Environmental Epidemiology of Essential Tremor

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Abstract

Background: Essential tremor (ET) is one of the most common neurological disorders. Despite this, the disease mechanisms and etiology are not well understood. While susceptibility genotypes undoubtedly underlie many ET cases, no ET genes have been identified thus far. As with many other progressive, degenerative neurological disorders, it is likely that environmental factors contribute to the etiology of ET. Environmental epidemiology is the study in specific populations or communities of the effect on human health of physical, biologic and chemical factors in the external environment. The purpose of this article is to review current knowledge with regards to the environmental epidemiology of ET. *Results:* As will be discussed, a series of preliminary case-control studies in recent years has begun to explore several candidate toxins/exposures, including harmane (1-methyl-9H-pyrido[3,4-b]indole), lead and agricultural exposures/pesticides. *Conclusions:* While several initial results are promising, as will be discussed, additional studies are needed to more definitively establish whether these exposures are associated with ET and if they are of etiological importance.

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Introduction to Essential Tremor as a Clinical Entity

Essential tremor (ET) is a chronic, progressive, degenerative brain disease whose most recognizable feature is a 4- to 12-Hz kinetic tremor (that is, tremor occurring during volitional movement) of the arms [1]. The tremor may range in severity from mild and functionally unimportant to severe and disabling [2–6]. Aside from arm tremor, head and voice tremors may occur as well [1, 7]. The clinical features can include a number of other types of tremor, other motor manifestations and nonmotor features. In terms of other types of tremor, many patients also have intention tremor (that is, tremor while approaching a target) and rest tremor occurs in some as well [8–10]. Other motor manifestations have been documented repeatedly. Thus, changes in tandem gait and balance can occur in some ET patients; this gait has been described as ataxic [11, 12]. ET patients with intention tremor have other cerebellar signs such as disdiadochokinesia [13]. Mild oculomotor abnormalities have been documented in ET as well [14]. The presence of a variety of nonmotor features, including specific personality traits [15, 16], anxiety [17], depressive symptoms [4, 18–20] and social phobia [21], is gaining wider recognition [22, 23]. Mild cognitive changes (especially executive dysfunction) have been documented in 6 studies [24–29] and increased odds and risk of dementia in 2 [30, 31]. Hence, the view of ET that is emerging from clinical studies is that this heterogeneous condition is probably a family of dis-

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eases whose central defining feature is action tremor of the hands but in which there is considerable clinical heterogeneity [1, 7, 32].

Epidemiology of ET

There have been more than 20 studies of the prevalence of ET [33, 34]. Estimates of the crude prevalence of this disorder have varied considerably from study to study, with a number of methodological considerations (for example, use of screening questionnaires in order to select participants for tremor examinations) contributing greatly to this variability. However, in a population-based study in Turkey, in which all individuals were examined by a study neurologist, the prevalence of ET was 4.0% among individuals aged 40 years and older and 6.3% among individuals ≥60 years of age [33]. In another population-based study in Finland that used a similar methodology [35], the prevalence was 5.6% in individuals aged 40 years and older and 9.0% among individuals ≥60 years of age. Although an age-associated increase in prevalence is a consistent finding across studies [34], and prevalence is highest after the sixth decade [33, 34], the disorder can on occasion begin in childhood [36, 37], with many of these young-onset cases being familial [3, 38, 39]. While prevalence appears to be similar in men and women, it has been reported to be marginally higher in Caucasians than African-Americans [40–42].

Two studies have provided estimates of the incidence of ET. In one study [43], which used a records linkage system to capture all health encounters with individuals with ET, the age- and sex-adjusted incidence was 23.7 per 100,000 White US population. Another study [44], which sampled ET cases directly from the population in the Madrid region, reported an incidence (age ≥65 years) of 616 per 100,000, which was substantially higher than that of the prior study.

Despite the fact that it is a progressive disorder [45–47], there are few longitudinal data in patients with ET. In one study [48], 44 patients were followed prospectively for 4 years and accelerometric data demonstrated an approximately 7% increase in arm tremor amplitude per year, while in another clinical study, an approximately 12% annual change was reported in clinical tremor ratings [49]. These studies confirm the clinical anecdotal sense that the action tremor of ET worsens over time.

A wealth of clinical data centers on the apparent links between ET and Parkinson's disease (PD) [50–56]. The development of PD has often been described in ET patients [50, 56, 57]. In recent studies, ET patients were 2–4 times more likely to develop PD (that is, ET plus PD) when compared to persons without ET [57, 58]. ET-like action tremor is more common in PD families than control families [52], further supporting the links between ET and PD, and postmortem studies have now shown that a subset of ET patients has brainstem (mainly in the locus ceruleus) Lewy bodies [59–61].

Mild cognitive changes (especially executive dysfunction) have been documented in 6 studies of ET, several of which had a case-control design [24–29]. One study further showed an increased odds of prevalent dementia and then an increased risk of incident dementia in older-onset ET cases when compared with age-matched controls [30, 31].

Studies of mortality are conflicting. While the traditional belief had been that ET was not associated with mortality, there were few data and these data were retrospective [43]. Recent data from a prospective, population-based study in Spain, showed a 45% increased risk of mortality in ET, suggesting that the disease may be associated both with increased morbidity and mortality [62].

A number of factors may influence the clinical expression of ET. First, there seems to be an association between age of onset and rate of clinical progression, with older-onset cases having a faster rate of progression [46]. Furthermore, the odds of developing head tremor are markedly higher in women with ET than men with ET [63–65].

Underlying Disease Mechanisms

It is important to consider the underlying pathological anatomy and mechanistic basis of a disease when investigating how and where a putative etiological agent like a toxin enters the brain and then how it produces pathogenic effects. The underlying anatomic pathology of ET has been elusive, although recent postmortem studies have begun to reveal some of the basic underlying degenerative brain changes in patients with this disease. These studies demonstrate 2 different pathologically defined subgroups of ET patients: the majority has degenerative changes [Purkinje cell loss and torpedoes (swellings of the Purkinje cell axon)] in the cerebellum (cerebellar ET), while a smaller number has brainstem Lewy bodies (mainly in the locus ceruleus) with a relatively preserved cerebellum (Lewy body variant of ET) [59, 66, 67]. The presence of Lewy bodies in some ET cases is intriguing

and, as noted above, may explain the apparent clinical links between ET and PD. From an epidemiological perspective, this raises the possibility that the same set of environmental risk factors might trigger both diseases.

Etiology of ET

ET is often considered to be largely a genetic disorder [68–74]. There are numerous published examples of families in which the proband and multiple relatives have ET [68, 70–72, 74–79] and in which the pattern of inheritance is most consistent with an autosomal dominant model. In 1997, linkage was demonstrated to a region on chromosome 2p22-25 in several American families [70] and, in that same year, to chromosome 3q13 in 16 Icelandic families [74]. Since then, one other study has demonstrated linkage to a region on chromosome 6p23 in several North American families [73]. Other studies have failed to demonstrate linkage to these 3 regions, indicating further genetic heterogeneity [69, 72, 80, 81]. Studies have not progressed further and no ET genes have been identified so far [69, 70, 73, 74]. A number of studies have also explored the role of genetic polymorphisms in ET [77, 82–90], with single reports of associations between ET and polymorphisms in the following genes: glutathione-S-transferase P1 (involved in metabolism of carcinogens) [84], δ-amino-levulinic acid dehydrogenase (involved in lead kinetics) [86], methylenetetrahydrofolate reductase (involved in folate- and vitamin B_{12}-dependent homocysteine metabolism) [83] and CYP2C19 (possibly related to primidone metabolism) [85].

Although widely considered to have a large genetic component, it is likely that environmental factors contribute to the etiology of ET as well. First, it is commonly stated in the literature that 50% or more of ET cases have a genetic basis, although some estimates are as low as 17% [91]. In the only familial aggregation study of ET [92], 55% of ET cases had no affected first- or second-degree relatives, despite examination of 4.5 relatives per case, on average. This was consistent with data from other series, among whom the majority (>50%) of ET cases do not report affected relatives [20, 91, 93–97]. Second, in twin studies [98, 99] concordance in monozygotic twins was <100% (that is, it was 60% in one study and 63% in another). Third, the existence of intrafamilial differences in age of onset and severity of tremor [100, 101] also suggests that environmental (or perhaps other genetic) factors may be serving as modifiers of an underlying susceptibility genotype. Fourth, temporal trends in disease inci-

dence can support the notion that environmental factors may be contributing to the etiology of ET. A temporal trend in the annual incidence of ET was reported in Rochester, Minnesota [43], where the annual age-adjusted incidence per 100,000 rose from 5.8 in the period from 1935 to 1949, to 15.8 in the period from 1950 to 1964 and 23.5 from 1965 to 1975. These data, however, should be approached with caution as this trend could also be the result of increased recognition and diagnosis of the disorder rather than a true rise in disease incidence.

Environmental factors are also thought to play a substantial role in other neurological disorders (PD, Alzheimer's disease, amyotrophic lateral sclerosis) [102–113], so that it is not inconceivable that they could play a role in ET. Using the commonly cited value of 50% for the percentage of cases that occur on a familial basis [91, 114], and given its population prevalence of 4.0% after age 39 years [33], this then suggests that approximately 2.0% of the population aged ≥40 years has a nonfamilial form of ET [33]. Despite the apparent extent of the problem, the environmental correlates for this tremor are just beginning to be explored.

Possible Environmental Toxins in ET

Harmane (1-methyl-9H-pyrido[3,4-b]indole)
In the selection of possible toxic causes of ET for investigation, the β-carboline alkaloids are a reasonable choice. They are a group of naturally occurring chemicals that include harmane, norharman, harmine, harmaline and others [115–117]. β-Carboline alkaloids are a type of heterocyclic amine; structurally, they are comprised of a combination of 5- and 6-ringed (that is, cyclic) carbon structures, which contain an amine group [118]. There is a structural similarity with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which forms the basis for one of the main toxin-induced animal models for PD [119, 120]. Like MPTP, β-carboline alkaloids are highly neurotoxic, and it has been known for approximately 100 years that administration of β-carboline alkaloids to a wide variety of laboratory animals produces an intense and generalized action tremor resembling ET [121]. β-Carboline alkaloid administration is currently the main animal model for ET and it has been proposed that new pharmacotherapies be tested using exposed animals [122–126]. The β-carboline alkaloid tremor shares many features with ET, including its principal clinical features (such as tremor frequency), drug response characteristics (responsive to benzodiazepines, ethanol and

barbiturates) [126–131] and underlying brain changes (changes in the cerebellum, including Purkinje cell loss, have now been documented in ET [67, 132–137]; similarly, β-carboline alkaloids produce toxic damage with significant loss of cerebellar Purkinje cells) [121, 126, 127, 138–141]. Among human volunteers exposed to intravenously administered harmine, neurological effects include an acute, coarse tremor [142, 143].

Harmane (1-methyl-9H-pyrido[3,4-b]indole) is among the more potent tremor-producing β-carboline alkaloids [115]. Harmane itself is also very lipid soluble [116] and broadly distributed within the rat brain [144–146]. Brain concentrations are several fold higher than those in the blood [116, 145].

While β-carboline alkaloids are produced endogenously [147, 148], one study estimated that dietary sources were 50 times greater than these endogenous sources [149]. β-Carboline alkaloids are found in particularly high nanogram/gram concentrations in muscle foods (beef, chicken and pork) and cooking leads to furthermore increased concentrations [150–153]. Indeed, the formation of β-carboline alkaloids in cooked meat is a function of cooking temperature and time, with β-carboline alkaloid concentrations increasing most rapidly with time at higher temperatures [154, 155]. Pan frying and grill/barbequing produce the highest concentrations of β-carboline alkaloids. In addition to their high concentration in meat, β-carboline alkaloids are also present in varying concentrations in plant-derived foods/substances, including coffee, ethanol and tobacco [156].

In 2002, Louis et al. [157] demonstrated that blood harmane concentration was elevated in 100 ET patients at the Neurological Institute of New York compared to 100 matched control subjects (median blood harmane: 5.21 g^{-10}/ml in cases vs. 2.28 g^{-10}/ml in controls, p = 0.005). In analyses that adjusted for age and other confounders, there was a robust association between log blood harmane concentration and ET diagnosis: odds ratio (OR)$_{ET\ vs.\ control}$ = 1.80, 95% confidence interval (CI) = 1.10–2.93, p = 0.02 (that is, each 1 g^{-10}/ml increase in blood harmane concentration was associated with an 80% increased odds of ET) [157]. With continued enrollment from the years 2002–2007, a larger replicate sample of 150 ET cases and 135 matched controls was assembled [158]. While overall concentrations were lower in this sample, the case-control difference persisted (median blood harmane: 2.61 g^{-10}/ml in cases vs. 1.82 g^{-10}/ml in controls, p = 0.016) [158].

Using magnetic resonance spectroscopic imaging, Louis et al. [159] also demonstrated a strong inverse cor-

relation between cerebellar N-acetyl aspartate to creatine ratio (a marker of neuronal damage) and blood harmane concentrations (p = 0.009, adjusting for age and gender) in a small study of 12 ET cases. This correlation was not found in other brain regions (such as thalamus and basal ganglia) or with other neurotoxins (such as lead) [159]. These findings suggest that increased blood harmane concentration could be associated with greater cerebellar neuronal damage, consistent with the animal study data that harmane and other β-carboline alkaloids produce cerebellar damage [121, 126, 127, 138–141]. Studies of human postmortem tissue are needed to further test this association.

As noted above, harmane is found in high concentrations in cooked meats. In an initial study in 2005, Louis et al. [160] compared animal protein consumption in 106 ET cases versus 161 controls. Total daily animal protein consumption was similar in cases and controls (50.2 ± 19.6 vs. 49.4 ± 19.1 g/day, p = 0.74). However, the study used a standardized food frequency questionnaire [161]. In a follow-up study [162], a more detailed meat consumption questionnaire was used. In that study, total meat consumption was greater in men with ET versus men without ET (135.3 ± 71.1 vs. 110.6 ± 80.4 g/day, p = 0.03) but not in women with versus without ET (80.6 ± 50.0 vs. 79.3 ± 51.0 g/day, p = 0.76). Male ET cases had a higher odds of being in the highest versus lowest quartile of current meat consumption than did male controls (unadjusted OR = 9.29, 95% CI = 2.29–37.64, p = 0.002; adjusted OR = 21.36, 95% CI = 3.52–129.51, p = 0.001). That study provided preliminary evidence of a dietary difference between males with ET versus males without ET [162], raising the question whether this possible dietary difference, through harmane consumption, could be linked with ET.

The study of harmane and its association with ET has been intriguing, yet the links need to be further developed and convincingly established. There are a number of basic unanswered questions. First, although elevated harmane concentrations have been observed in ET cases in blood, it is not known whether brain concentrations of this neurotoxin are elevated in ET. Second, current data were derived from a single study of ET cases mainly from a tertiary referral center and they need to be reproduced elsewhere. Third, one small study found elevated blood harmane concentrations in patients with PD [163], which raises the question as to whether elevated blood harmane is specifically linked with ET or if it is merely a more general, global marker of neurological illness. Addressing these basic questions would further delineate the possible

association between ET and this neurotoxin. Additional studies would also be required to demonstrate that the exposure preceded the disease and was of etiological importance.

Lead

Human beings may be exposed to organic and inorganic forms of lead through a number of occupational and nonoccupational sources [164, 165]. In both laboratory animals and human beings, lead exposure may result in an acute or chronic progressive disorder in which action tremor is a prominent feature [164, 166–170]. Lead exposure produces a destructive cerebellar pathology. Thus, rat pups fed a diet containing 4% lead acetate demonstrated changes in Purkinje cell morphology [171]. Perinatal exposure to inorganic lead results in degenerative changes in rabbit Purkinje cells [172]. Postmortem examination of humans with chronic organic lead exposure revealed marked destruction of Purkinje cells [169]. This is of particular interest given the observation, noted above, of cerebellar pathology in ET [67, 132–137].

Preliminary evidence suggests that there may be an association between lead exposure and ET. In an initial study at a tertiary referral center in New York [173], blood lead concentrations were measured and a lifetime occupational history was assessed in 100 ET patients and 143 matched controls. Although blood lead concentrations were low in absolute terms, these concentrations were higher in ET patients than in controls (median: 2.7 vs. 2.3 mg/dl; p = 0.038). In an adjusted logistic regression model, blood lead concentration was associated with ET diagnosis: OR = 1.19; 95% CI = 1.03–1.37, p = 0.02 (that is, each 1 mg/dl increase in blood lead concentration was associated with a 19% increased odds of ET). Whether the observed association was due to increased exposure to lead or a difference in lead kinetics/metabolism was not investigated. The prevalence of a history of lifetime occupational lead exposure was similar in ET patients and controls. In a second study [86], the mechanism was explored further. The δ-amino-levulinic acid dehydratase (ALAD) gene codes for ALAD, the principal enzyme involved in lead kinetics. Carriers of the ALAD-2 allele may be more susceptible to lead toxicity. Eighteen (28.6%) of sixty-three ET cases versus 17 (16.8%) of 101 controls had an ALAD-2 allele (OR = 1.98, 95% CI = 0.9–4.2, p = 0.077) and there was an interaction between blood lead concentration and ALAD allele status; the odds of ET were greatly elevated (OR = 80.3; 95% CI = 3.1–2,096.4, p = 0.008) in individuals with both an ALAD-2 allele and an elevated blood lead concentration. Blood lead concentra-

tion was later evaluated in a second study of ET patients at a hospital in Turkey [174]. In that study, the median blood lead concentration was 2.7 mg/dl in 105 ET cases versus 1.5 mg/dl in 105 controls (p < 0.001). In a logistic regression model, blood lead concentration was associated with ET diagnosis: OR = 4.0; 95% CI = 2.5–6.4, p < 0.001 (that is, each 1 mg/dl increase in blood lead concentration was associated with a 4-fold increased odds of ET). These data replicated those of the previous study in New York.

The possible association of lead exposure with ET is intriguing, yet it needs to be further explored with additional replicate samples, preferably from population-based studies. Furthermore, bone lead concentration, which is a more valid measure of chronic lead exposure than blood lead, needs to be assessed in ET cases and controls.

Pesticides

There is a sizable literature on the association between pesticide exposure and PD [104, 107, 108]. As a class of chemicals, pesticides can produce tremor (including action tremor), and organochlorine pesticides (OCPs) are particularly tremorogenic in animals and humans [175–178]. The literature on pesticide exposure and ET, however, is limited to few studies [177]. In a study in New York [177], 6 serum OCP concentrations and lifetime occupational histories were assessed in 136 ET cases ascertained from a tertiary referral center and 144 matched control subjects. The 6 serum OCP concentrations were similar in cases and controls. Three (2.2%) ET cases versus 9 (6.3%) controls had past occupational exposure to OCPs. This apparent lack of a case-control difference in self-reported exposure to pesticides was confirmed in a second study in Spain of 142 ET patients and 284 controls [179] as well as a third study in Singapore of 79 ET patients and 100 controls, which demonstrated no difference in terms of self-reported pesticide exposure [180]. Exposure histories in each study, however, were brief. These studies represent a beginning and additional studies of ET are needed to assess a wider array of pesticides in more detail, using occupational histories, assessments of residential exposures and biological measures.

Other Exposures

A small number of studies have examined other potential exposures and their relation to ET. One study at a tertiary referral center in New York examined whether occupational exposures to manganese or organic solvents were associated with ET, but did not find an association

[181]. This lack of association was confirmed in a second study in Spain of 142 ET patients and 284 controls [179]. In a study in Italy of 27 dental technicians (mean age 49.1 years, no controls), 4 (14.8%) had mild postural tremor [182], raising the issue of occupational toxin exposure, but these results are difficult to interpret given the high prevalence of postural tremor in the population [183]. While the issue of pesticide exposure was discussed above, 2 studies have raised questions about the more general association between agricultural exposures and ET. A small door-to-door survey in Italy that included 28 ET cases and 28 controls noted that the odds for habitual exposure to agricultural chemicals and domestic animals were 2.5 and 2.7 times higher in ET cases, respectively (results not significant) [95]; each of these factors has been reported to be associated with PD [184]. A study of 142 clinic patients and 282 controls in Spain similarly reported that exposure to agricultural work was associated with ET (for agricultural exposure, OR = 25.4, 95% CI = 1.43–4.51, p = 0.002); however, reported family history was more strongly associated with ET in that study (OR = 34.2, 95% CI = 18.1–64.7, p < 0.001) [179]. Additional studies are needed.

Ethanol

Patients with ET may use ethanol to temporarily lessen the amplitude of their tremor [185, 186], although quantitative studies on relative ethanol consumption in ET cases versus controls have yielded mixed results [187]. The generally accepted causal pathway is that having ET might lead to increased ethanol consumption rather than the converse. Given this model, ethanol would not be considered a risk factor for ET. However, ethanol is a known cerebellar toxin, resulting in profound Purkinje cell loss [188]. Given the emerging links between ET and cerebellar pathology [66], this raises the question as to whether ethanol consumption might be associated with increased risk of incident ET, earlier age of onset of incident ET or more rapid rate of progression of prevalent ET. These issues have not been studied.

Possible Protective Exposures (Cigarettes)

Numerous studies have demonstrated an association between cigarette smoking and lower risk of PD [189, 190]. Three studies, all in Spain, have examined smoking habits in ET cases compared to controls [179, 191, 192]. In the first of these [179], the proportion of ET clinic patients and controls who smoked was similar, yet the number of cigarette pack years was marginally lower in cases than in controls. The second of these studies was a population-based study in Madrid [191]. In that study, ever smokers were approximately one half as likely to have prevalent ET when compared with never smokers (OR = 0.58, 95% CI = 0.40–0.84, p = 0.004) and ever smokers in the highest cigarette pack year tertile were one third as likely to have ET when compared with never smokers (adjusted OR = 0.39, 95% CI = 0.22–0.69, p = 0.001). Finally, in the same study, the association between baseline smoking and incident ET was later examined [192]. Five (6.5%) of seventy-seven incident ET cases had been smokers at baseline compared with 392 (12.0%) of 3,271 controls (p = 0.14). Baseline pack years were lower in incident ET cases than controls (9.2 ± 17.7 vs. 15.7 ± 28.4, p = 0.002). In Cox proportional hazards models, highest baseline pack year tertile was associated with lower risk of incident ET; those in the highest baseline pack year tertile were one third as likely to develop incident ET when compared to nonsmokers (adjusted relative risk = 0.29, 95% CI = 0.09–0.90, p = 0.03).

The biological basis for an association between cigarette smoking and possible lower risk of incident ET is not clear. Nicotine has been the focus of this effect for several reasons. First, nicotine is known to protect against the degenerative effects of toxic insults in different experimental systems [193–195]. Nicotine pretreatment consistently reduces the detrimental effects of excitotoxin exposure in cultured cells [193–195], including neurotoxin-induced degeneration of nigral dopamine-containing neurons [196]. Finally, in rats and mice, nicotine can protect against Parkinsonism-inducing neurotoxins like MPTP and methamphetamine [197].

While early epidemiological studies appear to show an inverse dose-dependent association between smoking and the risk of ET, additional prospective studies are needed to further explore the possible protective effects of smoking on risk of ET. Even if such studies were to be confirmatory, given the other adverse health effects of smoking, this activity should not be considered a prudent strategy for reducing the risk of ET.

Caveats

ET is a common and very widespread disorder whose etiology is likely to be the result of a complex variety of factors. A particular neurotoxin is likely to play an etiological role only in subsets of ET cases, which makes it more difficult to explore and establish such associations when one has no understanding of and has not yet identified those subsets.

Furthermore, while one scenario is that a neurotoxin/environmental factor is by itself sufficient to result in a neurological disease, another possibility is that the toxin merely increases the propensity for developing the disorder. For example, a toxin might result in a set of biological changes in the cerebellum (such as Purkinje cell loss), which then increase the exposed individual's sensitivity to the toxic effects of a second event.

Summary

While ET is widely considered to have a large genetic component [68–74], it is likely that environmental factors contribute to the etiology of ET as well. Such factors are similarly thought to play a substantial role in other progressive, degenerative neurological disorders [102–113].

Work over recent years has explored a number of exposures, including harmane, lead and agricultural exposures/pesticides in preliminary case-control studies, but further work is needed to more fully establish whether these toxins are risk factors for ET. Initial work also suggests that cigarette smoking might be protective of ET.

By some estimates, 2.0% of the population aged ≥ 40 years has a nonfamilial form of ET. Despite these high numbers, the environmental correlates for this tremor are just beginning to be explored.

Acknowledgments

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