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Reviews

Animal olfactory detection of human diseases: Guidelines and systematic review

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ABSTRACT

Animal olfactory detection of human diseases has attracted an increasing amount of interest from researchers in recent years. Because of the inconsistent findings reported in this body of research and the complexity of scent-detection research, it is difficult to ascertain the potential value of animal detectors in operational diagnostic algorithms. We have outlined key factors associated with successful training and evaluation of animals for operational disease detection and, using these key factors as points for comparison, conducted a systematic review of the research in this area. Studies that were published in peer-reviewed outlets and that described original research evaluating animals for detection of human diseases were included in the review. Most relevant studies have assessed dogs as detectors of various forms of cancer. Other researchers have targeted bacteriuria, *Clostridium difficile*, hypoglycemia, and tuberculosis. Nematodes and pouched rats were the only exceptions to canine detectors. Of the 28 studies meeting inclusion criteria, only 9 used operationally feasible procedures. The most common threat to operational viability was the use of a fixed number of positive samples in each sample run. Most reports included insufficient information for replication or adequate evaluation of the validity of the findings. Therefore, we have made recommendations regarding the type of information that should be included when describing research in this area. The results of this systematic review suggest that animal detectors hold promise for certain diagnostic applications but that additional research evaluating operationally viable systems for olfactory detection of human diseases is necessary.

Introduction

It is common knowledge that many animals possess and rely heavily on a highly developed sense of smell when locating food, avoiding predators, finding mates, and navigating their environments. Humans, who have a relatively poor sense of smell, often use other animals in the detection of targeted substances by training them to make an identifiable response in the presence of volatile compounds that emanate from those substances. Dogs have been trained to locate explosives, landmines, illicit drugs and other contraband, missing persons, disaster victims, and a wide variety of other targets (Browne et al., 2006; Williams & Johnston, 2002). Bees, pigs, mice, rats, and a number of other animals have also been successfully trained to identify targeted substances (Bodyak & Slotnick, 1999; Poling et al., 2010a; Rains et al., 2008; Talou et al., 1990).

Several anecdotal reports of dogs spontaneously showing interest in skin cancer on their owners have been published. Williams and Pembroke (1989) wrote of a patient whose dog persistently sniffed a mole on her leg. The dog's excessive interest in the mole prompted the patient to visit a dermatologist, who identified the mole as a malignant melanoma. Church and Williams (2001) reported a man whose dog constantly sniffed at a patch of eczema on his leg. After excision of the lesion, it was found to be a basal cell carcinoma. Campbell et al. (2013) described a case in which a man's

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dog persistently licked a lesion behind his right ear, which was later confirmed to be malignant melanoma. In each of these cases, the dog was hypothesized to be able to detect and was attracted to volatile organic compounds (VOCs) emanating from the affected area on its owner's skin.

VOCs are organic chemicals with high vapor pressure at typical room temperature, resulting in evaporation or sublimation of the molecules into the air surrounding the source. VOC profiles reliably associated with asthma, several types of cancer, cholera, cystic fibrosis, diabetes mellitus, dental diseases, gut diseases, heart allograft rejection, heart diseases, liver diseases, pre-eclampsia, renal disease, and tuberculosis (TB) have been identified (Corradi et al., 2010; Dent et al., 2013; Shirasu & Touhara, 2011). Disease-related VOCs may be found in the blood, breath, feces, skin, sputum, sweat, urine, and vaginal secretions of affected individuals. Research investigating the VOCs associated with various human diseases is underway, primarily driven by the goal of developing instrumentation for use in clinical diagnostics that is capable of reliably identifying specific disease-associated VOC marker profiles. Currently, the development of this technology is limited by the prohibitively high cost of the necessary laboratory instrumentation and difficulties in standardizing sample collection and preparation procedures in clinical settings (Sethi et al., 2013).

An increasing number of experimental analyses examining animal detection of human diseases have appeared in the literature since Pickel et al. (2004) reported the high detection accuracy of 2 dogs trained to detect melanoma. The cumulative number of relevant studies published between 2004 and 2016 is displayed in Figure. The steepening gradient in the data path suggests that interest in this topic has increased over time. This body of literature on which Figure is based has been reviewed from various perspectives (Bijland et al., 2013; Boedeker et al., 2012; Dent et al., 2013; Desikan, 2013; Freeman & Vatz, 2015; Jezierski et al., 2015; Johnen et al., 2013; Lippi & Cervellin, 2012; Luque de Castro & Fernandez-Peralbo, 2012; Marcus, 2012; McCulloch et al., 2012; Moser & McCulloch, 2010; Oh et al., 2015; Wells, 2012). Many reviewers and researchers have remarked that critical components of the training and testing procedures in the relevant studies are often unreported or are deficient. Therefore, it is difficult to ascertain the potential of animals as detectors of various human diseases (e.g., Elliker et al., 2014; Jezierski et al., 2015). The purpose of the present article was, first, to suggest required and preferred conditions for training and testing animals for operational disease detection and, second, to evaluate the existing research with respect to these conditions. Our hope is that the guidelines we propose will be useful for researchers, animal trainers, and medical practitioners who are interested in olfactory detection of human diseases.

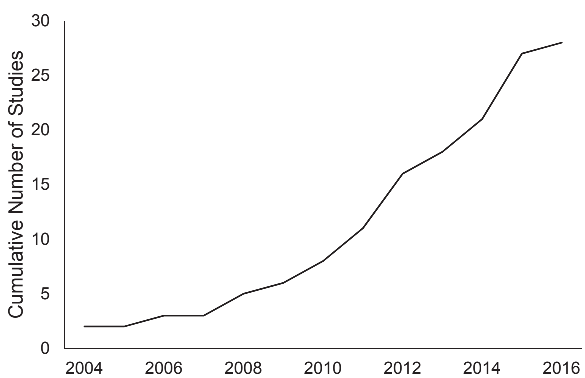

Figure. Cumulative number of studies examining animal olfactory detection of human diseases between 2004 and 2016.

Training conditions

Operant discrimination training, in which indication responses (e.g., barks by a dog) to samples known to be positive for the disease in question are reinforced (rewarded, as by delivery of a preferred food) and responses to samples not known to be positive for the disease are not reinforced, is used to teach animals to detect the disease. Once an animal reliably emits the indication response only in the presence of known-positive samples, samples of unknown status are presented and the animal's response to those samples is recorded. Samples that engender an identification response are considered to be disease-positive according to the animal detector, although additional confirmatory technology is often used to ensure that the patient who provided the sample actually has the disease. Responses to samples of unknown status are not reinforced and, to maintain performance, known-positive samples have to be included in the sample array. As in training, responses to such samples are reinforced. Details of training differ widely across studies, but certain aspects of training are of general, and critical, significance.

Required conditions for training

The conditions outlined in this section are necessary for training an animal to reliably indicate the presence of disease-related VOCs in novel samples.

Confirmed positive samples

Ideally, the status of every sample used in training (i.e., samples that are positive for disease as well as those that are negative for disease) is determined with the gold standard or best available diagnostic technology for the targeted disease. However, knowing the true status of "positive" samples that will be used to arrange reinforcement for correct indications is a required condition. Even occasional reinforcement of a positive indication to a disease-negative sample can lead to persistent false indications (positive indications of disease-negative samples). Intermittent reinforcement generates patterns of behavior that persist even when reinforcement is no longer forthcoming (Angle et al., 2015; Nevin, 1988). Persistent indication of disease-negative samples negatively a affects specificity (proportion of disease-negative samples that are accurately classified as such), negative predictive value (NPV; the number of correct rejections [negative indications] divided by the total number of rejections), and positive predictive value (PPV; the number of correct positive indications divided by the total number of positive indications).

Intermittent schedules of reinforcement for correct indication responses have the desirable effect of preparing the animal for conditions under which correct indication responses cannot be reinforced. Such conditions are inevitable if the animal will be used operationally because an animal detector would provide no additional value in an operational scenario in which the status of all samples is already known. For this reason, knowing the status of all "negative" samples used for training is not a required condition. If a positive sample is incorrectly classified as "negative" and the animal's correct identification response is not reinforced, the animal will learn to continue evaluating the remaining samples, as it would be required to do in an operational scenario. In early stages of training, although the search and indication behaviors are being shaped, a high ratio of reinforcement (i.e., continuous reinforcement) is necessary, but the schedule of reinforcement should be gradually thinned to match the schedule of reinforcement anticipated under testing and operational conditions. Under training conditions in which consequences are provided for correct or incorrect identification of negative samples