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There's Something in the Air: Empirical Evidence for the Effects of Negative Air Ions (NAI) on Psychophysiological State and Performance

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Abstract Numerous reports document advances made in our understanding of the effects of negative air ions on physiological functions and human health. Collectively, these reports demonstrate an increasing awareness of their mechanisms, and reflect contrasting findings about their influence. The purpose of the present paper was to review the evidence base for the beneficial effects of negative air ions (NAI) in improving neuropsychological performance and treating mood disorders. Underlying mechanisms, treatments parameters and the extent to which negative air ionization can represent a valuable treatment for affective disturbances are reported together with experimental data gathered from our laboratory. The analysis, particularly with randomized, controlled trials suggests that NAI treatment for mood disorders is in general effective with effects almost equivalent to those in other antidepressant non pharmacotherapy trials. Despite the growth in clinical research, there remained a substantial gap in mental health services to translate state-of-the-art treatments and incorporate them into mainstream practice.

Keywords: *negative air ion, depressive symptoms, performance, environment*

1. Introduction

Meteorological conditions are one of the factors influencing the morbidity and mortality of a population. Sudden changes in the weather may represent a risk factor, mainly to individuals with an existing chronic condition, e.g. cardiovascular, cerebrovascular or respiratory disease. Schneider et al. [1] showed that a change in weather parameters (such as a decrease/increase in air temperature and water vapour pressure) was associated with significant changes in heart rate and electrocardiography parameters. Ischeamic heart disease mortality in winter in the UK is related to air mass changes; the types of weather associated with increased mortality are (1) anticyclonic systems with advection of cold dry continental air, and (2) well-developed and deepening North Atlantic storm systems moving towards or over the UK with rapidly moving fronts [2]. Blood pressure may also be affected by changes in weather: transitions from an anticyclonic air mass (a day with settled weather conditions, high atmospheric pressure, low air temperature, and prevalently clear sky) to a cyclonic air mass (a day with opposite weather characteristics) were found to be characterized by a significant increase in ambulatory blood pressure in winter in Italy [3]. Finally, the periods around weather changes are associated with pronounced patterns in mortality: a significant increase in mortality is found after large temperature increases and on days of large pressure drops; a decrease in mortality occurs after large temperature drops, pressure increases, and passages of strong cold fronts. Temperature generally plays the most important role in day-to-day variations in mortality, and the sudden pressure changes should be considered in models for predicting excess mortality [4]. Therefore, it is important to study links between changes in weather and human health. The purpose of the present paper is to provide a review of the evidence for the effects of negative air ions (NAI), and their effectiveness as treatment of mood disturbances revealing underlying mechanisms.

There was some evidence that air ion concentrations an ion polarity ratio result in physiological effects [5,6,7,8]. Ions are charged particles that are formed in nature when enough energy acts upon a molecule such as carbon dioxide, oxygen, water, or nitrogen to eject an electron from the molecule leaving a positively charged Ion. The displaced electron attaches itself to a nearby molecule, which then becomes a negatively charged ion. The atmosphere we breathe contains positive and negative ions. The light atmospheric ions are represented by a group of 10-30 neutral molecules aggregated around the particle with electric charge. Their life time is not longer than few minutes. These particles perform chaotic motion which is generally known as the Brownian motion. In the case of sufficiently high concentration of ions ($n \approx 10^3$ cm^{-3}) and uni-polarity coefficient P (ratio of positive n^+ and negative n^- ions concentration) tends to 1, the micro-climate is taken as suitable for therapeutic usage. Roughly one-third of the population seems to be particularly sensitive to negative-ion depletion [9,10]. The normal count in fresh

country air is 2,000 to 4,000 negative ions per cubic centimeter. The concentration of atmospheric ions in a given environment depends on a multiplicity of factors. In an outdoor rural setting the air may contain 2000 positive and 1500 NAI per cubic centimeter. These levels can be modified both by natural factor (e.g. levels of background radiation, short-wave UVA light) and environmental factors (e.g. industrial pollution, air conditioning). Their main action seems to be through entry through the respiratory system.

There are two types of generating methods: one is by corona discharge, and the other is by water shearing similar to the Lenard's effect. The former method charges every substance in the air negatively, generating ozone as a by-product. The latter method only generates superoxide ions attached to microclusters of water and is essentially considered a natural source of negative air ions [11]. High levels of negative air ions created by water shearing are observed near waterfalls, ranging from 2000 to 10,000 ions/cm^3. Superoxide causes oxidative damage to various tissues and is suppressed by superoxide dismutase (SOD). However, an interesting study reported a low intensity of superoxide increasing SOD activity, whereas a high intensity decreased SOD activity [12]. Only recently it was suggested that their biological action is somehow related to free radicals [13]. Negative air ions function as "sparks", initiating and sustaining processes in which reactive oxygen species (ROS) participated accompanied by production of high grade electronic excitation. This energy can be used for bionergetic and bio-regulatory functions [9,14].

At present, two lines of empirical evidence suggest that NAI can affect organisms. The first of these involves epidemiological data. The possibility that air ions may influence human health has been suggested since the beginning of the 20^{th} century. Studies in the 1950's and 1960's indicated that human well-being was affected by weather conditions. Warm dry winds such as the Siroccoco (Italy), Sharkije (Egypt), Santa Ana (California), Hamsin or Sharav (Middle East) or the Foehn (Central Europe) are associated with a sudden increase in morbidity. With such winds, related to elevated levels of positive ions, about 30% of the general population reported migraine, depression, irritability, lethargy or respiratory symptoms. Physiological and neurological changes resulted in an increase in human errors. Sulman and Kreuger's work led to the hypothesis that serotonin was involved in a mechanism of interaction between air ions (concentrations and polarity ratio) and biological systems [15,16,17]. Because of NAI suppress serotonin levels in the same way that natural sunlight suppresses melatonin, evidence for the impact of ions on psycho-physiological status is provided by the findings of naturalistic and laboratory studies. Over the years, it has been claimed that NAI can influence, in several mammalian species, growth, metabolism, immunological responses, and reactions to environmental stressors [8]. This controversial literature has been reviewed by Kotaka [6]. NAI have been proved to slow growth of bacterial cultures and reduce viable cell count in bacterial aerosols [5,18]. In addition, a study found that negative ions significantly enhanced the cytotoxic activity of natural killer (NK) cells, and significantly decreased the incidence of cancer and inhibited tumor growths [19]. Anti-tumor effects were attributed to enhancement of NK activity, as showed by the efficacy of the Shinki Bioclean Room ® for preventing infection in neutropenic patients with acute leukemia who received intensive chemotherapy [20]. The decreased production of stress hormones may also partially contribute to the increased NK activity. Nevertheless, the use of ion generator was used mostly as a tool for bacterial and chemical decontamination in biological, genetic and food industries [5,7]. To investigate the effect of air quality on well-being and longevity, the Chinese Gerontological Society carried out a study in Zhongxiang, a city located in the Southeast of China in which historically had many residents with long life spans. Air quality values in both indoor and outdoor air samples resulted much greater than those typically present in an urban enclosed housing area [21]. All the negative ions contents in the selected sites were >300 ion/cm3, and almost all the positive to negative ion ratios were between 1 and 3. The SO_2 and the inhalable particulate levels in the air of Zhongxiang were within the grade I air quality standard suggesting that air quality can be considered a relevant factor for health and longevity.

The main reason for the poor and unfortunate use of NAI for clinical purposes was the lack of knowledge of the primary mechanisms of their action [12,14]. A second reason was that research about NAI effects suffered for methodological shortcomings, including failure to control NAI concentration, humidity, or temperature, and differences in apparatus used. Finally, the decrease of their application to clinical settings can be attributed at the appearance of numerous drugs, attractive to both physicians and patients.

2. Hypothesized Mechanisms of Influence and Preliminary Data

Kreuger [15] reported that in laboratory subjects serotonin could be affected by the polarity and concentration of air ions breathed. Serotonin produces neurovascular, endocrinal, and metabolic effects and plays an important role in mood and sleep patterns. Sulman and colleagues have reported that individuals suffering Sharav wind sensitivity have been successfully treated by inhalation of air containing excess negative ions, or by administration of serotonin blocking drugs [16]. The first pioneering observations have shown that levels of cerebral and tracheal 5-HT, a metabolite of serotonin (5-hydroxytriptamine) was decreased and the urinary level of 5-hydroxyindoleacetic acid (5-HIAA) was increased in rats following exposure to negative ions [13,17]. Alterations in 5-HT concentrations were implicated in sleep, activity level, pain, anxiety, somatic complaints and changes in the circadian rhythm [22,23].

Systems for NAI generation can be broadly divided into water-generated NAI arrangements based on the Lenard effect and electrically-generated NAI using corona discharge. It has been suggested that water-generated NAI have a longer lifetime and more beneficial effects on autonomic regulation, immunologic activation, and aerobic metabolism [14]. Is the gas-phase superoxide of atmospheric air (GS) that plays a key role in the biological activity of NAI [9]. The activation of the hypothalamic-pituitary complex and increase in ACTH secretion, which

may result in the increase in the sensitivity of the hypothalamic neurons to the signals and shortened latent period of responses, are considered as one of the principal physiological mechanisms underlying the effect of GS. A similar process was showed for NAI. Other structures and biochemical systems are in the basal ganglia, which are functionally connected with the hypothalamus and represent the subcortical link between the association and motor areas of the brain cortex involved in the modulation of activity of the serotonergic system and activation of endogenous opiod production.

2.1. First Empirical Evidence

In rats exposed to NAI hippocampal pyramidal neurons were more sensitive to microiontophoretically applied 5-HT than those of control rats. Recent data suggest a potential molecular mechanism within the serotonergic system by which a reduced capacity for negative feedback regulation of 5-HT release is associated with increased amygdala reactivity and, in turn may contribute to both the risk for major depression and the therapeutic effects of antidepressant drugs [22,23].

In addition, power spectral analysis of beat-to-beat intervals of heart rate (heart rate variability; HRV) it was performed, and the high-frequency component (HF component, 0.8-3.0 Hz) in the power spectrum of HRV was calculated in rats exposed to NAI or normal air. Since it has been suggested that HF power of the HRV spectrum is a measure of parasympathetic modulation of sinus node function, it was used as a tool to assess effects of NAI on parasympathetic control of heart rate. Data indicated that NAI exposure decreased HR and increased HF power of the HRV spectrum, suggesting that NAI could be effective in inhibiting sympathetic nervous activity and/or activating parasympathetic nervous activity. Focusing on neuronal activity in three brain regions responsible for autonomic regulation, findings indicated that exposure to NAI could decrease neuronal activity in paraventricular nucleus of the hypothalamus (PVN) and locus coeruleus (LC) and increase the activity of nucleus ambiguus (NA) neurons [25].

3. Evidence-based Effects on Neuropsychological Performance and Mood Disorders

The effect of NAI , on depressive symptoms or mood disturbances has initially yielded rather variable results [15,26,27,28]. Sometimes faulty experimental design has allowed the influence of extraneous factors, and results have been wrongly attributed to NAI action. Major factors causing errors of observation can be the neglect of the effect of ozone and nitrogen oxides produced by corona discharge ion sources, failure in monitoring ion densities, temperature and humidity of air containing particulate or gaseous pollutants or failure to hold experimental subjects at electrical ground potential [26].

It is well known in research design that evidence grading is highest for a systematic review with meta-analysis of randomized controlled trials (RCTs). Although many studies have reported the effects of NAI, there is no systematic review of the evidence of their effectiveness. The objective of the present paper was to summarize the evidence on the human health enhancement effects of NAI, and to assess the quality of those trials. PubMed, PsycLit and the Cochrane Library were searched using a list of terms available on request. The literature was searched up to 1980 for the earliest searches and 2012 for the latest ones. Articles were included if they reported treatment of individuals selected as having an anxiety disorder or a high level of anxiety symptoms, mood disturbances or depressive symptoms, performances in neuropsychological tasks in clinical and non-clinical samples. All research or review articles were considered for analysis, while historical articles, editorials, expert opinions and proceedings of congresses were excluded. Articles published in supplements or special issues and patents were not reviewed. Letters to the editor were included if they explicitly reported the results of a study (e.g. case reports). The selection and assessment of articles were based on analysis of the abstract.

The evidence was evaluated according to the modified Sackett's system [29]: randomized controlled trials (RCT) (Level I) and non-randomized controlled trials (CCT) (Level II) at the top, observational studies in the middle (Level III), and uncontrolled studies at the bottom (Level IV). Expert opinion was not included in this study. Studies with historical controls were included within the CCT category. Cross-sectional studies, case-control studies, cohort studies and studies without interventions were included in the Level III category. Further article categories were literature reviews (containing systematic reviews and reviews, Level V). It should be noted that these levels relate to the quality of the evidence, not the effectiveness of the NAI administration. A treatment could have been evaluated by rigorous methodologies and found to be ineffective or, conversely, evaluated by weaker methodologies, but found to be highly effective.

There was no restriction on participants (patients or healthy participants). Studies included at least one treatment group in which NAI treatment was applied for empirical investigations. Disagreements and uncertainties were resolved by discussion with other colleagues. Studies were selected when (a) the design was with humans participants, (b) one of the interventions was a form of NAI administration, and (c) contained relevant literature.

The literature searches included 20 relevant articles. Nine publications were excluded because they did not meet the eligibility criteria. The language of the eligible publications was English. A meta-analysis could not be performed as the main outcome measures were different and could not be compared between the eligible papers.

For Level I a total of sixteen articles was reviewed. Three of them showed the effects of NAI on improving selective attention, incidental memory and cerebral activation in learning impaired participants [30,31] but amplifying a time-phased information processing disorder in mentally retarded individuals [32]. There have been five randomized placebo-controlled studies of the effect of NAI on heart rate (HR) and temperature [33], reaction times [34], salivary chromogranin A (CgA), cortisol, reported anxiety [12,35,36] showing that NAI are effective for the reduction of and the prompt recovery from stress. The peripheral limbs of the stress system are the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic/adrenomedullary (S/A) system. The activities of the HPA axis and the S/A system can be biochemically

evaluated by measuring the catecholamines and cortisol, respectively. Examining the effects of NAI on computer operation using the salivary chromogranin A-like immunoreactivity (CgA-like IR) and self-report questionnaire (State-Trait Anxiety Inventory, Anxiety State- STAI-S), il was demonstrated that NAI attenuated CgA-like IR level that had increased after the task [35].

A placebo-controlled study [36] showed that musically based auditory stimuli, bright light and high-density ions produced rapid mood changes in healthy subjects. While both serotonergic and catecholaminergic activation may mediate response to light therapy, NAI effects may be mediated by both central and peripheral serotonergic activity but the mechanism of action of the specific auditory stimulus has not been investigate.

There have been a total of eight randomized controlled trials carried out by Terman's research group. In Seasonal Affective Disorder [37,38,39], the reduction in depression rating scale scores was significantly greater at the NAI higher dose, with a large effect size. No emergent side effects were identified [37]. High ion flow rate (e.g., 4.5×10^{14}ions/second^{13}), as used in the studies described above, may be needed to override uncontrolled modulating environmental factors such as relative humidity, room size, and the proximity of grounded objects. The antidepressant effect of high-density negative air ions has also been observed in patients with chronic depression >2 years in a 5-week randomized, controlled trial [40]. Both bright light and NAI treatments were found to be superior to placebo control, and the remission rates were similar to those for SAD, but without showing a seasonal dependency or mediation by circadian rhythm phase shifts. Background, treatment method and detailed description are reported in a United Stated Patent paper [41]. Although the antidepressant effect of NAI in Seasonal Affective Disorder has been independently replicated using post-awakening administration, the result for administration during sleep remains a novel observation [39]. Basing on higher levels of evidence, there was promising evidence (Level I) for high-density air ionization also as a treatment for acute mania phase [42] and bipolar depression [43]. Moreover, other investigators provided evidence for the effects of NAI in treating SAD [44].

In Level II of evidence category there have been a total of four articles. Three of them reported experiments carried out with undergraduate students. Their results suggested that moderate concentrations of NAI increased performance on cognitive tasks (baron 1) while high concentrations enhanced physiological arousal and errors [45], and interpersonal aggression by Type A individual [46]. With male healthy subjects a paper (Level II) Buckalew and Rizzuto [47] reported that the exposition to NAI for 6 hours increased subjective perception of relaxation. In a second paper Buckalew and Rizzuto [48] failed to found significant effect on cognitive or psychomotor performance and physiological condition with the same procedure. Finally, in two reviews (Level V of evidence) environmental aspects [49] and mechanisms of physiological action of exogenous reactive oxygen species are illuminated [9].

As expected, there was a tendency for a beneficial impact of NAI administration and articles reviewed show high level of evidence. RCTs are traditionally the gold standard for judging the benefits of treatments, because they are more able to attribute effects to causes. However, the use of RCTs may be limited by ethical, or practical factors. In fact, RCTs generally require more resources than other studies, sometimes there may be problems with randomization or recruitment, and the treatment of patients with an intervention believed to be ineffective is often considered to be unethical.

4. Data Gathered in Our Laboratory

4.1. Pilot Study

Using 10 male Wistar albino rats we investigated in our laboratory if air ion affect learning in a maze. All animals were kept in standard rat cages, 5 rats per cage and housed in an air-conditioned room with controlled lighting (12hr light/dark). Rats were divided into the control and experimental groups at random. All rats were allowed free access to water and rat chow. Our results indicated that as consequence of two weeks of 15 min. NAI exposition (the animals rested under constant temperature of 24±1°C and humidity of 47±1%) the experimental group show a significant reduction in error and time scores, confirming almost in part previous data [50].

4.2. Clinical Trials with Mood Disordered Participants

The proposal of our research plan was designed to evaluate the antidepressant effect of NAI as a potential treatment modality for mood disorders and also for patients who discontinue or cannot tolerate antidepressants, fail to maintain positive response, or are drug non-responders. The experimental equipment is based also on Prioré pioneer experimental work [51]. Our prototype consisted in a grounded box containing ion generators and lamp where many intervening variables are controlled (byproducts by the majority air ionizers, temperature, and air humidity). Basically, the fundamental part of the device are: a) air ionizers installed in a box of 2.20 x 2.70 x 2.70 m^2 that neutralize effect of ozone and nitrogen oxides produced by corona discharge included in the device; b) UV- lamp for producing artificial NAI at concentrations close to the natural background which do not affect the level of anti-oxidative protection of the organism, c) reader unit. Generally, the equipment is adjusted so that the ion level is approximately of 7.0-8.0 x $10^4/cm^3$. Production of ozone and nitrous oxides is reduced to a minimum. The tests were conducted in the box with a temperature of 24 ± 1°C and relative humidity of 45 ± 2% was maintained by an air-conditioning system. Upper-room UV light efficacy depends on adequate mixing of lower- and upper-room air through simple convection currents that may be augmented by mechanical ventilation systems, or inexpensive mixing fans, as in the current study. The devices contained a fan to re-circulate chamber air through the negative ionic air purifier. Design is according to international and European safety standards. The casing of the room is grounded which guarantees a stable and continuous ion flux.

The first study was designed to evaluate the effects of NAI on anxiety and depressive symptoms in asthmatic female patients. Twenty-height clinically stable adult patients (age range, 18-43 years) with persistent asthma

were randomly allocated to NAI treatment or placebo group (self-management of symptoms). The inclusion criteria were: a) ages of participants, b) a continuous use of inhaled steroids for at least last 1 year, c) stable phase of disease during the last 3 months. The exclusion criteria were: 1) smoking history of 10 or more years, and 2) other diseases that could influence bronchial symptoms and/or lung function.

Patients were instructed to measure their PEF three times every morning using a peak flow meter, and to record daily symptom scores (based on presence of cough, expectoration, wheeze, breathing difficulties, and nocturnal awakening) using a scale from 0 to 3. Patients were also requested to document if a supplemental beta-2 agonist was used. Self-management training required the implementation of an action plan and recording information on a diary. All participants who received NAI treatment (3 weeks of 25 min exposition) had improved scores on assessments of depression (Beck Depression Inventory, BCI) and anxiety (STAI-X) and showed a significant reduction on asthma outcomes (number of asthma exacerbation, doubling dose of inhaled corticosteroids, use of oral prednisolone and antibiotics, and asthma symptoms).

Zhang and Zu [52] confirmed that 254 nm UV irradiation conduces to high negative AIC (NAIC) [18], [53]. UV radiation is also responsible for cutaneous synthesis of vitamin (vit) D3, a substance that is then sequentially hydroxylated in the liver and kidney to yield 1,25 (OH) 2 vit D, a hormone critical for calcium homeostasis and skeletal maintenance. Several studies suggested an association between vit D deficiency and executive cognitive functions, depression, bipolar disorder, and schizophrenia. Vitamin D activates receptors on neurons in regions implicated in the regulation of behavior, stimulates neurotrophin release, and protects the brain by buffering antioxidant and anti-inflammatory defenses against vascular injury and improving metabolic and cardiovascular function. The second study was a randomized controlled, parallel group clinical trial. Inclusion criteria were: single depressive episodes, seasonal affective disorder (SAD), major depressive episode with dystymia, chronic depression, bipolar disorder, atypical depression etc. Thirty-two patients participated and were diagnosed by trained psychiatrists basing on the *Structured Clinical Interview for DSM-IV Axis I Disorders* (SCID) according to the DSM-IV [54]. Subjects were randomized in different exposure conditions. Group 1: NAI on/lamp on; Group 2: NAI off/lamp on; Group 3: NAI on/lamp off, and Control Group a placebo treatment (with NAI device disabled).

Treatments were taken in the early morning for 30 min over 21 days, followed by withdrawals. Short term outcomes immediately post-treatment were evaluated and compared across groups. Post-treatment session occurred at the end of treatment with the aim to evaluate Depressive symptoms (Hamilton Rating Scale for Depression – HAMS) [55]. Data showed group 1 and 2 treatments to be more effective. Negative air ionization with or without UV lamp both appear to act as specific antidepressants for man and women and appear to influence performance on cognitive tasks (self-report data on everyday activities and simple tasks). Although we may not be certain of the mechanism of vitamin D action on mood and cognition, it seems prudent to ensure that all adults receive an adequate intake of vitamin D. Additional understanding of these mechanisms are necessary.

5. Conclusions

Application of NAI in clinical e non-clinical settings was decreased during last years. Heterogeneity among studies and lack of standard approaches to NAI treatment procedure (parameters of active versus control conditions, NAI generation device and exposition duration) and rigorous designs (adequate group size, randomized assignment, inherent challenges in creating an acceptable placebo.

The limitation in much of the literature on NAI may have created the unsubstantiated impression that the treatment itself has limitations in terms of its efficacy. When we analyzed the data from all available studies, particularly in randomized, controlled trials a significant reduction in symptoms severity was demonstrated together with an increasing performance in healthy participants. While pharmaceutical industry has devoted considerable resources for potential new antidepressant pharmacotherapies, there has not been a similarly endowed industry to support the development and testing of NAI.

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