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Nasal cycle dominance and hallucinations in an adult schizophrenic female

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ABSTRACT

Nasal dominance, at the onset of hallucinations, was studied as a marker of both the lateralized ultradian rhythm of the autonomic nervous system and the tightly coupled ultradian rhythm of alternating cerebral hemispheric dominance in a single case study of a schizophrenic female. Over 1086 days, 145 hallucination episodes occurred with left nostril dominance significantly greater than the right nostril dominant phase of the nasal cycle. A right nostril breathing exercise, that primarily stimulates the left hemisphere, reduces symptoms more quickly for hallucinations.

1. Introduction

The lateralized ultradian rhythm of the autonomic nervous system (ANS) called the "nasal cycle," with periods ranging from 25 to greater than 200 min, is a tightly coupled marker of the lateralized ultradian rhythm of the central nervous system (CNS) that exhibits as an alternating dominance of cerebral hemispheric activity in humans during both waking and sleep (Werntz et al., 1983; Shannahoff-Khalsa, 1991a, 1991b, 1993, [*reviewed in* 2007, 2008]; Shannahoff-Khalsa and Yates, 2000). Werntz et al. (1983) first showed the tight coupling of the nasal cycle using a continuous and simultaneous monitoring of both left and right nasal airflows with independent thermistors and the alternating dominance of cerebral hemispheric activity using EEG in a study of 43 resting reclining stationary normal healthy humans with recording periods ranging from 40 to 215 min (mean 90 min). Twenty-two exhibited nasal cycles during this relatively short interval, and 19 had records suitable for analysis without excessive EEG artifact. All 19 showed how greater right nostril airflow was coupled to relatively greater left hemisphere EEG power and that conversely greater left nostril airflow was coupled to relatively greater right hemisphere EEG power (see Fig. 1). The first report directly supporting the existence in humans of alternating cerebral hemispheric activity using cognitive testing (verbal and spatial skill performance) during the waking state was by Klein and Armitage (1979). They found ultradian rhythms with significant peaks at 37 min, 96 min, and 4 h. They tested eight subjects (five females, three males, all right-handed) with a verbal and a spatial task every 15 min for 8 h. The best performances on one task occurred during the minimum performances on the other. They conclude "This finding is consistent with the hypothesis that in humans that the Basic Rest-Activity Cycle (BRAC) is characterized by oscillations in the relative activation or efficiency of the two cerebral hemispheres, which are specialized for the performance of verbal and spatial tasks." Subjects who were tested for immediate memory every 25 min with two modalities (semantic and graphic) presented a fluctuation in performance with a periodicity of about 100 min (Leconte and Lambert, 1988). The two modalities were in opposite phase. Others also pursued the cognitive study of the ultradian rhythm of alternating cerebral hemispheric dominance in humans in two populations, a group of right-handed males between 18 and 27 years old who were habitual hashish smokers and a control group of 24 right-handed males of similar age who had never used drugs (Leon-Carrion and Vela-Bueno, 1991). The subjects were administered right and left hemisphere related tests every 15 min for 8 h. For the non-hashish smokers, the right hemisphere ultradian rhythm test yielded the greatest spectral power between 85 and 100 min with a maximum peak at 90 min. For the left hemisphere, the maximum spectral power was between 95 and 120 min, with the peak at 110 min. For the drug users, the right hemisphere related task showed a maximum range between 90 and 120 min, with the peak at 90 min. On the left hemisphere related task, the distribution was the same as the control group, except that the distribution was not as steep and peaked at 105 min. For the control group the hemisphere relations are 193.62° out of phase for the two tests and for the hashish users it was 226.75° out of phase. These findings again support the alternating levels of activation for the two hemispheres and

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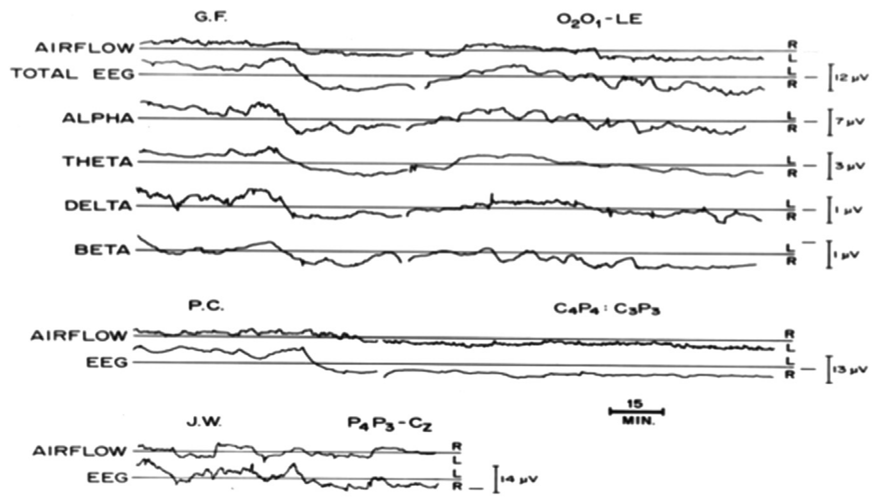

Fig. 1. Shows the continuous nasal airflow tracings and EEG records in 3 normal healthy naïve subjects (subjects G.F., P.C., and J.W. respectively). Airflow Tracings: points above the baseline indicate greater right nostril airflow and points below indicate greater left nostril airflow. Total EEG is 1–35 Hz, Alpha (8–13 Hz), Theta (4–8 Hz) Delta (1–4 Hz) and Beta (13–35 Hz) tracings were filtered through an analog filter before integration. This baseline is drawn to visually enhance the similarity of the basic correlation of the two phenomena. The dash to the right of the EEG tracings indicates the true zero line where the right and left EEG amplitudes are equal. The bar and its numerical equivalent next to the integrated EEG tracings represent the actual calibrated amplitudes in microvolts. This figure was previously published in Werntz, D.A., Bickford, R.G., Bloom, F.E., Shannahoff-Khalsa, D.S., 1983, Alternating Cerebral Hemispheric Activity and the Lateralization of Autonomic Nervous Function. Human Neurobiology, 2, 39–43 (With kind permission of Springer Science + Business Media.).

demonstrate how the rhythm may also be disrupted using intoxicants. Dichotic listening (DL) performance was also employed to assess the existence of alternating cerebral hemispheric activity in six males and six females (Meier-Koll, 1989). He found very distinct and convincing periodicities of 3–4 h in 10 subjects. "Such periodicities were obvious in both right-ear and left-ear DL performance and oscillated in counter phase. This suggests that competitive processing of dichotic verbal stimuli mediated by the cerebral hemispheres could be modulated by an endogenous oscillatory system." The studies on the ultradian rhythms in alternating cerebral dominance using EEG in humans and other mammals are numerous and have been reviewed (Shannahoff-Khalsa, 1993, 2008). In addition, the ultradian rhythms of alternating cerebral hemispheric EEG dominance have been shown to be coupled to rapid eye movement (REM) and non-rapid eye movement (NREM) stage 4 sleep in humans, where greater left hemisphere EEG power is coupled to REM sleep and greater right hemisphere EEG power is coupled to NREM stage 4 sleep (Shannahoff-Khalsa, et al., 2001). The ultradian rhythm of alternating cerebral hemispheric dominance has also been shown to be coupled to the nasal cycle during sleep with greater EEG power contralateral to the dominant nostril (Shannahoff-Khalsa and Yates, 2000).

This lateralized ANS–CNS rhythm is regulated by the hypothalamus and a clock-like physical model of hypothalamic regulation of this rhythm has been published (Shannahoff-Khalsa, 1991b, 1996, 2008). This ANS–CNS rhythm exhibits with sympathetic tone dominating on one side of the body with a relative venous constriction in the ipsilateral turbinate that results in greater ipsilateral nasal airflow, along with a simultaneous and greater parasympathetic tone dominating on the contralateral side of the body with a relatively greater venous dilatation, nasal congestion, and relatively reduced nasal airflow. The cerebral hemisphere contralateral to the nostril with greater airflow exhibits greater cognitive performance efficiency (Klein et al., 1986) and greater amplitudes of EEG activity across all frequency bands (Werntz et al., 1983) presumably by enhanced parasympathetic tone and greater arterial dilation in the cortex (for reviews see Shannahoff-Khalsa (2007, 2008)). This lateralized ultradian ANS–CNS rhythm also exhibits with alternating levels of plasma catecholamines throughout the two sides of the periphery that are tightly coupled to the nasal cycle (Kennedy et al., 1986). In addition, the "hourly-like" ultradian rhythms in the cardiovascular, neuroendocrine, and fuel regulatory hormone systems are coupled to this ANS–CNS rhythm as marked by the nasal cycle (Shannahoff-Khalsa, et al., 1996, 1997).

The contralateral pattern of dominance, both in nasal airflow and cerebral activity, is accounted for by the fact that most fiber systems of the ANS travel uncrossed between hypothalamus and periphery (Netter, 1972; Saper et al., 1976), and from the hypothalamus to the cortex (Saper, 1985, 2000). Therefore, the hemisphere contralateral to the dominant nostril would have relatively greater blood flow as a result of the respective dominance in the cerebral parasympathetic influences on the circulation and the hemisphere ipsilateral to the dominant nostril would have greater sympathetic influences, and a relative reduction in blood flow. It is known that cerebral circulation is diminished during increased sympathetic activity (Gomez et al., 1976), and this further suggests that greater nasal airflow would correlate with increased metabolic or mental activity in the contralateral hemisphere. The study by Klein et al. (1986) that shows relatively greater verbal skills during right nostril dominance and relatively greater spatial skills during left nostril dominance confirms this view. The ANS physiology and the lateralized influences of the sympathetic and parasympathetic nervous system on the nasal cycle as controlled by the hypothalamus have been reviewed (Eccles, 2000; Eccles and Eccles, 1981; Eccles and Lee, 1981).

This phenomenon of the lateralized ultradian alternation of ANS–CNS coupling is an extension of Kleitman's (1961, 1967, for review see 1982) ultradian BRAC Hypothesis. The ANS–CNS rhythm as the underpinning of the BRAC now presents as a new spatio-temporal perspective on psychophysiological states (for reviews see Shannahoff-Khalsa (2007, 2008)).

In addition, there is an endogenous feedback mechanism that yogis discovered in ancient times that can be used to alter this ANS–CNS rhythm. This technique is called "unilateral forced nostril breathing" (UFNB), whereby one nostril is plugged and the breath is selectively forced through the contralateral nostril leading to hemisphere-specific effects via selective unilateral autonomic activation (for review see Shannahoff-Khalsa (2007, 2008)). Left UFNB leads to greater activation of the right cerebral hemisphere and right UFNB leads to greater activation of the left hemisphere. This was first demonstrated by Werntz et al. (1987) using EEG. Left nostril breathing was shown to induce greater EEG amplitudes in the right cerebral hemisphere and right nostril breathing was shown to induce greater EEG amplitudes in the left hemisphere in naïve untrained subjects. Later, the same pattern of activation was demonstrated by using UFNB and cognitive performance testing (Shannahoff-Khalsa et al., 1991; Jella and Shannahoff-Khalsa, 1993, for review see Shannahoff-Khalsa (2007, 2008)).

Two studies suggest that EEG activity generated by nasal (versus oral) breathing is produced by a neural mechanism in the superior nasal meatus (Kristof et al., 1981; Servit et al., 1981). This activating effect could also be produced by air insufflation into the upper nasal cavity without inflating the lung. Local anesthesia of the nasal mucosal membrane suppressed the cortical effects of airflow stimulation. They also showed how deep breathing through one side of the nose could activate abnormalities in epileptic patients with unilateral focal or lateralized paroxysmal abnormalities in the fronto- or occipito-temporal region. "The abnormalities of this type were significantly more activated from the ipsilateral nasal cavity (Servit et al., 1981)." However, these paroxysmal abnormalities were also generated with contralateral breathing to the foci in 60% of the patients. These abnormalities are not equivalent to the sustained contralateral increases in EEG activity produced in the Werntz et al. (1987) study, as this paroxysmal activity manifests as intermittent spikes in only a small fraction of the record with epileptic patients.

Right and left UFNB also have differential effects on heart rate and end diastolic volume (Shannahoff-Khalsa and Kennedy, 1993), oxygen consumption and galvanic skin responses (Telles et al., 1994), eye blink rates (Backon and Kullok, 1989), intraocular pressure (Backon et al., 1989), glucose levels (Backon, 1988), and is a natural endogenous correlate to electrically-induced unilateral vagus nerve stimulation (for reviews on UFNB see Shannahoff-Khalsa (2007, 2008)).

Another method to unilaterally activate the cortex is by the use of transcranial direct-current stimulation (tDCS). TDCS has been used to treat medication-refractory schizophrenics with auditory verbal hallucinations, when the anode is placed over the left dorsolateral prefrontal cortex and the cathode is placed over the left temporal cortex. The study of this approach showed a mean reduction in hallucinations of 31% when compared to sham stimulation, with effects lasting up to 3 months (Brunelin, et al., 2012). A meta-analysis of 15 studies from 1999 to 2006 of yet another method for unilateral activation employs slow repetitive regional transcranial magnetic stimulation (rTMS) over the left temporoparietal cortex. When compared to sham treatment for resistant auditory hallucinations in schizophrenics, the data "provides evidence for the efficacy of rTMS as an intervention that selectively alters neurobiologic factors underlying auditory hallucinations" (Aleman et al., 2007).

Here we report on one schizophrenic female (Ms. E.) with auditory and visual hallucinations. Ms. E. is highly trained with the use of Kundalini Yoga meditation techniques and is acutely aware of her hallucinations and her pre-episode aura. Her history and the rationale for this case study are reported below. She kept a detailed record for 3 years (starting in January 2009 at age 31) of all her hallucination episodes and initial nasal dominance along with details about the episode duration, severity, and time to the onset of a yogic practice that was then designed to help curb hallucinations (see below).

2. Methods

2.1. Subject case history

Ms. E, age 19, while attending a university began using tobacco, alcohol, amphetamines, marijuana, and psychedelics. At age 24 she was diagnosed with depression and prescribed citalopram. After two weeks of citalopram she experienced her first manic episode and was hospitalized, prescribed olanzapine, topiramate, and ECT that helped stabilize her condition. Soon she began working full time. At age 25 she quit amphetamines and psychedelics. After 1 year she stopped all medications, due to their side effects, without informing her psychiatrist. Shortly thereafter, she stopped working and began living with her mother and quit using marijuana, alcohol, and tobacco. At this point she began to experience visual and auditory hallucinations, and delusions that lasted for days or weeks at a time. In the earliest stages she claimed that the hallucinations were "pleasurable like a fantasy, mythical, cosmic, and grandiose."

At age 26 she sought psychiatric help again and was diagnosed with bipolar disorder with psychotic features and borderline personality disorder. She was prescribed olanzapine and lithium. At this point she sought help from *author* DSK on how to use Kundalini Yoga meditation techniques to help cope with her bipolar disorder, without informing him of her psychosis or her personality disorder diagnosis. She was taught a yoga protocol specific for her bipolar condition (Shannahoff-Khalsa, 2006, 2012), and seen twice over a 1.5 year period. The yoga and medications helped her maintain "a stable though light level of mania without hallucinations." Again without notifying her psychiatrist (or DSK) she went off medications and later reported "the hallucinations that came were at their worst." She was admitted to a long-term locked facility where "the visions and voices took on a synergistic nature and these experiences became increasingly painful and I felt increasingly out of control." The hallucinations fed her delusional thoughts and her visions included transformations of the physical bodies of other patients and objects, which she believed to be real. While she was still interested in yoga, she then proceeded to devise her own yoga routines. While the medications had no effect on her hallucinations, that started every afternoon and lasted for 6–10 h, the self-prescribed yoga eventually brought the episodes down to twice a week.

Ms. E. was not in contact with DSK for two more years until her mother requested a new consult for her at age 30. Whereupon Ms. E. informed DSK of her earlier diagnosis with psychotic features and the chronic hallucinations and that her new psychiatrist had diagnosed her now with schizophrenia and a narcissistic personality disorder along with the bipolar condition and borderline personality disorder. She started living in a mental health board and care facility in August 2007 (age 30), prescribed clozapine 275 mg and fluphenazine 10 mg, and started attending college part-time. Her hallucinations had stabilized but "remained intolerable but came unexpectedly at about regular intervals twice a week." DSK then taught her a completely new set of Kundalini Yoga exercises and meditation techniques to also help her treat her hallucinations (see Shannahoff-Khalsa (2010), *chapter* 2, *pp.* 54–74). In November 2008, after 4 weeks of the new practice her hallucinations were reduced to once a week and the duration of her episodes was reduced from 6–10 h at a time to 2–3 h. At this point she stopped fluphenazine, again without permission.

Due to her new commitment with a difficult set of exercises and meditation techniques DSK noted that she was not only progressing but had developed a high level of skill and strong interest in the techniques. In January 2009 (age 31), DSK suggested that she start to observe if one of her nostrils was more patent than the other during the onset of her hallucinations. In a few days she said "Yesterday I experienced mild hallucinations for half an hour after a stressful day. During the hallucinations my breath was left nostril-dominant, and as soon as it was over my breath switched to right-nostril dominance." DSK found this instantaneous switch a very interesting result, and asked her to continue to observe and note the relationship of her nostril dominance and other details of her hallucination episodes. After some months and at least 15 episodes it was clear that she was only left nostril dominant during the hallucinations, but on a rare occasion they would start during the short transition phase where both nostrils are equal but then leading only into left nostril dominance.

Several days after the first observation in January 2009 of her left nostril dominance at the beginning of a hallucination, DSK suggested that she attempt slow deep breathing only through her right nostril during her hallucinations. This quickly led to some relief in severity and duration. In March of 2009, DSK developed a 4-part "mini-protocol" to be practiced only during an episode of hallucinations that included a unique 4-part stepped broken breath inhale and 4-part stepped broken breath exhale pattern only through the right nostril along with two mantra techniques before the 4-part right nostril breath technique and one mantra technique after (Shannahoff-Khalsa, 2010, 2012). Ms E. immediately reported that this protocol "quickened the recovery from my hallucinatory state and took away the sense of dread that accompanied the hallucinations."

From January 2009 to June 2010, Ms. E. was alternating days with 200 and 225 mg of clozapine. On June 10, 2010, she was hospitalized until June 23 and her clozapine was increased to 300 mg a day and slowly decreased after her release. In December 2011 her clozapine was alternating days with 225 mg on one day and 200 mg the next. In November 2012 she was at 200 mg. In December 2012, she went to 175 mg, 200 mg, and 200 mg and remains at this dose at the time of this submission (June, 2013). She remains stable with reduced hallucination episodes in time, frequency, and severity.

2.2. Method for data collection and statistical analysis

Ms. E. does not have a deviated septum, partial chronic nasal occlusion, or any other nasal defects. She has never had a broken nose or head trauma. Given her training and sensitivity she is skilled at determining her nasal dominance. When she began to experience the initial phase of a hallucination she would monitor her nostril dominance and chart the dominant nostril and time, and the time when she started the 4-part mini-protocol. When the hallucination episode ended she charted the end time, the practice time for the 4-part mini-protocol, the place of occurrence (home or place away from home) and any other significant details about her episode, and on August 8, 2010, day 573 of the record, the severity of the episode was then started to be recorded with a self-devised severity rating scale with a range of 1–10, with 10 being the most severe. However, her maximum severity score during the period of severity record keeping never went above 8. She kept a diary for the days of record.

Data were examined initially for missing values. Descriptive statistics were obtained for all variables and tests of normality of continuous measures were made using the Shapiro–Wilk W and the Kolomogorov D statistics in conjunction with plots of the distribution of data and descriptive measurements. Data were also examined for homogeneity of variance. No significant variation from the normal distribution was found. Data were analyzed using analyses of variance (using a Bonferroni correction for multiple comparisons) for continuous variables and Chi-square analyses for dichotomous variables. These analyses were performed using the SPSS version 19. All analyses were two-tailed, where applicable, with $\alpha = 0.05$.

3. Results

Fig. 2 plots the times series of hallucination events, their duration in hours, and whether the event is left or right nostril dominant, or on rare occasion undetermined over a time period of 1086 days. The number of hallucinations for left nostril dominant events, right nostril dominant, and unknowns was 86 (59%), 41 (28%), and 18 (13%), respectively. When comparing only left versus right there was a significantly higher number of hallucinations for left nostril dominant events ($\chi^2 = 15.95$, d.f.$=1$,$P < 0.001$). There was no significant difference on mean duration in hours of the episode for left versus right nostril dominant events (L: 1.43 ± 1.1; R:1.35 ± 0.9; $f=0.193$; d.f.$=1125$; $P=0.661$). There was a significant difference between left and right nostril dominant events on the time elapsed before starting the 4-part mini-protocol treatment (L:0.42 ± 0.6; R:0.70 ± 0.8 h; f:5.1; d.f.:1123; $P=0.026$). The duration of this treatment for the left versus right nostril dominant episodes was nearly identical (L:0.45 ± 0.2; R:0.44 ± 0.2 h; f:0.007; d.f.:1124; $P=0.931$). There was a significant difference on the total time after the end of the practice of the 4-part mini-protocol until the end of the hallucination episode (L:0.56 ± 0.9; R:0.21 ± 0.6; f:5.01; d.f.:1123; $P=0.027$). Limited measurement of the severity of hallucinations was collected from 8-8-2010 to 12-31-11. A total of 60 events toward the end of the record were analyzed for severity. Although values were higher for right nostril, it was not significantly different from the left nostril (L:0.93 ± 1.7, $n=44$; R:$1.31 \pm 0.1.8$, $n=16$; f:0.566; d.f.:1,58; $P=0.455$).

When we cross-referenced this data with her recorded location status (home or away from home) we found that she had recorded location and nostril dominance in 109 of the 127 left or right events. With these 109, 71 hallucination events were left and 38 events were right nostril dominant. There was a significant association between left and right nostril dominance and her location ($x^2=5.37$, d.f.$=$ 1, $P=0.021$). Seventy Seven percent of left dominant and 95% of right dominant events occurred while she was away from home. Therefore, the ratio of left to right events for home versus away favors the left for at home and the right away.

There was a significant negative correlation between hallucination duration and number of days that Ms. E. was recording this information ($r=-0.337$, d.f.$=127$, $P=0.0001$). Furthermore, there was a significant difference between the 3 years of data collection on the hallucination duration ($f=9.14$; d.f.$=2124$; $P=0.0001$). This duration was significantly shorter in the third year compared to the previous 2 years (1st: 1.75 ± 0.9, 2nd year: 1.59 ± 1.3, and 3rd year: 0.89 ± 0.6).

4. Discussion

This single case report documents the initial nasal cycle dominance at the onset of hallucinations in an adult schizophrenic female over a period of 1086 days, during which 145 hallucination episodes occurred. Fifty nine percent (86) occurred when the subject was left nostril dominant, 28% (41) occurred during right nostril dominance, and 13% (18) were undetermined. Thirteen of the 18 undetermined events occurred during the first 190 days, the time of the first 36 hallucination episodes. The time until treatment with the 4-part mini-protocol was longer for the right events. The time for treatment was nearly identical for both. However, the same formula was used regardless of the initial nostril dominance. The time after treatment for the hallucinations to stop was longer with the left nostril dominant events. While there was a greater rating of severity for the right events, the difference compared to the left events was not significant. Since the events that occurred at home were significantly more left than right, and those away from home were significantly more right than left events, this may explain why it took longer for Ms. E. to administer the protocol after onset for the right events. She was not always able to engage treatment while she was away from home. In addition, the duration and frequency of occurrence of hallucinations significantly diminished over time.

Overall, in this subject, the frequency of hallucination events occurred significantly more often during left nostril dominance and took longer to resolve after the acute mini-protocol treatment. While the right nostril events were slightly, but not significantly more severe, it may be that the experience of a hallucination when the patient was away from home, which was significantly more frequent for the right nostril events, affected this rating measure. Since left nostril dominance correlates with right cerebral hemisphere dominance (Shannahoff-Khalsa, 2007, 2008; Werntz, et al., 1983; Klein, et al., 1986), this suggests that this patient was more prone to hallucinations when her right hemisphere was the dominant hemisphere. A key component of the yogic protocol was primarily specific for activating the left cerebral hemisphere to help reduce the hallucinations, and this corresponds with the tDCS and rTMS studies that also stimulated the left hemisphere. In addition, the ratio of left to right nostril events occurred more often at home, and the reverse was true for events away from home. It may be that the activity phase of the BRAC, which corresponds to the right nostril-left hemisphere dominant mode of the ultradian ANS–CNS rhythm, helps explain why the right nostril hallucination events occurred proportionately more often when Ms. E. was away from home, a period of relatively greater activity.

This single case history and therapy are directionally in line with the new conventional therapies (tDCS, rTMS) for acute treatment and provides additional insight to the possible physiological basis for hallucinations, and also suggests another approach for treating acute hallucinatory states. In addition, the use of Kundalini Yoga for the treatment of schizophrenia in general, along with the complete description of the 4-part mini-protocol for treating acute hallucinations is described in complete detail elsewhere (Shannahoff-Khalsa 2010, 2012).

5. Limitations and alternative hypotheses

This is a single case subject with a female that experiences hallucinations. While it may have been problematic, and perhaps not too practical, the data would have been more rigorous if there was an objective instrumental measure of her nasal cycle dominance. In addition, while this left nostril-right hemisphere predominant result is consistent with the tDCS and rTMS studies, additional and controlled studies with many more additional subjects would add greatly to the field. One could test to see if left nostril (instead of right nostril) UFNB actually worsens the severity and duration of the hallucinations. However, this may be a

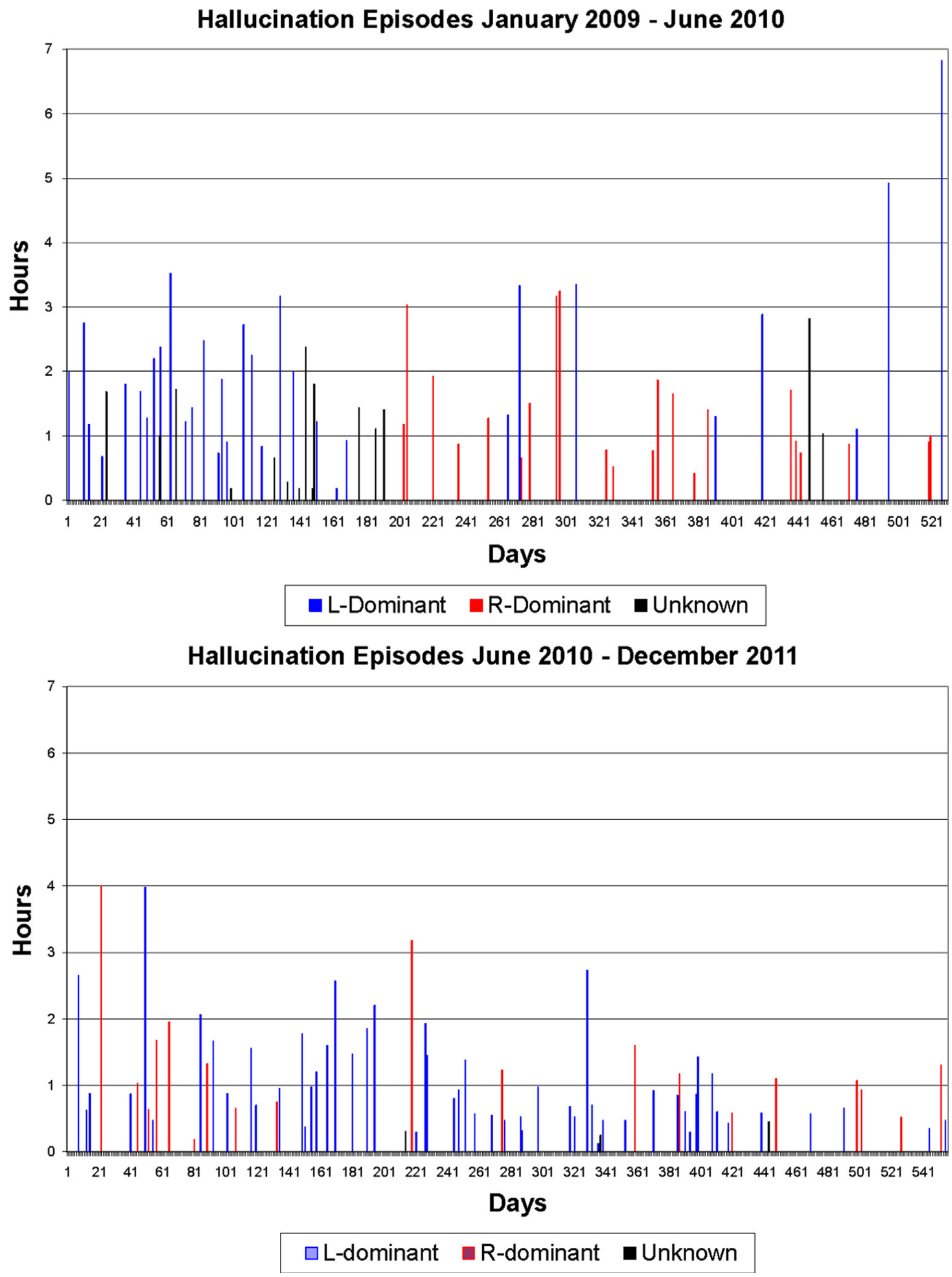

Fig. 2. Plots the times series of hallucination events, their duration in hours, and whether the event initially is left nostril dominant, right nostril dominant, or undetermined over a time period of 1086 days. Blue lines represent left nostril dominant events, the red lines represent right nostril dominant events, and the black lines represent events when the subject could not determine the nostril dominance. The top portion of the figure includes days for January 2009 through mid-June 2010, and the lower portion of the figure are days from mid-June through December 2011.

problem for some internal review boards, given the data here. An alternative hypothesis could be that the subject predetermined on her own that she would be left nostril dominant and that she skewed her findings to match her expectations. Perhaps other hypotheses could also be put forward.

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