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Review Article

Tree shrews at the German Primate Center

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Abstract. For many years, *Tupaia* (family Tupaiidae), most commonly known as tree shrews, have been studied almost exclusively by zoologists resulting in a controversial debate on their taxonomic status among mammals. Today, tree shrews are placed in the order Scandentia; they are valuable, widely accepted and increasingly used model animals as an alternative to rodents and non-human primates in biomedical research. After a brief description on how tree shrews entered science and their taxonomic odyssey, the present article describes the history of the tree shrew (*Tupaia belangeri*) colony at the German Primate Center and selected aspects of our work with special emphasis on the psychosocial stress model in these animals.

1 History and taxonomic odyssey

In a comprehensive survey of the family of Tupaiidae Lyon Jr. (1913) provides in the first chapters of his article the following historical summary on the discovery of tree shrews:

> The earliest published account of treeshrews is that of Ellis (1780[1], 1782[2]), one of the surgeons of Captain Cook's expedition. On Tuesday or Wednesday, 25th or 26th of January, 1780, Ellis remarks: "Our sportsmen ... having seen only a few monkeys, squirrels, and a cock and a hen, the latter of which they shot. According to Linnaeus this island is their native place." The island referred to is Pulo Condore, off the coast of Cochin China. The squirrels mentioned in the account are not squirrels, but Tupaias. One of them was evidently shot. A rough but very accurate sketch of the animal was made by Ellis and a Latin diagnosis of it written in his journal. This description of the animal was published by Gray in 1860[3]. A reproduction of a photograph of Ellis' drawing is here printed. There can be no doubt from Ellis' picture or description that his squirrels were Tupaias (see Fig. 1).
>
> Tupaias as such were first brought to the attention of the world by Diard, a French naturalist, at one time an assistant of Sir Thomas Stamford Raffles, in November, 1820, under the designation of *Sorex glis* (Diard, 1820[4]).
>
> Six months later, May, 1821, the genus *Tupaia* was first proposed by Sir Raffles (1821[5]), and the species *ferruginea* and *tana* described, the latter in the present paper being made the type of a new genus.
>
> Specimens of Tupaias had been seen by Europeans several years earlier, and one even sent to Europe. Geoffroy Saint-Hilaire (1835[6]) remarks:
>
> "The discovery of this remarkable group of Insectivores has been attributed to both M. Diard and Sir Raffles. The fact is that it belongs to neither of these celebrated travelers, but to Leschenault de la Tour, who had sent in 1807 to the Museum of Paris an individual of the species which has

[1]Description and colored illustration of *Tupaia dissimilis*. The description published by Gray (1860), p. 71. A copy of Ellis's drawing is Fig. 1 of this paper.

[2]On p. 340 of Vol. 2 the tree shrews of Pulo Condore are referred to as squirrels.

[3]Original publication of W. Ellis's account of "*Sciurus dissimilis*" (i.e., *Tupaia dissimilis*).

[4]The first published account of a tree shrew and original description of *Sorex glis* (= *Tupaia glis glis*) from Penang.

[5]Original description of the genus *Tupaia* and species *ferruginea* and *tana*; remarks on habits.

[6]Original description of *Tupaia belangeri*.

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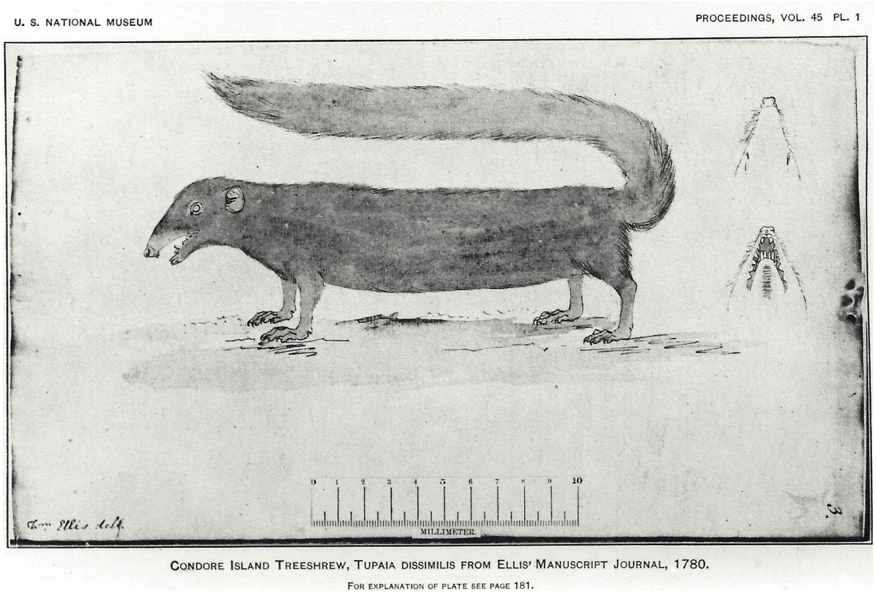

Figure 1. *Tupaia dissimilis*, Pulo Condore. Reproduction of the original Figure of William Ellis' *Sciurus dissimilis*, in his natural history journal, written during Captain Cook's third voyage, 1776–1780; now in the British Museum (Natural History). A scale of 100 mm was laid on the page when the photograph was made. Picture taken from Lyon Jr. (1913).

> since been called *Tupaia javanica*. Nevertheless it is only since 1820 that the attention of naturalists has called to Tupaias, and that these animals have really entered the domain of science.
>
> Geoffroy was naturally quite unaware of the existence of Ellis's manuscript notes and drawings. Since Diard's and Raffles's time the group has become better and better known and its geographic range widely extended."

Uncertainties concerning the taxonomic affinities of tree shrews originated with Ellis' description in which tree shrews were designated "squirrels", a confusion that still occasionally persists today. The Malay word *tupai* is used for both tree shrews and squirrels (Nowak, 1991). In this context it is interesting to mention that Tupaia was the name of a legendary leader of the Polynesian island of Raiatea and a navigator who traveled with Captain Cook's ship *Endeavour* acting as the expedition's interpreter (http://www.bbc.co.uk/history/british/empire_seapower/cook_tupaia_maori_01.shtml). Thus it remains a matter of discussion whether the generic name is derived from the Malay word or is a tribute to the Polynesian navigator.

Despite their name, tree shrews have nothing to do with real shrews and most species of tree shrews are semi-arboreal and usually forage on the ground. In general, they all are relatively small, agile and omnivorous animals with a preference for fruits and invertebrates, especially arthropods. Although there are clear differences between tree shrew species, they share a basic common pattern that can be described with reference to the well known Belanger's tree shrew, *Tupaia belangeri* (Fig. 2). The geographic distribution of tree shrews extends from India to the Philippines and from southern China to Java, Borneo, Sumatra, and Bali. Natural habitats are tropical forests and plantation areas.

For many years, a variety of reports described similarities between tree shrews and primates, and the conclusion that there was a direct phylogenetic relationship between tree shrews and primates was predominantly made by Le Gros Clark (1924), largely on the basis of brain anatomy. His view was confirmed in Simpson's classification of the mammals (Simpson, 1945). In the following years, several authors had doubts about this phylogenetic link and, as a result, excluded tree shrews from primates. An intensive discussion of tree shrews and their phylogenetic relationships is provided by, for example, Luckett (1980), Martin (1990) and Emmons (2000). Today, tree shrews are placed in their own order, Scandentia (see also Knabe and Washausen, 2015). According to recent molecular phylogenetic studies they are placed together with primates and Dermoptera within the clade Euarchonta (Kriegs et al., 2007). In 2008, the Broad Institute provided the first assembly of the genome of *Tupaia belangeri* (http://www.ensembl.org/Tupaia_belangeri/Info/Index). On the basis of more advanced genome information of the Chinese tree shrew (*Tupaia belangeri chinensis*), Fan et al. (2013) postulated that tree shrews have a relatively close relationship to non-human primates. Nevertheless, the long-running debate regarding the phylogenetic position of the tree shrew within eutherian mammals seems not fully settled.

Figure 2. Adult male tree shrew (*Tupaia belangeri*) from the DPZ colony.

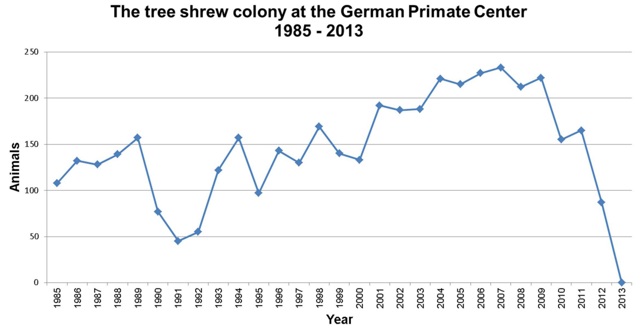

Figure 3. The development of the tree shrew colony of the DPZ from 1985 to 2013.

2 The tree shrew colony at the German Primate Center

In December 1983, Hans-Jürg Kuhn transferred a group of 18 male and 23 female *Tupaia belangeri* from the Zoological Institute, University of Munich, to Göttingen. Originally housed in the former Department of Forensic Medicine at the University of Göttingen, more than 50 tree shrews moved in January 1985 to the animal facility of the German Primate Center (DPZ). This was the starting point for nearly 30 years of successful work in the author's group resulting in more than 100 publications on tree shrews.

With substantial support of Hans-Jürg Kuhn and Eckhard W. Heymann, the housing and breeding protocol was optimized with the aim to become independent of imports from Thailand and to generate animals with known background for our own investigations. Routine colony health screening procedures were carried out and veterinary as well as pathological assistance was available. Tree shrews from the DPZ colony experienced relatively few health problems; the most frequent ones are summarized in the contribution by Brack (2015). A detailed description of housing and breeding tree shrews at the DPZ is given by Fuchs and Corbach-Söhle (2010).

Parallel to the colony at the DPZ Hans-Jürg Kuhn maintained a back-up colony at the Department of Anatomy, University of Göttingen, until his retirement. From time to time tree shrews from other colonies were introduced – in particular from Elke Zimmermann, now director of the Institute of Zoology, University of Veterinary Medicine Hanover, Germany – to avoid inbreeding. Over the years animals from the tree shrew colony at the DPZ were provided to other research institutes in Germany and Europe.

As shown in Fig. 3, the DPZ colony constantly developed with a maximum of more than 200 animals between 2004 and 2009. With the help of Klaus Nebendahl (at that time head of the animal facilities of the University Medical Center, University of Göttingen) we extended in 2004 the housing capacity mainly for breeding tree shrews at Gut Holtensen, located about 5 km away from the DPZ. In the processes of closing the Clinical Neurobiology Laboratory at the DPZ and the author's retirement, the tree shrew colony was also closed. Most of the animals were moved to the Department of Behavioral Physiology, Center for Behavior and Neurosciences, University of Groningen, the Netherlands. The history of tree shrews at the DPZ ended on 24 September 2013 with the transfer of a view remaining animals to the Institute of Anatomy, Faculty of Veterinary Medicine, University of Leipzig, Germany.

3 Tree shrews in laboratory

Tree shrews have proved to be useful experimental animal in many instances where a small omnivorous non-rodent species is required (e.g., Cao et al., 2003). They can be investigated in many fields of preclinical research such as toxicology and virology, in particular in studies investigating herpes and hepatitis viruses (Hunt, 1993; Zhao et al., 2002; Xu et al., 2007; Amako et al., 2010). Further, various aspects of behavior including learning (Ohl et al., 1998; Nair et al.,

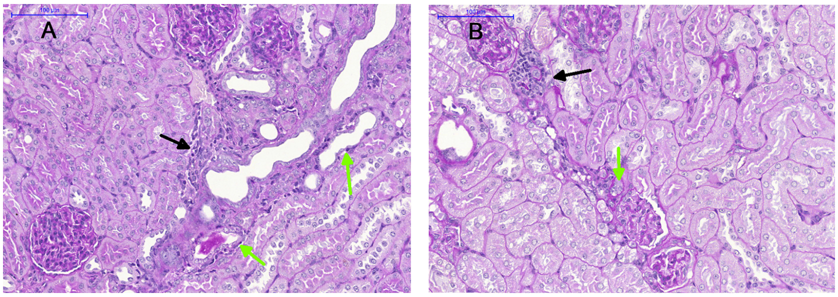

Figure 4. Kidney sections of a control **(a)** and a stressed **(b)** male tree shrew. The black arrows indicate inflammatory infiltrating cells, while the green arrows indicate atrophic tubuli. Qualitative analysis did not reveal any indication of stress-induced renal damage. Blue bars represent 100 µm.

2014), infant development, communication, social structures (e.g., Martin, 1968a, b; Hertenstein et al., 1987; Binz et al., 1990), emotions (Schehka et al., 2007; Schehka and Zimmermann, 2009, 2012) and various neurobiological questions (e.g., Norton et al., 2006; Kaas et al., 2013, and Table 1) including the effects of psychosocial stress (e.g., Fuchs, 2005) can be studied in tree shrews.

Based on a study by von Holst (1972), psychosocially stressed male tree shrews were thought to be a suitable model to study the mechanisms of acute renal failure. However, we (see Fig. 4) and others (Steinhausen et al., 1978) were unable to replicate these results.

A high degree of genetic homology between tree shrews and primates was found for several receptor proteins of neuromodulators (see Fuchs and Flügge, 2002) and the amyloid-beta precursor protein (Pawlik et al., 1999). The 3–4 times longer life span of tree shrews than rodents (Keuker et al., 2005) suggests that tree shrews may be useful for studies focusing on aging-related brain changes (e.g., Michaelis et al., 2001; Yamashita et al., 2012).

4 The psychosocial stress model

In their natural habitats male tree shrews defend their territories vigorously against intruding conspecifics (Kawamichi and Kawamichi, 1979). Originally developed by Raab (1971) and later adopted by von Holst (1972) we used this pronounced territoriality (Sorenson, 1974) to establish a naturally occurring challenging situation under experimental control in the laboratory. All animal experimentation was carried out in accordance with the European Council Directives and the German Animal Welfare Acts in force and was approved by the responsible authorities of the federal state of Lower Saxony, Germany.

For the stress exposure we developed the following standard protocol (e.g., Schmelting et al., 2014). In brief, in the first experimental phase (pre-stress) – during which all animals remained undisturbed – body weight and behavior was recorded daily, and morning urine samples were collected daily by a slight massage of the hypogastrium. After this period animals were divided into two groups: the non-stressed control and stressed group. The animals from the stress group were exposed to daily psychosocial conflict, while the non-stressed controls remained undisturbed elsewhere in the animal facility. Psychosocial stress was induced by introducing a inexperienced animal into the cage of another male that had already become dominant in previous confrontations with a subordinate. During confrontation the animals were closely monitored; in case of severe fights, the animals were separated immediately by a wire mesh barrier to avoid physical injuries. Thus, direct physical contact was only allowed for approximately 1 h every day. During the stress phase, the wire mesh barrier was removed daily at random time points to enhance unpredictability. Using this procedure, the subordinate male was protected from repeated attacks but was constantly exposed to olfactory, visual, and acoustic cues from the dominant male (Fig. 5). To exclude the effects of individual differences in the intensity of attacks by the dominant male and to avoid habituation, the subordinate animal was confronted daily with another dominant male according to a Latin square design.

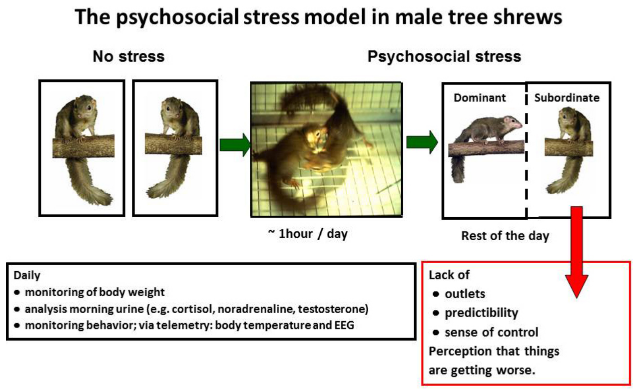

Figure 5. Schematic presentation of the psychosocial stress model in male tree shrews. For the subordinate male the situation is characterized by a lack of outlets, no predictability and no sense of control.

Table 1. Summary of stress-induced changes in male tree shrews. With modifications from Fuchs and Flügge (2002).

	Effects of chronic psychosocial stress
Physiological and neuroendocrine parameters	
Body weight	Decreased (Fuchs et al., 1993)
HPA axis	Non-adapting increase of urinary cortisol – no suppression by dexamethasone (Kramer et al., 1999; Kohlhause et al., 2011) and enlarged adrenal glands (Fuchs et al., 1993)
Sympathetic nervous system	Increased urinary adrenaline and noradrenaline (Fuchs et al., 1993)
Gonadal system	Decreased testosterone (Kohlhause et al., 2011) and testes weight (Fischer et al., 1985)
Sleep	Reduced slow wave sleep, more/longer awake phases (Fuchs and Flügge, 2002)
Circadian rhythm	Elevated core body temperature (Kohlhause et al., 2011; Schmelting et al., 2014), heart rate (Stöhr, 1986) and oxygen consumption (Fuchs and Kleinknecht, 1986) during resting period
Behavior and memory	
General motor activity	Reduced (Kramer et al., 1999; Schmelting et al., 2014)
Self-grooming	Reduced (Kramer et al., 1999)
Scent marking activity	Reduced (Kramer et al., 1999)
Food and water intake	Reduced (Kramer et al., 1999)
Hippocampus-mediated memory	Persistently impaired (Ohl and Fuchs, 1999)
Structural and functional changes in the brain	
Neurogenesis in the dentate gyrus	Inhibition of the proliferation of granule precursor cells (Gould et al., 1997; Czéh et al., 2001)
Retraction of dendrites	Retraction of apical dendrites of pyramidal neurons in the CA3 of the hippocampus (Magariños et al., 1996)
Volume of the hippocampal formation	Volume reduced by approximately 10 % (Ohl et al., 2000; Czéh et al., 2001)
Brain metabolites	Significantly decreased in vivo concentrations of *N*-acetyl-aspartate, creatine/phosphocreatine, and choline-containing compounds (Czéh et al., 2001)
Hippocampal gluco- and mineralocorticoid receptors	Downregulation of glucocorticoid receptors; regional up- and downregulation of mineralocorticoid receptors (Meyer et al., 2001)
CRH receptors	Downregulation of binding sites for ^{125}I-ovine corticotropin releasing hormone (CRH) in anterior pituitary, dentate gyrus, CA1 and CA3 of the hippocampus, area 17, superior colliculus; upregulation of binding sites for ^{125}I-ovine CRH in cortical regions, amygdala, choroid plexus (Fuchs and Flügge, 1995)
5-HT_{1A} receptors	Gradual downregulation of heteroreceptors in hippocampus and cortical regions; fast renormalization after stress or hormonal replacement (Flügge, 1995; Flügge et al., 1998)
$Alpha_2$-adrenoceptors	Downregulation in brain regions involved in autonomic functions (Flügge, 1996; Flügge et al., 1992; Meyer et al., 2000)
$Beta_1$-adrenoceptors	After 4 weeks downregulation in hippocampus and parietal cortex; transient effects in prefrontal cortex, olfactory area, and pulvinar nucleus (Flügge et al., 1997)
$Beta_2$-adrenoceptors	After 4 weeks upregulation in pulvinar nucleus; transient effects in prefrontal cortex (Flügge et al., 1997)

Subordinate tree shrews show significant changes in behavior, physiology, endocrine function and neuronal activity. They lose body weight and have reduced locomotor activity; their sleeping pattern is characterized by an increasing number of early morning waking episodes, and their circadian rhythm is profoundly disturbed. Analysis of endocrine function in subordinates reveals consistently elevated concentrations of the adrenocortical hormone cortisol, enlarged adrenals, increased concentrations of noradrenalin and adrenalin indicating enhanced sympathetic activity and reduced gonadal function (see Table 1). Since the distinct, stress-induced behavioral, physiological, and central nervous system alterations in subordinate animals result exclusively from cognitive interpretation of the continuous visual presence of the dominant conspecific (Raab and Storz, 1976; Raab and Ostwald, 1980), this paradigm has been termed

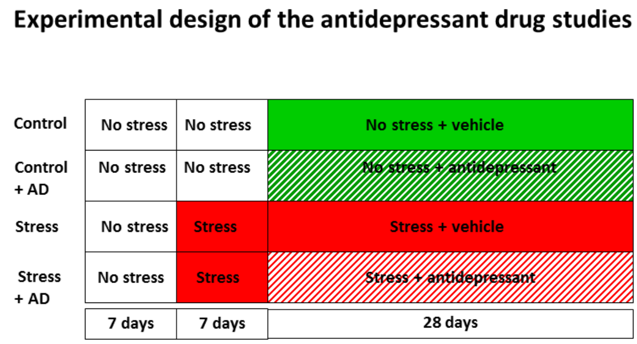

Figure 6. Schematic presentation of the experimental design of antidepressant drug studies. Control: no stress; AD: antidepressant.

"psychosocial stress". Importantly, the bio-behavioral responses observed in subordinate tree shrews are similar to the signs and symptoms seen in depressed patients. Thus, the chronic psychosocial stress model in tree shrews has clear "face validity" (Willner, 1984) for human depression (for review see Fuchs, 2005).

To investigate whether the tree shrew model also possesses predictive validity (Willner, 1984), we treated subordinate shrews with established and as well as potential antidepressants such as clomipramine, fluoxetine, tianeptine, agomelatine and different NK1 receptor antagonists. It is important to note that (i) we determined and used the appropriate dose of the antidepressants necessary to reach therapeutically relevant serum concentrations (e.g., Czéh et al., 2006); (ii) the daily oral treatment commenced only when the stress-induced behavioral and endocrine changes became obvious; (iii) the psychosocial stress situation was continued during the treatment; and (iv) the therapeutic action of the drug was assessed for the clinically appropriate period of time of 4 weeks (Fig. 6).

Using this approach we found in subordinate animals a time-dependent restoration of endocrine, behavioral and central nervous parameters such as neurogenesis, hippocampal volume and brain metabolism (Czéh et al., 2001, 2005; Fuchs et al., 1996; van der Hart et al., 2002, 2005; Schmelting et al., 2014). In contrast, the anxiolytic diazepam was ineffective in this experimental setting (van Kampen et al., 2000).

Despite its obvious attractiveness there are, as in other stress models, limitations of the tree shrew psychosocial stress paradigm. One major limitation is housing and breeding, which are space and time consuming, and therefore only a limited number of experimental animals is available. Obviously, this constraint explains why only a few other laboratories are capable of using this model. One is at the Kunming Institute of Zoology, Chinese Academy of Sciences, China, performing intensive research on *Tupaia belangeri chinensis* a close relative of *Tupaia belangeri*. Using a similar stress model Wang et al. (2013) could confirm our finding with clomipramine showing that depression-like core symptoms in subordinate tree shrews could be reversed by a chronic treatment with this established tricyclic antidepressant.

5 Conclusion

The chronic psychosocial stress paradigm in tree shrews characterized and validated at the DPZ can be regarded a "homologous model" of depression. It mimics several aspects of the human disease in the subordinate animal; the state of the animal is induced by similar stimuli that cause the condition in humans, and pharmacotherapy, which is efficacious in human illness, is effective in the model. The advantage of such a homologous model is that it can probably contribute to the understanding of the pathophysiology of depression and it might also lead to the development of new effective drugs for treatment of the illness. Although more research is required to further validate the tree shrew model, it provides an adequate and interesting non-rodent experimental paradigm for preclinical research on depression.

The work on tree shrews conducted for nearly 3 decades at the German Primate Center would not have been possible without the encouragement of Hans-Jürg Kuhn, the never-ending great enthusiasm of all members of the research group and the substantial support provided by many collaborators, grant agencies and industrial partners.

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