ABSTRACT

Major Depressive Disorder (MDD) is a lifelong and recurrent illness, such that many individuals require multiple courses of antidepressant medication treatment. While some patients respond completely to each course of treatment, many do not, and with each unsuccessful antidepressant trial the likelihood that a patient will respond decreases. This raises the possibility that neurophysiologic response in subsequent antidepressant treatment may be influenced by learning processes including sensitization, habituation, and/or classical conditioning. Classical conditioning would entail the association of cues such as pill-taking (conditioned stimuli; CS) with the effects of active medication (unconditioned stimulus; US), such that later presentation of the CS alone would come to elicit a conditioned response (CR). Such effects could be revealed by blinded administration of placebo following a period of treatment with active medication. Habituation effects (tolerance), or sensitization effects (increased response), which require only repeated exposure to a stimulus, might be evidenced after repeated courses of antidepressant treatment. Knowledge of how learning processes impact neurophysiologic response to successive courses of antidepressant treatment would have relevance for clinical populations. Specific hypotheses, however, may be tested in healthy non-clinical samples to avoid potential confounding factors related to severity or chronicity of illness. Learning theories would suggest two hypotheses: (1) neurophysiologic response to placebo will differ between subjects who were previously treated with antidepressant treatment as compared to placebo (classical conditioning hypothesis); and (2) neurophysiologic response to an initial course of antidepressant treatment will differ from response to a repeated course of antidepressant treatment. Pilot data addressed these hypotheses in healthy never-depressed women who had previously received four weeks of venlafaxine IR, 150 mg (antidepressant-experienced subjects; $n = 2$) or matching placebo (antidepressant-naïve subjects; $n = 4$) under double-blind conditions. Six-and-a-half years later, we treated these six women with placebo for one week, followed by four weeks of double-blind treatment with venlafaxine IR, 150 mg. Brain functional changes over the course of treatment were assessed using quantitative electroencephalography (qEEG) to compare prefrontal neurophysiologic responses between subjects who had, versus had not, previously been exposed to venlafaxine. Antidepressant-experienced versus antidepressant-naïve subjects showed greater decreases in prefrontal cordance (PFC) during venlafaxine administration (sensitization hypothesis) but did not show significantly different PFC changes during treatment with placebo in this small pilot sample (classical conditioning hypothesis). Data suggest that brief treatment with antidepressant medication may have an enduring impact on neurophysiologic responses to a subsequent course of antidepressant treatment. Hypotheses should be tested in larger samples.

© 2013 Elsevier Ltd. All rights reserved.

Introduction

Antidepressant medications are the most prescribed drugs in the United States [1] and are used by an estimated 11% of

Americans ages 12 and older [2]. Whereas some persons undergo only a single course of antidepressant treatment, patients with Major Depressive Disorder (MDD) commonly suffer recurring depressive episodes that require multiple courses of treatment over

^{*} Corresponding author. Address: 760 Westwood Plaza, Rm. 57-455, Los Angeles, CA 90024-1759, USA. Tel.: +1 (310) 206 2237; fax: +1 (310) 825 7642.
E-mail address: amhunter@ucla.edu (A.M. Hunter).

successive episodes of illness. Knowledge of how the brain responds to multiple courses of antidepressant medication may have implications for treatment. Neurophysiologic response to antidepressant treatment may change over subsequent periods of drug exposure due to learning processes.

A major challenge in the treatment of MDD is treatment resistance: when an individual fails to respond to a course of medication treatment, he or she is commonly “switched” to a different medication, and with each successive change in medication, the likelihood of response diminishes. The decreasing likelihood of response in subsequent trials raises the possibility that in some patients, response to pharmacologic agents may be subject to learning effects including sensitization, habituation, and classical conditioning effects [3–6]. Repeated exposure to antidepressant medication may constitute a conditioning procedure wherein cues in the treatment environment including the act of pill taking become conditioned stimuli (‘CSs’) due to their pairing with the physiologic effect of drug (the unconditioned stimulus or ‘US’). Subsequent exposure to the CSs alone can then produce a conditioned response (CR) that either mimics the drug effect (an agonistic process thought to underlie some “placebo responses”), or counters the drug effect as in a “compensatory response” (an antagonistic process that is a putative mechanism of drug tolerance). Conditioned stimuli have been shown to modulate behavioral and physiological effects of drugs in the experimental setting [3,7,8]. Other learning processes, sensitization and habituation, require only repeated exposure to a single stimulus, and may underlie increased and decreased responsivity, respectively. Because most patients with MDD experience repeated exposure to antidepressants, these phenomena may have great relevance for clinical pharmacotherapy [9].

Sustained or repeated exposure to a drug can elicit different forms of conditioning including compensatory physiologic responses resulting in tolerance [10]. In the context of antidepressant treatment, a clinical literature suggests that the clinical efficacy of antidepressant treatment may decrease over prolonged or repeated administrations [11], such as in ‘tachyphylaxis’ [12–16]. Alternatively, repeated presentation of drug can also induce sensitization effects, i.e., increased physiologic and behavioral responses [17,18] such as in stimulant-induced behavioral sensitization [19–22].

Preliminary evidence suggests that the neurophysiologic response to an initial course of antidepressant treatment differs from the neurophysiologic response during a later course of treatment. Such brain functional changes during antidepressant treatment have been studied using quantitative electroencephalography (qEEG). Specifically, qEEG cordance, a measure that is correlated with cerebral perfusion [23], has repeatedly been demonstrated to capture prefrontal effects of antidepressant treatment in patients with MDD [24–29] and in healthy subjects [30]. Previously, we found that ‘antidepressant-experienced’ subjects differed from ‘antidepressant-naïve’ subjects in their prefrontal neurophysiologic response to blinded treatment with antidepressant medication or placebo [31]. That is, we observed a larger prefrontal neurophysiologic response to medication or placebo among subjects who had a prior history of antidepressant treatment. The larger neurophysiologic response of antidepressant-experienced subjects during treatment with placebo would likely reflect classical conditioning effects, while the increased neurophysiologic response of antidepressant-experienced subjects during treatment with medication could reflect classical conditioning and/or sensitization processes.

Whereas these prior results demonstrate an altered brain functional response associated with prior antidepressant exposure, it is possible that in persons with recurrent MDD, the apparent effects of prior medication exposure could have been influenced by the biology of the illness, the effects of multiple prior antidepressant

trials, the particular medications utilized, and/or clinical responses to prior treatment. For this reason, the potential influence of learning process effects of prior antidepressant treatment may be easier to isolate in healthy non-clinical samples.

Examining the effects of sequential treatments delivered to healthy subjects in an experimental setting could help to elucidate the potential influence of learning processes on neurophysiologic response to treatment. Specifically, a classical conditioning hypothesis would propose that neurophysiologic response to placebo would differ between subjects who were previously treated with antidepressant treatment as compared to placebo only. Learning theory hypotheses more generally (whether sensitization, habituation, or classical conditioning) would propose that the neurophysiologic response to an initial course of antidepressant treatment would differ from response to a repeated course of antidepressant treatment.

Below we present pilot data that address these hypotheses. We recruited never-depressed subjects who had completed a prior study of the effects of venlafaxine or placebo on normal brain function [31] and subsequently examined neurophysiologic response to placebo and to venlafaxine re-administration. Subjects who had received venlafaxine (i.e., ‘antidepressant-experienced’ subjects) or lookalike placebo (i.e., ‘antidepressant-naïve’ subjects) in the initial study six-and-a-half years prior were treated with one week of placebo, followed by four weeks of venlafaxine, in the present investigation. Prefrontal neurophysiologic measures were examined at baseline, and over the course of treatment, to assess differences in neurophysiologic response between subjects who had, versus had not, received a prior course of antidepressant treatment.

Methods

Subjects

Subjects were recruited from the 32 healthy, never-depressed individuals who had completed our prior study of venlafaxine effects on brain function [30]. We contacted all subjects who had completed the prior study, as provided for by our IRB-approved procedures, and invited them to contact us to determine eligibility for participation in this follow up study. Exclusion criteria included current or lifetime diagnosis of MDD as determined via structured assessment with the Mini-International Neuropsychiatric Interview for DSM-IV Axis I Disorders (MINI) [32]; suicidal; any illness known to influence brain function; past or current use of antidepressant or other psychotropic medication; and, head injury or use of medication known to influence the EEG. Written informed consent was obtained at the screening visit before any assessment. Seven women responded and were screened, one of whom was excluded on the basis of chronic indomethacin use for pain. Six women completed the present study; two had previously been randomized to four weeks of treatment with venlafaxine 150 mg (antidepressant-experienced, $n = 2$) and four had been randomized to placebo (antidepressant-naïve, $n = 4$).

Subjects were required to abstain from use of any primarily CNS active medications including sedative-hypnotics, or other medications with significant CNS activity for 10 days prior to entering as well as during the course of the study. Urine toxicology screens were performed to rule out use of psychoactive medications. All recruitment and experimental procedures were approved by the UCLA IRB.

Design

After a one-week single-blind placebo lead-in, all subjects received double-blind treatment with venlafaxine 150 mg for a

period of four weeks. Subjects and study personnel were informed that all subjects would receive a placebo at some point in the study, and that they might receive venlafaxine. Both the research coordinators and subjects were blinded to the actual study design. Brain function and mood were assessed at: baseline, end of placebo lead-in, 48 h after start of venlafaxine, and at weeks 1, 2, and 4 after start of venlafaxine. All procedures and conditions including study capsules, dosing, treating physicians and nurse, and the clinical laboratory, were identical to the prior study. As before, subject safety procedures were in place such that any subject with a significant change in mood and/or suicidal ideation during the five-week trial would be removed from the study and referred to their primary care physician and for evaluation. A study psychiatrist was available for consultation in the event of clinical necessity until the primary physician could be contacted.

Dosage and administration of study drug

Matching capsules containing either venlafaxine IR 37.5 mg or placebo were prepared by the UCLA Pharmacy. After a one-week placebo lead-in, subjects received one capsule of venlafaxine, with a dosage increase of 37.5 mg every two days (added on a b.i.d schedule) until subjects received four capsules daily (to achieve a dose of 150 mg of venlafaxine after seven days). Dosing and encapsulation of the study material were identical to the initial study [30]. At the end of five weeks, each subject was unblinded and was tapered off medication over the span of one week with a decrease in dosage of 37.5 mg every 2 days.

Mood and side effect assessments

Mood was assessed at each visit using the 17-item Hamilton Depression Rating Scale (HamD₁₇) [33]. Although the HamD₁₇ is designed to assess depressive symptoms in the context of clinical depression (and this sample did not meet criteria for mood disorder), we collected HamD₁₇ ratings for comparability with other studies and utilized the 'suicide' item to verify the absence of suicidality at pretreatment baseline, as well as to identify any potential changes in suicidal thoughts or behaviors over the course of treatment.

Side effects were assessed at each visit using the 3-item Frequency and Intensity of Side Effects Rating/Global Rating of Side Effects Burden (FISER/GRSEB) measure which was developed for use in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) protocol [34]. Subjects rated side effect frequency, intensity, and burden, respectively, on 7-point Likert-type scales ranging from '0' to '6'.

QEEG techniques and cordance calculations

EEGs were obtained at baseline and at the end of placebo lead-in, as well as at 48 h, and 1, 2, and 4 weeks after beginning double-blinded treatment with venlafaxine. We recorded EEGs using 35 Ag/AgCl electrodes positioned with an electrode cap (ElectroCap, Inc.; Eaton, OH) according to an extended International 10–20 System with Pz reference (Fig. 1). Subjects rested in the eyes-closed, maximally alert state in a sound-attenuated room with subdued lighting. Subjects were alerted frequently to avoid drowsiness, and were instructed to remain still and inhibit blinks or eye movements during each recording period. Electrode impedances were balanced and under 5 k Ω for all channels. Vertical and horizontal electro-oculograms (EOG) were recorded for identification of eye movement artifact using bipolar electrodes placed at the supra-orbital and infra-orbital ridge of the right eye and the outer canthi of the left and right eye, respectively. Impedance was maintained below 5 k Ω in all electrodes. EEG data were recorded for a minimum

of 10 min using a 16-bit resolution QND Neurodata system (Neurodata, Inc.; Pasadena, CA) at a sampling rate of 256 Hz, with a high-frequency filter of 70 Hz, a low-frequency filter of 0.3 Hz, and a notch filter at 60 Hz. Data were imported into Brain Vision Analyzer (BVA) software (Brain Products GmbH; Gilching, Germany) to remove offsets, optimize scaling, and re-reference and segment the data into non-overlapping two-second epochs. Epochs containing eye movement, muscle, or movement-related artifacts, or amplifier drift were removed using a semiautomated interactive process. Two technologists inspected the data independently using multiple bipolar and referential montages, and removed those data segments containing artifacts.

The power spectral frequency of the artifact-free EEG data was calculated using the BVA fast Fourier transform (FFT) function. The 512-point FFT was calculated for artifact-free two-second epochs with a rectangular window, 0.5 Hz overlap at the limits of the band, and yielding a frequency resolution of 0.5 Hz. Power was calculated in four frequency bands, corresponding to delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–20 Hz), for all nearest neighbor bipolar pairs of electrodes.

Cordance values were calculated from the conventional qEEG power measures 'absolute power' (the total amount of power in a given frequency band at a given site) and 'relative power' (the amount of power in a given frequency band, relative to the total power across frequencies, at a given site). The three-step procedure described briefly here, and elsewhere in greater detail [23], has been employed in a number of prior reports [25,27,31,35,36]. First, EEG power values were computed using a re-attributional electrode montage because this montage affords a higher correlation between EEG measures and PET measures of cerebral perfusion than other montages [37] (Fig. 1). Second, the absolute and relative power values were z-transformed to measure deviation from the mean values for each electrode site s in each frequency band f for that recording, yielding $A_{\text{norm}(s,f)}$ and $R_{\text{norm}(s,f)}$, respectively. Third, these z-scores were summed to yield a cordance "intensity" value, Z , for each electrode in each frequency band where $Z_{(s,f)} = A_{\text{norm}(s,f)} + R_{\text{norm}(s,f)}$. Analyses for this report focused on change in theta-band cordance in the prefrontal region (electrodes Fp1, Fpz, Fp2) (Fig. 1).

Statistical analyses

Analyses were conducted using IBM SPSS statistics version 20 with the threshold for significance set at $p \leq 0.05$. Where t-tests were used to examine group differences, we first used Levene's test to assess equality of variances. When Levene's test was significant, t-tests were evaluated with equal variances not assumed. Change in PFC over time was assessed using linear mixed model analysis as detailed below. We used Wilcoxon-Mann-Whitney tests to compare FISER/GRSEB side effect ratings (ordinal scales).

We initially assessed the comparability of baseline clinical and demographic characteristics between groups. Subsequent analyses of brain functional differences addressed three questions of interest. Using independent samples t-tests, we first asked whether prior treatment with antidepressant medication had long-term effects on resting state prefrontal brain function by comparing baseline PFC between 'antidepressant-experienced' and 'antidepressant-naïve' subjects (i.e., subjects from the initial study who had previously been randomized to venlafaxine or placebo, respectively). We then compared change in PFC during single-blind placebo administration (i.e., during the one-week placebo lead-in) between antidepressant-experienced and antidepressant-naïve subjects. Change in cordance was calculated as the difference between the value at the end of placebo lead-in, minus the value at pretreatment baseline. Finally, we compared brain functional changes over the course of venlafaxine treatment between

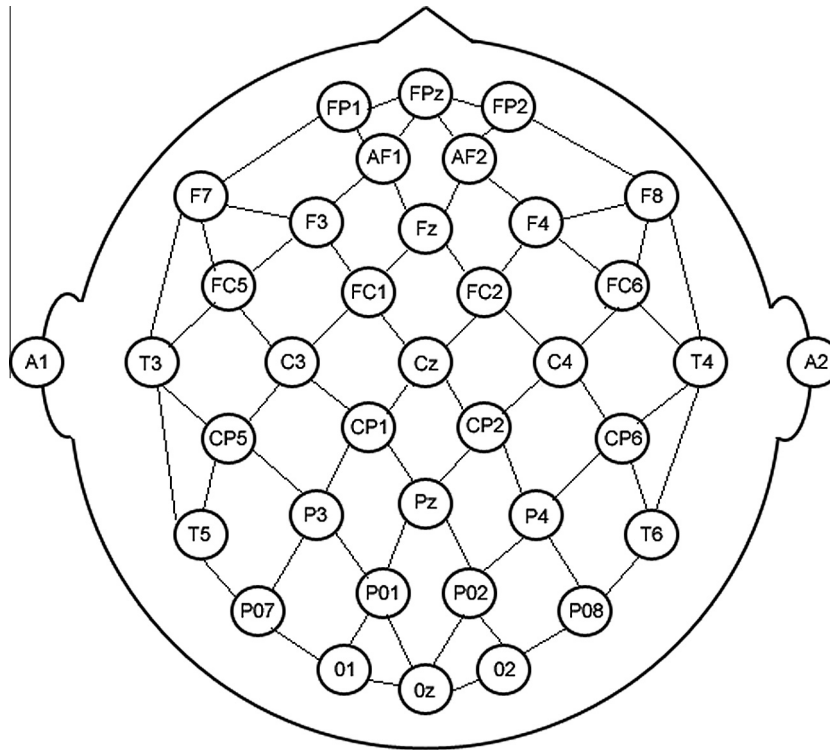


Fig. 1. Electrode montage.

antidepressant-experienced and antidepressant-naïve subjects using linear mixed model analysis (random intercept model) conducted using full maximum likelihood estimation (MLE). Changes in PFC were calculated from the end of placebo lead-in to 48 h, and 1, 2, and 4 weeks, yielding a within-group factor of time with four levels. We employed a first-order autoregressive covariance structure to reflect our assumption that PFC measurements closer together in time would be more highly correlated.

HamD₁₇ total scores, and FISER/GRSEB ratings were compared between groups at the end of placebo lead-in, and over the four weeks of venlafaxine treatment (mean of visits: 48 h, and weeks 1, 2, 4). We also compared groups regarding the change in HamD₁₇ and FISER/GRSEB score from the placebo lead-in phase to the venlafaxine treatment phase. The suicidality focused item of the HamD₁₇ was examined to determine any change in suicidal ideation.

Results

Characteristics of the sample

Groups did not differ significantly on age, HamD₁₇ score, or on time since prior treatment (Table 1).

Brain function

Baseline measures: Table 2 shows PFC values for antidepressant-experienced and antidepressant-naïve subjects at baseline of the

initial study (Leuchter et al. [30]), baseline of the present study, as well as change in baseline PFC since the initial study. No statistically significant differences were observed.

Brain changes during placebo lead-in: No significant between-group difference in PFC was observed during placebo lead-in. PFC changed $-0.54 (\pm 0.44)$ in the treatment-experienced group, and $-0.09 (\pm 0.46)$ in treatment-naïve subjects; $t_{(4)} = 1.14$, $p = 0.32$.

Brain changes during antidepressant treatment: Linear mixed model analysis found a significant effect of prior treatment ($F = 6.56$, $p = 0.04$). As shown in Fig. 2, subjects who had previously been treated with venlafaxine showed greater decreases in PFC during venlafaxine treatment than did subjects who had not previously been exposed to antidepressant medication. Because subjects in the antidepressant-experienced group were numerically (but not statistically) older, we examined age as a predictor of change in PFC. The linear mixed model examining only age as a predictor was not significant ($F = 1.00$, $p = 0.35$); a linear mixed model examining treatment history and age as simultaneous predictors did not find a significant effect of age ($F = 4.13$, $p = 0.85$) or prior treatment ($F = 4.13$, $p = 0.09$).

Mood outcomes

The mean HamD₁₇ total scores for the sample were 2.5 ± 2.9 at the end of the placebo lead-in, and 3.9 ± 2.8 during venlafaxine treatment. There was no significant difference between groups at any time point, nor was there a significant group difference in HamD₁₇ change from the end of placebo lead-in, as compared to

Table 1
Baseline clinical and demographic characteristics of the sample.

	All subjects (n = 6)	Antidepressant-experienced (n = 2)	Antidepressant-naïve (n = 4)	Test statistic	p-Value
Age (years)	54.7 ± 16.8	67.5 ± 5.0	48.3 ± 17.3	$t_{(4)} = -1.46$	0.22
HamD ₁₇	2.0 ± 1.9	2.0 ± 0.0	2.0 ± 2.4	$t_{(4)} = 0.00$	1.00
Months since initial treatment	77.8 ± 4.1	76.5 ± 0.71	78.5 ± 5.07	$t_{(4)} = 0.53$	0.63

Table 2
Prefrontal cordance (PFC) at baseline, and change in baseline since the initial study, for groups previously treated with venlafaxine or placebo.

	Antidepressant-naïve (n = 4)	Antidepressant-experienced (n = 2)	t-Test, 2-tailed p-value
PFC initial study baseline	-1.04 (± 0.75)	-1.23 (± 0.06)	$t_{(4)} = 0.34, p = 0.75$
PFC present study baseline	-0.88 (± 1.55)	-0.09 (± 0.86)	$t_{(4)} = -0.65, p = 0.55$
Change in baseline PFC since initial study	0.16 (± 0.80)	1.14 (± 0.93)	$t_{(4)} = -1.35, p = 0.25$

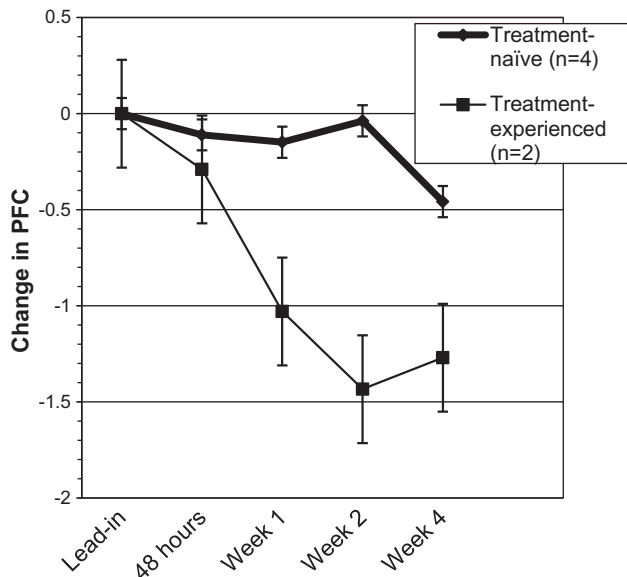


Fig. 2. Changes in prefrontal cordance (PFC) \pm SE from end of placebo lead-in across four weeks of blinded treatment with venlafaxine. Healthy subjects who had previously been treated with venlafaxine showed greater decreases in PFC as compared to subjects who had previously received placebo.

during antidepressant treatment. No subject reported an increase in suicidality (thoughts or behaviors) as assessed by the suicide-focused item of the HamD₁₇, or otherwise during subject assessments, at any point during the study.

Side effects

Mean side-effect ratings during the placebo lead-in period were clinically insignificant ranging from '0' ('no side effects') to '1' ('trivial') and did not differ significantly between antidepressant-experienced, and antidepressant-naïve groups.

Over the four weeks of venlafaxine treatment, mean side effect ratings in the antidepressant-naïve group were less than 1, whereas the antidepressant-experienced group ratings of intensity, frequency and burden were 3.4, 3.4, and 2.5, respectively, indicating side effects of 'moderate' to 'marked' severity, present 50–75% of the time, resulting in 'mild' to 'moderate' impairment. Side effect intensity during venlafaxine treatment was significantly greater in antidepressant-experienced subjects, as compared to the antidepressant-naïve group ($p = 0.049$); side effect frequency ($p = 0.064$) and burden ($p = 0.064$) showed trend relationships in the same direction (Table 3). Changes in side effect ratings from placebo lead-into active treatment were not statistically significantly different between groups.

Discussion

These pilot data suggest that neurophysiologic response during a second period of exposure to antidepressant medication differs from the brain response to an initial period of exposure. Across four weeks of venlafaxine treatment administered to healthy

non-depressed subjects, we observed greater decreases in PFC among those subjects who had received a prior course of venlafaxine as compared to those who had not. This observation aligns with our previous finding in MDD where 'antidepressant-experienced' subjects also showed greater decreases in PFC as compared to 'antidepressant-naïve' subjects [31]. In the MDD study, prior antidepressant treatment was associated with a greater decrease in PFC even when controlling statistically for symptom severity, symptom improvement, and family history of depression; however, it is possible that other illness-related factors were responsible for the apparent effect of prior exposure. Our present finding in healthy never-depressed subjects suggests that exposure to a prior course of antidepressant treatment itself may influence neurophysiologic response to a subsequent course of antidepressant treatment independent of illness effects.

Viewed another way, the larger decreases in PFC among antidepressant-experienced subjects may serve as an indicator that the brain has previously "seen" drug. In our initial placebo-controlled study of venlafaxine effects in healthy subjects, the drug group showed small decreases in PFC whereas the placebo group showed increases in PFC over the same time period [30]. In the present data, it appears that the neurophysiologic effect of drug registered more strongly among subjects for whom this constituted a second exposure to venlafaxine treatment.

Antidepressant-experienced subjects reported numerically greater side effect frequency, intensity, and burden during venlafaxine treatment. In contrast to the antidepressant-naïve group whose "trivial" and "minimal" side effects were present 10% of the time, the antidepressant-experienced group endorsed side effects of "moderate" to "marked" intensity, resulting in "mild" to "moderate" impairment, present more than 50% of the time. The group difference reached statistical significance regarding the side effect intensity measure. During the placebo lead-in phase, however, we did not observe any group difference in side effects even though prior exposure to venlafaxine might have been expected to yield greater side effects during blinded treatment with placebo due to classical conditioning effects.

The present observation of greater neurophysiologic and behavioral effects of antidepressant administration in subjects who were previously exposed to medication is consistent with aspects of drug sensitization paradigms. One such paradigm, stimulant-induced behavioral sensitization, is a well-established phenomenon wherein behavioral reactivity to the same dose of a stimulant increases over time [18,19]. In this model, behavioral sensitivity to cocaine is demonstrated to reflect both context-specific and context-independent conditioning effects depending on parameters of the conditioning procedure. For example, whereas the sensitization effects of day one drug pretreatment on day two test treatment may be explained fully by contextual (environmental) cues (i.e., sensitization occurs only when pretreatment and test are conducted in the same environment), sensitization effects of chronic treatment include both context-enhanced, and context-independent, conditioning effects such that some sensitization to drug is apparent even in a novel environment [18]. In the present study, drug administration conditions including the research laboratory site, staff, and the medication capsule itself were highly similar to those of the subjects' first exposure to drug six and a half years

Table 3Frequency, intensity, and burden of side effects during treatment with venlafaxine for groups previously treated with venlafaxine or placebo (mean \pm standard deviation).

	Antidepressant-naïve (<i>n</i> = 4)	Antidepressant-experienced (<i>n</i> = 2)	Wilcoxon-Mann-Whitney, 2-tailed <i>p</i> -value
Frequency	0.65 (\pm 0.34)	3.40 (\pm 1.70)	$z = -1.85, p = 0.064$
Intensity	0.85 (\pm 0.30)	3.40 (\pm 1.13)	$z = -1.97, p = 0.049$
Burden	0.35 (\pm 0.34)	2.60 (\pm 1.41)	$z = -1.85, p = 0.064$

earlier. Whereas these similarities could support contextual conditioning, we do not what role the environment played, if any, in the present results.

Another paradigm, ‘time-dependent sensitization’ (TDS) [9,22,38,39], describes increased biological effects of drug as a consequence of the passage of time following acute or brief treatment. Although a specific mechanism has not been identified, TDS is thought to reflect a non-pharmacokinetic process wherein the biological effect of initial drug exposure grows stronger with time, rather than by prolonged, regular (e.g. daily) dosing. Clinical implications of TDS include the possibility that brief intermittent exposures to drug might achieve increasing clinical effects over time, as considered in ‘pulsed therapy’ or the ‘pulse loading strategy’ [40,41]. Whereas TDS has been demonstrated up to months following intermittent exposure [42] our study suggests enduring effects of an initial course of daily antidepressant exposure, with no intervening exposure. In this sense, our present observation does not directly parallel the TDS, although these phenomena may be related.

Regarding qEEG biomarkers of treatment response, decreases in PFC in the first week of antidepressant treatment have been associated with clinical response to pharmacotherapy in MDD [24–29,36]. Most MDD subjects in prior studies of qEEG cordance have had multiple depressive episodes and have previously been treated with medication. Prior antidepressant treatment has been associated with poorer outcome [43–45] including in the STAR*D trial [46] and in our own data [47]. One might therefore expect that subjects previously exposed to antidepressant medication (a population with generally poorer outcomes) would show smaller, rather than larger decreases in PFC upon re-exposure to medication. Given the current pilot results, further work is needed to address the role that prior antidepressant exposure may play as a potential moderator of the relationship between qEEG biomarkers and clinical response in MDD. It is possible that antidepressant treatment history, and attendant learning processes inherent in prior exposures to antidepressant medication may play a critical role in the interpretation of other brain imaging results as well.

Conclusion, caveats, and future directions

We hypothesize that prior antidepressant exposure may influence the brain’s response to antidepressants in subsequent treatment trials. Learning theories would suggest that a series of courses of antidepressant treatment could lead to sensitization, habituation, and conditioned responses. The pilot data examined here provide support for an effect of prior treatment on neurophysiologic response to a subsequent course of treatment. We observed a greater prefrontal neurophysiologic response early in the course of acute treatment in antidepressant-experienced subjects that is consistent with sensitization processes; however, further repeated or prolonged exposure could result in habituation. Future longitudinal brain imaging studies in clinical populations undergoing extended treatment could help elucidate the time course of potential sensitization and habituation effects on neurophysiologic and clinical response. Whereas this small pilot cohort allowed us to compare the neurophysiologic effects of an initial well defined course of antidepressant treatment (4 weeks of venlafaxine IR) to a second identical course of antidepressant treatment, without the potential

confounds of psychiatric illness or intervening periods of antidepressant treatment, the influence of learning processes in clinical populations would be more complex. For example, patients with depression might have a history of responding either favorably or unfavorably, clinically, to prior treatments. To the extent that a patient’s personal history involves ‘successful’ prior treatment, antidepressant treatment may come to be associated with a reduction of symptoms wherein conditioned responding accentuates the clinical benefits of treatment. Conversely, some patients with depression, when they experience many days of antidepressant medication ingestion without any relief of symptoms, may become conditioned to not respond to clinically to treatment. In these patients, conditioning effects such as ‘learned irrelevance’ could contribute to the treatment-resistant depression.

The pilot data results presented in this paper should be interpreted with the understanding that replication in larger samples is imperative. First and foremost, small sample sizes increase the possibility of spurious findings, render low power to detect significant effects, and preclude meaningful examination of covariates. Second, it is possible that subjects in this investigation may have differed from the larger pool of subjects from the prior study, or from the general population. For example, those individuals who better tolerated treatment in the initial study may have been more likely to pursue the follow up study. Third, despite no statistically significant difference in age between groups, our sample included a wide range of ages spanning into older age, and brain responses to drug may change in later life. However, we did not observe an effect of age on brain functional changes. Fourth, it should be noted that treatment-experienced subjects were observed to both show greater decreases in PFC, and report greater side effects. It is possible that the increased side effect profile might underlie the greater changes in brain function. Finally because this study examined the effects of a repeated course of only one medication, venlafaxine IR, we do not know how these results would generalize to other antidepressants or classes of antidepressant medication.

The observation that the healthy subjects who were previously exposed to antidepressant medication had neurophysiologic responses that differed from those not previously exposed, even years later, suggests enduring effects of medication exposure. More study is warranted to replicate this finding, explore the learning processes or other bases of this phenomenon, and to further address its potential implications for clinical treatment, and for the design of studies that examine brain functional effects of antidepressant treatments.

Support

This research was supported by a seed grant from the UCLA Academic Senate. Medication was provided by Pfizer, Inc.

Conflict of interest statement

Dr. Hunter is an inventor of a UCLA-assigned patented method to predict antidepressant effects.

Dr. Cook, over his career, has received research support from Aspect Medical Systems/Covidien, Cyberonics, Eli Lilly and Company, High Q Foundation, John E. Fetzer Foundation, John A. Hartford

Foundation, MedAvante, Merck, NARSAD, NIH, Neuronetics, Novartis, Pfizer, Sepracor/Sunovion, Seaside Therapeutics, and the West Coast College of Biological Psychiatry, as Principal Investigator or Co-Investigator. He has served as an advisor or consultant to Allergan, Ascend Media, Bristol-Myers Squibb, Cyberonics, Eli Lilly and Company, Forest Laboratories, Janssen, Neuronetics, NeuroSigma, Pfizer, Scale Venture Partners, and the US Departments of Defense and Justice. He has spoken on behalf of Bristol-Myers Squibb, CME LLC, Eli Lilly & Company, Medical Education Speakers Network, Pfizer, Neuronetics, NeuroSigma, and Wyeth. Dr. Cook's biomedical device patents are assigned to the University of California. He has been granted stock options in NeuroSigma, the licensee of some of his inventions.

Michelle Abrams has no potential conflicts to disclose.

Dr. Leuchter has received research support from Covidien, Neuronetics, NeuroSigma, NIMH, and Shire Pharmaceuticals. Dr. Leuchter further serves, or has served, in the following capacities for biomedical companies: Chair, Neuroscience Advisory Board, Covidien, Newton, MA (2002–2012); Chair, Data Safety and Monitoring Board for study H9P-MC-LNBM and H9P-MC-LNBQ, Lilly Research Laboratories, Indianapolis, IN (2012–present); Consultant, Neosync, Inc., Newport Beach, CA (2010 – present); Consultant, Brain Cells, Inc., San Diego, CA (2010–present); Consultant, MedGenesis Therapeutix, Inc., Oakland, CA (2012); Consultant, Taisho (2012–present).

Acknowledgements

We thank Robert Pechnick, Ph.D. for helpful comments on a prior draft. This research was supported by a seed grant from the UCLA Academic Senate. Medication was provided by Pfizer, Inc. The sponsors did not play any role in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

References

- [1] Lindsley CW. The top prescription drugs of 2011 in the United States: antipsychotics and antidepressants once again lead CNS therapeutics. *ACS Chem Neurosci* 2011;3(2012):630–1.
- [2] Pratt LA, Brody DJ, Gu Q. Antidepressant use in persons aged 12 and over: United States, 2005–2008. In: NCHS data brief, no 76, National Center for Health Statistics, Hyattsville, MD; 2011.
- [3] Ader R. The role of conditioning in pharmacotherapy. In: Harrington A, editor. *The placebo effect*, Harvard University Press, Cambridge: MA, London; 1997. pp. 138–165.
- [4] Flaten MA. Drug effects: agonistic and antagonistic processes. *Scand J Psychol* 2009;50:652–9.
- [5] Siegel S. Pharmacological conditioning and drug effects. In: *Psychoactive drugs: tolerance and sensitization*. Clifton, NJ: Humana Press; 1989. p. 115–80.
- [6] Stewart J, Badiani A. Tolerance and sensitization to the behavioral effects of drugs. *Behav Pharmacol* 1993;4:289–312.
- [7] Flaten MA, Simonsen T, Waterloo K, Olsen H. Pharmacological classical conditioning in humans. *Hum Psychopharmacol* 1997;12:369–77.
- [8] Benedetti F, Arduino C, Costa S, et al. Loss of expectation-related mechanisms in Alzheimer's disease makes analgesic therapies less effective. *Pain* 2006;121:133–44.
- [9] Antelman SM, Soares JC, Gershon S. Time-dependent sensitization—possible implications for clinical psychopharmacology. *Behav Pharmacol* 1997;8:505–14.
- [10] Siegel S, Baptista MA, Kim JA, McDonald RV, Weise-Kelly L. Pavlovian psychopharmacology: the associative basis of tolerance. *Exp Clin Psychopharm* 2000;8:276–93.
- [11] Fava GA, Offidani E. The mechanisms of tolerance in antidepressant action. *Prog Neuropsychopharmacol Biol Psychiatry* 2011;35:1593–602.
- [12] Amsterdam JD, Williams D, Michelson D, et al. Tachyphylaxis after repeated antidepressant drug exposure in patients with recurrent major depressive disorder. *Neuropsychobiology* 2009;59:227–33.
- [13] Posternak MA, Zimmerman M. Dual reuptake inhibitors incur lower rates of tachyphylaxis than selective serotonin reuptake inhibitors: a retrospective study. *The J Clin Psychiatry* 2005;66:705–7.
- [14] Solomon DA, Leon AC, Mueller TI, et al. Tachyphylaxis in unipolar major depressive disorder. *The J Clin Psychiatry* 2005;66:283–90.
- [15] Thase ME. Preventing relapse and recurrence of depression: a brief review of therapeutic options. *CNS Spectr* 2006;11(12 Suppl 15):12–21.
- [16] Zimmerman M, Thongy T. How often do SSRIs and other new-generation antidepressants lose their effect during continuation treatment? Evidence suggesting the rate of true tachyphylaxis during continuation treatment is low. *J Clin Psychiatry* 2007;68:1271–6.
- [17] Eikelboom R, Stewart J. Conditioning of drug-induced physiological responses. *Psychol Rev* 1982;89:507–28.
- [18] Ramsay DS, Woods SC. Biological consequences of drug administration: implications for acute and chronic tolerance. *Psychol Rev* 1997;104:170–93.
- [19] Ellinwood EH, Kilbey MM. Fundamental mechanisms underlying altered behavior following chronic administration of psychomotor stimulants. *Biol Psychiatry* 1980;15:749–57.
- [20] Post RM, Weiss SRB, Fontana D, Pert A. Conditioned sensitization to the psychomotor stimulant cocaine. *Ann N Y Acad Sci* 1992;654:386–99.
- [21] Post RM, Weiss SRB. Sensitization and kindling phenomena in mood, anxiety, and obsessive-compulsive disorders: the role of serotonergic mechanisms in illness progression. *Biol Psychiatry* 1998;15:749–57.
- [22] Antelman SM, Gershon S. Clinical application of time-dependent sensitization to antidepressant therapy. *Prog Neuropsychopharmacol Biol Psychiatry* 1998;22:65–78.
- [23] Leuchter AF, Uijtdehaage SHJ, Cook IA, O'Hara R, Mandelkern M. Relationship between brain electrical activity and cortical perfusion in normal subjects. *Psychiatry Res Neuroimaging* 1999;90:125–40.
- [24] Bares M, Brunovsky M, Kopecek M, et al. Changes in QEEG prefrontal cordance as a predictor of response to antidepressants in patients with treatment resistant depressive disorder: a pilot study. *J Psychiatric Res* 2007;41:319–25.
- [25] Bares M, Brunovsky M, Kopecek M, et al. Early reduction in prefrontal theta QEEG cordance value predicts response to venlafaxine treatment in patients with resistant depressive disorder. *Eur Psychiatry* 2008;23:350–5.
- [26] Bares M, Brunovsky M, Novak T, et al. The change of prefrontal QEEG theta cordance as a predictor of response to bupropion treatment in patients who had failed to respond to previous antidepressant treatments. *Eur Neuropsychopharmacol* 2010;20:459–66.
- [27] Cook IA, Leuchter AF. Prefrontal changes and treatment response prediction in depression. *Seminars Clin Neuropsychiatry* 2001;6:113–20.
- [28] Cook IA, Leuchter AF, Morgan M, et al. Early changes in prefrontal activity characterize clinical responders to antidepressants. *Neuropsychopharmacol* 2002;27:120–31.
- [29] Cook IA, Hunter AM, Abrams M, Siegman B, Leuchter AF. Midline and right frontal brain function as a physiologic biomarker of remission in major depression. *Psychiatry Res Neuroimaging* 2009;174:152–7.
- [30] Leuchter AF, Cook IA, De Brota DJ, et al. Changes in brain function during administration of venlafaxine or placebo to normal subjects. *Clin EEG Neurosci* 2008;39:175–81.
- [31] Hunter AM, Cook IA, Leuchter AF. Does prior antidepressant treatment of major depression impact brain function during current treatment? *Eur Neuropsychopharmacol* 2012;22:711–20.
- [32] Sheehan DV, Lecrubier Y, Sheehan KH, et al. The mini-international neuropsychiatric interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998;59(Suppl 20):22–33.
- [33] Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56–6.
- [34] Fava M, Rush AJ, Trivedi MH, et al. Background and rationale for the sequenced treatment alternatives to relieve depression (STAR*D) study. *Psychiatry Clin N Am* 2003;26:457–94.
- [35] Broadway JM, Holtzheimer PE, Hilimire MR, et al. Frontal theta cordance predicts 6-month antidepressant response to subcallosal cingulate deep brain stimulation for treatment-resistant depression: a pilot study. *Neuropsychopharmacology* 2012;37:1764–72.
- [36] Hunter AM, Leuchter AF, Morgan ML, Cook IA. Changes in brain function (quantitative EEG cordance) during placebo lead-in and treatment outcomes in clinical trials for major depression. *Am J Psychiatry* 2006;163:1426–32.
- [37] Cook IA, O'Hara R, Uijtdehaage SH, Leuchter AF. Assessing the accuracy of topographic EEG mapping for determining local brain function. *Electroencephalogr Clin Neurophys* 1998;107:408–14.
- [38] Antelman SM, Chiodo LA. Dopamine autoreceptor subsensitivity: a mechanism common to the treatment of depression and the induction of amphetamine psychosis? *Biol Psychiatry* 1981;16(8):717–27.
- [39] Antelman SM, Levine J, Gershon S. Time-dependent sensitization: the odyssey of a scientific heresy from the laboratory to the door of the clinic. *Mol Psychiatry* 2000;5(4):350–6.
- [40] Pollock BG, Perel JM, Shostak M, Antelman SM, Brandom B, Kupfer DJ. Understanding the response lag to tricyclics. I. Application of pulse-loading regimens with intravenous clomipramine. *Psychopharmacol Bull* 1986;22:214–9.
- [41] Pollock BG, Perel JM, Nathan RS, Kupfer DJ. Acute antidepressant effect following pulse loading with intravenous and oral clomipramine. *Arch Gen Psychiatry* 1989;46:29–35.
- [42] Antelman SM, Kocan D, Edward DJ, Knopf S, Perel JM, Stiller R. Behavioral effects of a single neuroleptic treatment grow with the passage of time. *Brain Res* 1986;385(1):58–67.
- [43] Amsterdam JD, Maislin G, Potter L. Fluoxetine efficacy in treatment resistant depression. *Prog Neuropsychopharmacol Biol Psych* 1994;18:243–61.

- [44] Amsterdam JD, Shults J. MAOI efficacy and safety in advanced stage treatment-resistant depression—a retrospective study. *J Affect Disord* 2005;89:183–8.
- [45] Leykin Y, Amsterdam JD, DeRubeis RJ, Gallop R, Shelton RC, Hollon SD. Progressive resistance to a selective serotonin reuptake inhibitor but not to cognitive therapy in the treatment of major depression. *J Consult Clin Psychol* 2007;75:267–76.
- [46] Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry* 2006;163:1905–17.
- [47] Hunter AM, Cook IA, Leuchter AF. Impact of antidepressant treatment history on clinical outcomes in placebo and medication treatment of major depression. *J Clin Psychopharmacol* 2010;30:748–51.