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Title: *Canis familiaris* as model for non-invasive comparative neuroscience

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Abstract:
There is an ongoing need to improve animal models of human behaviour and the biological underpinnings thereof. The domestic dog (Canis familiaris) is a promising model in cognitive neuroscience. However, before it can contribute to advancements in this field in a comparative, reliable, and valid manner, some methodological questions first warrant attention. Here, we review recent non-invasive canine neuroscience studies, primarily focusing on: 1) variability across dogs and between dogs and humans in cranial characteristics and 2) generalizability across dog and dog-human studies. We argue not for methodological uniformity but for functional comparability in methods, experimental design, and neural responses. We conclude that the dog may become an innovative and unique model in comparative neuroscience, complementing more traditional models.

Animal models in comparative neuroscience

Animal model research is grounded in the idea that animals share behavioural, physiological, and other characteristics with humans. One benefit of such research is increased understanding of phenomena that could not be directly studied in humans or without cross-species comparison. Neuroscience research into socio-cognition has been extended from traditional primate and rodent models to the domestic dog – an alternative, complementary model that permits for non-invasive measurement of behaviour and its neural correlates. Recently, there has been an increase in canine neuroscience studies, necessitating establishment of methodological guidelines that ensure scientific rigor. To this end, complementing available reviews that are heavily [1] or solely [2] focused on available fMRI findings from a conceptual perspective [1,2], we review the non-invasive canine neuroscience literature, focusing on methodology and experimental design. Primarily guided by principles of comparative anatomy, we highlight advantages and remaining challenges of the dog as a model for comparative cognitive neuroscience.

We begin with an overview of animal models of human behaviour, then narrow our focus onto neuroscience. Mainly focusing on non-invasive canine fMRI and EEG research, we evaluate the domestic dog as a model for comparative neuroscience in light of three main considerations. These centre on within- and between-species variability, in particular in cranial characteristics, though are also varied in terms of the degree to which they potentiate (1) advantages and disadvantages for the dog as an animal model and, in case of disadvantages, whether solutions addressing those (2) have or (3) have not been developed.

Animal models for comparative cognitive neuroscience

A goal of comparative research is to establish principles of **proximate and ultimate causation** (see Glossary), via between-species comparisons and study of individual organisms. Animal models for comparative cognitive science include avian [3–5] as well as rodent and primate species that have emerged as primary models for comparative cognitive *neuroscience* [2]. Advantages of rodents include feasibility of handling the animals under laboratory conditions; cost-efficiency; and utility in pre-clinical and clinical studies [6]. Advantages of primates include similarity to humans in development, neuroanatomy, physiology, and reproduction, as well as in cognition and social complexity and thus suitability for studying a range of mental processes [7]. Yet, use of these models is increasingly problematic for animal welfare and ethical reasons [8]. Conversely, the role of the domestic dog in research has been becoming increasingly important, with studies initially focused on informing treatment for human medical diseases with laboratory dogs [e.g., 4] and more recently involving basic research on sensation and perception and extending into socio-cognition with family dogs (Box 1). One reason for this increase in importance is that dogs, having been encultured in human society, naturally exhibit *cooperativeness* and *trainability, obviating need for fluid and/or food restriction (common features of the rodent and primate models) as a motivational tool.* Thus, relative to other species, preparation of the dog for an experiment is more similar to preparation of humans in terms of corresponding physiological and social state and there is less limitation to generalizability of interaction with experimenters and environmental (e.g., lighting and sound) and experimental stimuli [1]. *Cooperativeness and trainability* also *permit for non-invasive methods*; although techniques have been developed for awake scanning of monkeys, pigeons, and rats [1], unlike these animals but like humans, dogs do not need to be restrained (e.g., via surgically implanted posts [10]) but can be trained to hold still, yielding more valid cross-species comparisons. Finally, given their evolutionary history and integration in the human social environment, dogs and humans

Box 1. Key socio-cognitive skills dogs share with humans

Recent comparative research with wolves and human infants has revealed key functional analogies between dog and human behavior. This specific suits of convergent cognitive skills places the dog in a unique position with regard to increasing opportunity for understanding the evolution of such abilities in humans [12]

Affective and emotional processing	Affect recognition: [58] Emotional contagion: [94] Social referencing: [95]
Attachment	Attachment to owner: [65] Attachment formation in adulthood: [98] Separation-related behaviour in adults: [99]
Attention	Attention-deficit/hyperactivity disorder: [100] Social relation-dependent attention: [101]
Executive functions	Social bias on inferential reasoning: [102] Cognitive strategies in problem solving: [103] Social bias in problem solving: [104]
Communication	Lexical processing: [37] Emotional state dependent vocal signalling (barking) [105] Initiation of communication in heterospecific context [106] Use of verbal referents [107]
Memory	Declarative memory (deferred imitation): [108] Episodic memory about behaviour of others: [109]
Metacognition	Attention attribution: [110] Perspective taking: [111]
Social processing	Selective imitation: [112] Inequity aversion: [113] Social cause and effect (contingency) detection: [114] Socio-cognitive representation formation: [115]
Perception	Biological motion perception: [116]

exhibit a range of socio-cognitive skills that share key behavioural and functional characteristics [11]. It is for the ability to study these very skills and corresponding functions (Box 1) that the dog may be a credible species for investigating certain aspects of the evolution of human socio-cognition [2] in *comparative* neuroscience [11].

Given the above, it stands to reason that the domestic dog is a suitable model for comparative neuroscience and that the non-invasive methods to study brain circuits, physiology, and behaviour used with the dog ideally complement the invasive methods appropriate for studying molecules and cells used with traditional models. In combination with over 20 years of canine ethological research [12] and capitalizing on exciting advancements in non-invasive measurements, there has been an increase in the number of canine neuroscience studies, with an overwhelming majority conducted in the past 3 years. These are mostly fMRI and EEG studies, although other methods have also been used [13].

Basic standards for measures and methods include reliability and validity [14] and, in case of comparative research, for them to also be *relevantly* comparative. Related pressing questions pertain to the degree to which methods are comparable across dog-dog and dog-human studies as well as the degree to which employed methods allow for comparability and generalizability across studies (Table 1, Key Table); with the impetus behind such questions stemming from within- and between-species variability, especially in cranial characteristics. Some of this variability presents advantages for the dog as a model and some may be limiting. In the latter cases, methods to address limitations are either already being developed and evaluated or are in need of development and evaluation.

Differences that present advantages

Differences in skull formation and brain anatomy. Across humans, variation in skull formation and brain size is relatively trivial; the average female brain volume is 90% of the male [15] and the average brain volume of a 7-11-year old child is 95% of the volume of a sex-matched adult [16]. Conversely, there are large differences across dogs in skull shape and size and brain anatomy. Canine skull length ranges from 7 to 28 cms [17] (i.e., the shortest dog skull is 25% of the longest), making *Canis familiaris* the species with the most within-species morphological variation in this regard [18].

In addition to skull length, differences across **dolichocephalic, brachycephalic**, and **mesaticephalic** dogs include dissimilarities in the craniofacial angle (angle between the **basilar axis** and **hard palate**) [19], in neuroanatomy (e.g., in brachycephalic dogs the brain is rotated with respect to its mediolateral axis) and the anatomy of the cerebral cortex [20], temporomandibular joint (i.e., jaw joint) [21], and **cribriform plate** [22].

These differences across dogs *allow for examining the relation among brain structure, function, and behaviour within the same species* and the effects of differences in skull- and brain-morphology on neuro-socio-cognition. As the ≥400 documented breeds exhibit a variety of genetically fixed morphologic traits that correspond to differences in behaviour, longevity, size, skull shape, and disease susceptibility [20], better understanding of these was proposed to increase understanding of mammalian biological and embryonic development [20]. Although the number of breeds involved in fMRI studies to date is considerably lower, they include dogs from diverse breeds suggesting that there is no limitation (e.g., given trainability) to within-species comparisons.

In support of stated advantages, differences in dog skull shape are associated with differences in brain organization, e.g., brachycephalic brains are relatively rounded and shortened in the anterior-posterior plane, the brain pitched ventrally at the anterior pole, with a pronounced shift in the position of the olfactory lobe [18] (see Box 2 for additional examples). Differences in skull shape are further associated with differences in behaviour in that brachycephaly, relative to dolichocephaly, is associated with increased ability to focus and rely on human gestures [23]. Morphological differences across individuals in other species, such as humans, are less (or not) suitable for addressing these questions (but see [24] for exception).

Box 2. Correspondence of neural structures in dogs and humans

Although unlike some birds' and mammals' (e.g., mice and rats) **lissencephalic** brains, the dog brain is **gyrencephalic** [105], questions about anatomical and functional correspondence between neural structures across dogs and humans is nonnegligible.

Specifically, there are differences between dogs and humans in cortical growth and folding (i.e., organization and structure of gyri and sulci) and there is obscurity with regard to homologies [106]. Regarding cortical growth or size, relative to subcortical structures, the evolutionary expansion of the cerebral cortex of humans is dramatic [107] and there are differences in scaling (i.e., the relationship between changes in the relative size of structures and the size of the entire brain) between primates and carnivores. Primate frontal cortex hyperscales relative to the rest of both the neocortex and the brain and this results primarily from differences in frontal cortex (and not the rest of the cortex or both), indicating substantial differences in frontal cortex structure and development between the two groups [108] and potentially also that the primate frontal cortex might contain structures that are absent in carnivores [108]. Indeed, prefrontal granular cortex is found only in primates who are unique among mammals in possessing a dorsolateral prefrontal cortex [109]. Other examples of cross-species differences include that in primates, the levels of gene expression in layer 4 of primary visual cortex are higher (the closer they are related to humans the higher these are) compared to carnivores and rodents, where these are very low [110]. Across species, the **somatotopic** organization of the somesthetic cerebral cortex reflects the density of bodily receptor organs and, in many animal species relative to humans, there is an abundance of receptors associated with prehensile organs (the lips and tongue in case of the dog) and thus a respectively large area of representation in the somesthetic cortex [111]. Together, these data indicate that the anatomical and functional comparability between canine and human brains is likely considerably less in functions attributed to the cortex, especially the frontal cortex and that dogs probably do not provide useful models of human (dorsolateral)(pre)frontal lobe functions and dysfunctions, especially executive functions such as attention maintenance, organization of input from diverse sensory modalities, working memory, and coordination of goal-directed behaviors, despite being valuable for understanding other regions.

In addition to the between-species differences, differences across dogs further complicate methodological challenges. With regard to cortical functions observed in humans and the differentiation thereof given frontal, parietal, occipital, and temporal lobes and corresponding circuitry, canine lobar designations lack functional utility [112]. Although canine lobes are named given their relation to the position of the **calvaria** that covers them, this relationship varies across breeds [113]. Further, in dogs, given variation in gyri and sulci patterns, distinct gross landmarks separating the lobes (with the with the exception of the piriform lobe) are either absent [114] or there is disagreement about such landmarks [115], e.g., the frontal lobe as caudally demarcated by the cruciate sulcus [116] vs. the frontal lobe encompassing the postcrucial gyrus [115].

Differences in experimental design: sample composition. Compared to the human neuroscience literature, there is significant overlap in groups of dogs across studies. This is due to challenges (e.g., limited subject availability and need for extensive training) and to advantages that make the dog a multi-experiment model (e.g., longer life-span of dogs relative to rodents). For example, in canine fMRI studies, 100% of the sample of [25] was included in [26], and there was

a 92% overlap in the samples of [26] and [27], and a 67% overlap in the samples of [26] and [28], and all dogs in [29] came from one of these samples. Similarly, in EEG studies, there was a 100% overlap in the samples of [30] and [31], and a 68% overlap in the samples of [32] and [33].

Awake fMRI testing necessitates that dogs are trained to get used to scanner coil; place their heads in-between their paws [34–38] or on a chinrest [25–29,39–41], and hold this position until a release signal and then while wearing canine ear muffs; get used to recordings of scanner noise and being in a mock scanner; and to adhere to these procedures inside the scanner room and ultimately the scanner [26,34]. Training is extensive and typically involves behavioural shaping, conditioning and social learning (e.g., the "**Model/Rival" training method** [34]). Different training methods allow for different lengths of time during which dogs are able to hold a position, which has implications for design. For example, in some studies, consistent with human studies, dogs do not exit the scanner between runs [34,35,37,38,42] whereas in others, they do [25–29,39–41]. Movement artefacts are also handled differently: some authors, consistent with human studies, exclude scans with head translation >3mm or rotation >1º [34,37,41]; whereas others exclude scans with >1% scan-to-scan signal change [25]; >0.1 fraction of outlier voxels in each volume or >1% scan-to-scan signal change, in combination with >1mm scan-to-scan displacement [27–29,39,43], and yet others exclude runs with >10mm total displacement [35,42]. As the dog brain is much smaller than the human brain, arguably, even a 3mm translation could results in inaccurate anatomical localization. However, in most studies where the translation >3mm or rotation >1º criteria were used, translation did not exceed 1mm [34,44], indicating that dogs are capable of exhibiting minimal movement. In addition, there is indication that relative displacement (i.e. between consecutive volumes) is more critical to correct for than absolute displacement (i.e., across the whole run) of a similar scale [45]. Acceptable relative movement is also achievable with dogs, e.g., in [37], the average movement between two consecutive volume acquisitions was below 0.45 mm for each translation direction, and below 0.01º for each rotation direction.

Finally, depending on study design and research group, dogs need anywhere from five sessions [34] to 18 months of training [26]. For comparison, human adults do not receive training and human children as young as 6 years of age receive minimal (a one-to-two-occasion, 30-60-minute familiarization with a mock-scanner and recordings of scanner noise) or no training [46] (Table 1).

The overlap in groups of dogs included across studies also has advantages for examination of reliability and validity of measures as it allows for assessment of *within-subject stability vs. change of measures of neural function over time* and of *within-subject correspondence of neural correlates and performance across social, cognitive, and affective paradigms*. Regarding *within-subject stability vs. change over time*, the reliability, including test-retest reliability, of neuroimaging [14] was a relatively neglected area in early human neuroscience work. The overlap in groups of dogs across studies presents a natural opportunity to attend to questions of psychometrics early on in canine comparative neuroscience [47]. Regarding *within-subject correspondence of neural correlates and performance across paradigms*, it is important that these exhibit convergence and divergence, where expected. Establishing correspondence across different indices of phenomena of interest (e.g., social and cognitive indices of self-regulation) but that these provide unique information about variables examined, is key to the innovative dimensional frameworks that are currently championed (e.g., the Research Domain Criteria [RDoC]; [48]).

Differences that potentiate disadvantages but solutions are available

Within-species differences in skull formation and brain anatomy. These within-species variabilities (Figure 1) are relevant for normalization. In fMRI research, advantages of normalization are that when a set of coordinates is referenced, the location to which those coordinates correspond is known and that results can be: generalized to a larger population; compared across studies; and averaged across subjects for group-level analyses. Disadvantages are that it reduces spatial resolution and increases probability of error in identification of anatomical location.

Normalization requires a "standard" brain, i.e., template. In the adult human literature, the Montreal Neurological Institute (MNI) template (MNI-305) is commonly used (Table 1), which is based on combination of 152 healthy adult MRI scans [49]. Given relatively little difference between adult and child brains, the MNI-305 is suitable for use with children over age 6 years [50] and studies have generally followed suit, with some attempts at developing a child template for a wider range of ages (e.g., from 2 weeks-4.3 years [51] and 4.5 years-19.5 years (on age increments of 6 months [52]). Conversely, at present, there is no widely-accepted and used dog template. Authors of canine fMRI studies have addressed this issue by omitting group-level analyses altogether or, where group-level analyses were conducted, by using the brain of a selected individual, or using a template based on the brains of 15 mesaticephalic dogs (Table 1).

Besides the said advantages of population-based templates, there are advantages of study-specific templates such as preservation of fine details [53] (a special case of which is use of the brain of a selected individual). Regarding both population-based templates such as the one by [54], and study-specific templates, one limitation is that head length and width may influence cortical folding in a manner that an affine transformation may not correct for, indicating that this template may not be appropriate for non-mesaticephalic animals. Given the degree of within-species variability in dogs, instead of normalization by using automated algorithms with nonlinear transformations, an anatomically-informed, supervised normalization may be more appropriate. The advantages of this later approach may become most prominent in case of templates that preserve fine detail, especially those based on a selected individual.

Challenges resulting from within-species differences in skull formation and brain anatomy across dogs have been addressed differently in canine continuous EEG and in event-related potential (ERP) studies. Regarding **continuous EEG**, presumably due to differences in skull morphology (e.g., thickness of frontal and parietal bones), absolute EEG power (μV^2) varies greatly across dogs (e.g., 3-fold across our samples; [32,33]). Thus, group-level analyses are best conducted using relative EEG spectrum values [32,33]. This is common practice in human EEG studies as absolute EEG power is less psychometrically sound than relative EEG power. Regarding **ERP** research, challenges have been addressed either via use of a homogenous group of dogs (e.g., laboratory-bred and -kept beagles of the same age and similar weight [30,31]) or via report of results at the level of individual dogs [55].

Relevant for both continuous EEG and ERP studies, an additional methodological issue is electrode placement. Despite canine methods having been adopted from human studies, given variability in dog head shape and size, the distance between electrodes placed on anatomical landmarks is different across dogs. Although this difference is difficult to address, such variation in absolute distances is compatible with the **International 10-20 system** used in human studies [56], which keeps not the absolute but the relative distance between electrodes constant.

Between-species differences in skull formation and brain anatomy (Box 2; Figure 1). In fMRI, these differences highlight issues of correction for multiple comparisons [57]. Given that the smaller brain volume of dogs (relative to humans) results in a smaller number of voxels (if the same or similar sized-voxels are used), the multiple comparison problem is less relevant in canine fMRI. Nevertheless, although there are widely used methods for correction in human studies employed in most (if not all) adult and child studies [58], there is heterogeneity across dog studies (Table 1). No meaningful comparison can be made between results obtained without and with correction, with varying degrees of stringency.

In EEG research, differences between dog and human skull and brain morphology necessitate differences in electrode placement. Because dogs have a smaller but more muscular head, their heads permit less sites for electrode placement. The number of electrode holders in human EEG head caps range from 16-256 compared to 3 [55,59], 4 [33], or 5-7 [30–32] electrodes placed on dogs' heads. Nevertheless, as these sites correspond to human electrode sites, a *functional comparison* between species can be made, even if restricted to a small number of EEG channels, which may be further increased with methodological advancements.

Differences in experimental design: sample composition. Available findings having been obtained with a small group of dogs and the noted overlap in included dogs may be disadvantageous for generalizability to larger populations. This can be addressed through careful sample selection, e.g., ensuring that dogs of different ages, breeds, sexes, and level of prior training (e.g., from training-naïve to service dogs), are included and then tested. Such selection has been attended to with varying degrees, with some variability in laboratory [30,31,35,38,42] vs. family [25–29,32–34,37,39–41,55,59] dogs, single [30,31,35,38,42,59] vs. multiple [25–28,32–34,37,39,41,55] breeds (with [29,40] not specified), and ages ranging from 1-12 years.

The noted small sample sizes and overlap in included dogs also means a very small overall number of tested dogs. The sample sizes of all but one [33] canine neuroscience studies published to date are <15 (which is approximately half of the average sample size of the canine cognitive studies published since 1911), leaving the research underpowered and effects difficult to detect [60]. A few pertinent consideration are worthy of note. First, arguably, in early and exploratory stages of a research area, small N studies are not only warranted but also desired to establish that larger (necessitating more funds and participant and researcher time) studies are indicated. Second and related, taking an average sample size of all canine cognitive studies might not at this stage of neuroscience research be informative from a practical standpoint as these domains of research also operate with different sample sizes in humans (e.g., largest samples are needed for genetic studies, with smaller samples for rating scale measurements, and even smaller samples for behavioural paradigms and yet smaller for neuroscience, especially fMRI studies). Third, although nuanced effects may not be detectable with small samples, the obtained results may reflect effects that are large and robust for the very reason that they are detectable even with small samples.

Differences that potentiate disadvantages and solutions need to be identified

Between-species differences in skull formation, brain anatomy, and physiology. Although further research is needed about *the degree* to w*hich dogs' anatomical structures and circuits correspond to humans',* the knowledge that is available is encouraging. There is evidence of correspondence between the species in, for example, primary sensory areas and associated functions [34]. Yet, whether other areas, especially the frontal and prefrontal cortex are organized – including with regard to subdivisions – in a manner that allows for characterization of structures,

circuits, and subdivisions as associated with similar cognitive functions across dogs and humans is largely unknown. One pertinent issue is whether or not similar differentiation and thus subdivisions exist and if those are associated with comparable functions (Box 2). As such, when a specific human structure is referenced (e.g., rostral anterior cingulate cortex [rACC], it is, at present, unclear whether the rACC in dogs is anatomically delineable from other areas of the ACC *and* functionally (e.g., attentional control over emotional conflict or distracters [47,61]) the same or at least meaningfully comparable across the species. Yet, even in the absence of similar differentiation, comparable functions may nevertheless exist. Similarly, neither from comparable anatomical location nor from absence of functional analogy, does absence of a homology but presence of convergent evolution necessarily follow.

Best methods for establishing the absence vs. presence of homologies (i.e., whether these similarities either originated from the last common ancestor passing down neuronal bases of executive functions or evolved independently due to the species facing similar challenges [5]) in brains whose differentiation differs and that developed differently through evolution will be key to address these types of questions. As an example to illustrate some of these points, although there are differences between birds and apes in neural structures, e.g., birds do not have a cerebral cortex for processing complex mental tasks [5], both species have prefrontal entities that control comparable executive functions [5].

Between-species differences in skull formation and brain anatomy are also source of methodological shortcomings in fMRI as the obtained images are of suboptimal quality due to use of radiofrequency (RF) coils (human head/neck, flex, [25,27–29,43,62] or knee coils [34,35,38,41,42,44]) whose geometries have been optimized for different purposes and have not been tailored to dogs' heads and neuroanatomy, making them less than ideal for canine fMRI. Together, as was the case with other species (e.g., marmosets, rats, mice, and rhesus monkeys) where use of dedicated animal coils has been shown to improve signal-to-noise ratio (SNR) [10], there is need for development of dedicated dog coils that satisfy the anatomical constraints imposed by these animals [1].

Between-species differences in cranial musculature and size are relevant for artefact rejection in EEG [63]. In human studies, artefact rejection includes correction for ocular artefacts and quantitative procedures (e.g., removing artefacts with voltage step between sample points that is greater than e.g., 50μV; with voltage difference of e.g., 300μV within a trial; and maximum voltage difference within e.g., 100msec intervals of e.g., <0.5μV [64,65]) and rejection via visual inspection. In dog studies, there are no well-established quantitative procedures, given difficulty in distinguishing muscle artefact from EEG signal and artefact rejection is typically done using simpler methods. The authors of ERP studies used only a single crude method [63] for rejecting trials with artefacts, in which a trial is rejected if the voltage during the epoch exceeds a user-defined threshold (amplitudes higher than 100μV [55,59] or 200μV [30,31]) and the authors of sleep EEG studies conduct artefact rejection by visual inspection only [32,33].

Although the user-defined method works for rejection of artefacts resulting from blinks, it is inadequate for detecting more subtle artefacts, such as those resulting from eye (or ear) movements [63]. As such, the used methods are problematic for awake continuous EEG measurement and ERP data collection where there is need for more stringent artefact rejection, given greater canine cranial muscle mass; another example where methodological uniformity between human and dog studies is neither possible, nor warranted. As an example, if the dog moves its eye (or ear) every time there is an event (i.e., stimulus), it is difficult to determine whether what appears to be a voltage change reflects the movement or differential neural activation. It may be for this reason

that there are no established methods for non-invasive measurement of ERPs in dogs, albeit some non- [30,31] and semi-invasive studies suggest progress [42,44].

Potential solutions to the artefact problem in non-invasive canine ERP research is to collect data from dogs with less cranial muscle and/or in a state of drowsiness (i.e., canine equivalent of light sleep) or sleep. In support, the Mismatch Negativity (MMN) component can be elicited during light sleep in humans [66,67], indicating an auditory ERP method may be useable with drowsy dogs. Notably, dogs spend at least 30 minutes in drowsiness during a 3-hour-long spontaneous EEG recording [33]. Not unlike sleep, drowsiness is characterized by lowered muscle tone, indicating it permits a considerable amount of artefact-free EEG data that ERP studies could potentially capitalize upon.

Between-species differences are pertinent beyond skull formation, brain anatomy and include differences in resting state physiology. Specifically, while normal respiratory rate in an average adult dog (24 breaths/min [68]) is not considerably different from a healthy human adult (12–20 breaths/min [69]), heart rate might show considerable differences between the two species (adult dogs: 60-140 bpm [68,70], humans: 50–90 bpm [71]).

These between-species differences are important as differences in brain shape and size also results in between-species differences in the hemodynamic response function (i.e., the course of the hemodynamic response to an external stimulus – the most common functional imaging signal; HRF) [1]. Although preliminary data on the canine HRF indicates it is similar to human HRF [25], replication is needed in larger samples for robust estimates of the shape of the canine HRF.

Unlike in human fMRI studies where temporal resolution is fast enough to model respiratory or heart rate, the temporal resolution in canine fMRI studies (repetition time [TR] varies between 1-2secs) may be insufficient to sample these physiological variables, despite them being major sources of fMRI confounds as they are correlated with changes in BOLD signal [72]. Regarding run length, there is a trade-off where longer runs are beneficial because they can contain more trials of the same condition but shorter runs are beneficial because they are more feasible with and comfortable for dogs. As such the number of acquired volumes is limited by how long dogs are able to hold still with experiments typically necessitating 5- [25], 6- [28,34,39], 7.5-minute runs [37]. In some cases, runs were 10- [73] and in some, they were 14-minutes [27]) long (no information is provided in [29,38,41]) but in these instances dogs were fed during runs, resulting in motion and thus a larger amount of discarded data. To identify an optimal parameter setup, different anatomical and functional sequence parameters should be tested with phantom and ex-vivo measurements. Similarly, protocols should be optimized with respect to signal- and contrast-to-noise ratio in pilot samples sufficiently similar to the intended experimental samples, but without the constraints on measurement time and motion of in vivo measurements. The ultimate goal of adapting sequence parameters to the dog brain is maximizing image quality via combination of high spatial and high temporal resolution. Such adaptation will have account for the smaller size of the dog brain, differences in dog compared to human physiology, and limits on run length by how long dogs are able to hold still. Importantly, there are methodological [74] and ethical advantages to shorter runs as these minimize image deterioration due to motion artefacts and prevent rises in specific absorption rates (SAR) of radio frequency levels (see *Ethics and Safety*) [1].

Differences in skull formation and brain anatomy: within- and between-species. Combined, differences across dogs and between dogs and humans in cranial characteristics will make it difficult to determine whether measured electrocortical signal originates from a

meaningfully comparable population of neurons across dogs and dogs and humans. Even the human source localisation literature is in its early stages, with only a few studies on the association between BOLD signal and ERPs recorded during the same session [75]. As noted, little is known about the degree to which certain neural structures in dogs are anatomically *and* functionally the same as humans' and advancing the literature in this domain will also be important for source localization.

Differences in experimental design: active vs. passive paradigm. In the human neuroscience literature, there are examples of studies where no behavioural response is required (passive task) and where a response is required (active task). Passive tasks do not involve movement, thus, from the perspective of introducing additional movement that results in additional motion artefact, they are not problematic. In humans, active tasks are also feasible via behavioural responses like a button press. In dogs, requiring an active response would mean that images obtained following an active condition would have to be discarded.

Indeed, in all but one canine fMRI study, the functions that have been examined are ones that do not necessitate an active response, including *passive auditory paradigms* [34,37], *passive visual paradigms* [25,28,29,41,43], *passive olfactory paradigms* [35] or, finally, probes of resting state activity. In the only canine fMRI study, with an active, go/no-go paradigm, a "go" signal indicated an active behavioural response is to be executed, which, in this case involved dogs touching a target with their noses while in the scanner. When analysing human go/no-go data, go trials are typically compared to no-go trials [76]. Here, however, activation during no-go trials was compared with activation during neutral trials as successful "go" trials could not be analysed due to the head motion produced by the nose-touch. This is an important limitation to the current state of the canine neuroscience field as there are socio-cognitive functions that are best probed in active paradigms.

In addition, the likelihood of prematurely attributing connections between brain structure and function is enhanced in dogs, as in the absence of concurrent behavioural response, the relevant cognitive processes are difficult to know with certainty. One solution to ameliorate risk of reverse inference (i.e., *post hoc* attribution of presence of a certain cognitive process given activation) is ensuring that dogs have pre-fMRI training on a behavioural paradigm that probes the same cognitive process the fMRI task in question is intended to probe [1] (see, for example, [28]). On a related note, as discussed in relation to the overlap in groups of dogs included across studies, the most ideal assessment battery will comprise measurement methods representing different levels of the measurement continuum (ranging from micro level measurement of brain circuits via fMRI, through less micro level measurement of physiology through EEG, to macro level measurement of observable behaviour via observation or rating scales; [77]) as data obtained at these different levels provide unique information on characteristics of interest [47,64,65,78,79].

Ethics and safety

As noted, a main advantage of dogs is that being a domestic animal they can be tested without need for laboratory breeding, raising and keeping. As such, focus on family dogs is what makes the advantage of the dog model ethically permissible. Nevertheless, as aptly discussed by others [1], care should be exercised that no harm is caused, e.g., that scanner noise and high sound pressure levels do not lead to discomfort and hearing damage or that specific absorption rates (SAR) of radio frequencies do not reach harmful levels of rise in tissue temperature [1]. Undue stress should also be minimized both for reasons of ethics and because it can lead to increases in

physiological activity which, as noted, introduce non-neural noise. Stress should also be monitored e.g., via pre- and post-scanning measurement of physiological indices (e.g., cortisol) of stress such as from saliva or urine [1].

Concluding remarks

There has been a notable recent increase in canine neuroscience studies, necessitating establishment of methodological guidelines and standardisation to inform the next generation of studies in this area. Here, we have discussed the foremost questions related to methodology and experimental design in the canine neuroscience literature. As a result, we were able to identify critical areas for further empirical inquiry. Capitalizing on advantages of the dog as a research model, such as its cooperativeness and trainability, these include the relation among brain structure, function, and behaviour in dogs; within-subject temporal stability of neural measures; and within-subject correspondence of neural correlates and performance across social, cognitive, and affective paradigms, in particular those probing socio-cognitive skills that share key behavioural and functional characteristics across dogs and humans.

Regarding challenges for which solutions are already being employed, it will be important that such solutions are adopted and used in a reasonably standardised fashion. Regarding unresolved challenges, it will be important to ensure that samples of dogs reflect variation in the larger population to increase generalizability. Specific to fMRI, it will be key to improve sensitivity of imaging protocols and image quality including via improved spatial and temporal resolution that also allow for sampling heart and respiratory rate as well as development of radiofrequency coils and scanning sequences that are tailored to the specifics of dogs and their neuroanatomy. It is unknown whether non-invasive ERP research is possible with dogs. Addressing this question may require more sophisticated methods either for minimizing eye-movement and muscle artefact during experiments and/or for artefact rejection (e.g., filtering) that is appropriate to the magnitude and type of artefact that occurs in dogs. The degree to which neural structures in dogs are anatomically *and* functionally comparable to those of humans will need to be established, including to set the stage for future studies with simultaneous neuroimaging and electrophysiological measurement aimed at source localisation. Source localisation will, in turn, help uncover the degree to which what appears to be meaningfully comparable electrode placement across dogs (and across dogs and humans) reflects signal from a meaningfully comparable population of neurons. Regarding difficulty with active behavioural paradigms, methods need to be identified that either permit dogs to exhibit a behavioural response without data loss (e.g., behavioural response that does not result in head motion, such as eye-movement) or, alternatively, passive paradigms that probe functions that currently can only be manipulated in active paradigms need to be developed.

In closing, we argue that, carefully considering inherent advantages, the domestic dog may become an innovative and unique model for comparative cognitive neuroscience. This argument becomes relevant if the highlighted advancements take place as these will be necessary for measuring the neural bases of canine socio-cognition in a relevantly comparative, reliable, and valid manner that is informative for basic comparative, clinical, and translational neuroscience. Addressing the noted challenges with dogs appears appreciably more feasible than addressing problems with traditional models, such as their non-cooperativeness, lack of a shared social environment with humans, and, in the case of primates, cost-inefficiency and paucity.

Glossary

Basilar axis: the axis corresponding to the base of the skull
Bradicephalic: short skulled
Calvaria: the bone that covers the cranial cavity containing the brain, i.e., the skullcap
Continuous EEG: continuous measurement of electrocortical signal, i.e., not measurement of change in such signal in response to a stimulus
Cribriform plate: a structure that forms the caudal boundary of the nasal cavity
Dolichocephalic: long skulled
ERP: measurement of negative and positive voltage changes in electrocortical signal in response to specific events (e.g., stimuli)
Gyrencephalic brain: with brain folds (gyri) and grooves (sulci), i.e., folded brain
Hard palate: a thin horizontal bony plate of the skull, located in the roof of the mouth
Homology: shared ancestry between a pair of genes or structures, in different taxa. A common example is the vertebrate forelimb, where bat wings, primate arms, whale front flippers, and dog forelegs are all derived from the same ancestral tetrapod structure. The opposite of homologous genes or structures are analogous ones, i.e., ones that serve a similar function across two taxa but were not present in their last common ancestor but evolved independently. For example, the wings of a bird and a sycamore maple seed are analogous (but not homologous), as they developed from different structures.
International 10–20 system: a method used to describe the location- and guide the application of scalp electrodes in an EEG examination or experiment, based on the relation between placement of an electrode and underlying cortex. The 10-20 system was developed to ensure reproducibility and standardisation. The "10" and "20" refer to the distances between adjacent electrodes being 10% and 20% of the total front–back or right–left distance of the skull, respectively.
Lissencephalic brain: without brain folds (gyri) and grooves (sulci), i.e., smooth brain
Mesaticephalic: a mesaticephalic skull is neither markedly dolichocephalic or brachycephalic and is of intermediate length and width
Model/Rival method: a social learning training method where during the training of an individual, another individual can be present and when the model is rewarded and praised for the wanted behaviour the rival is ignored
Prehensile organ: an organ adapted for seizing or grasping especially by wrapping around
Proximate causation: an explanation of biological functions and traits in terms of the effects of immediate environmental forces
Somatotopic organization: various portions of the body are represented topographically on specific regions of the cerebral gyri
Somesthetic cerebral cortex: the primary cortical processing mechanism for sensory information originating at the body-surfaces (e.g., touch) and in deeper tissues such as muscle, tendons, and joint capsules (i.e., position sense).
Ultimate causation: an explanation of biological functions and traits in terms of the effects of evolutionary forces

Outstanding questions

The next generation of studies

- may **capitalize on advantages of the dog** by addressing

- What are the characteristics of the relation between canine brain structure and function?
- What are the effects of differences in this relation on differences in neuro-cognition?
- Are and to what degree
    - neuroscience measures temporally stable (in dogs)?
    - is there correspondence between differences in neural activation and in task performance across social, cognitive, and affective paradigms?

- **address prudent challenges** by evaluating

- Is awake, non-invasive ERP research possible – wherein eye-movement and muscle artefact is minimized and artefact rejection improved – with dogs?
- Are and to what degree brain structures in dogs anatomically *and* functionally comparable to those in humans?
- Is source localization in canine fMRI-EEG research possible and via which methods?
- What active behavioural paradigms would permit for dogs to exhibit a behavioural response that does not make obtained data unusable? What passive paradigms would probe functions that at present can only be manipulated in active paradigms?
- What methods would permit application of a greater number of electrodes for EEG and ERP studies and e.g., improve current ability to examine lateralisation of electrocortical signal?

Trends Box

- shared social environment with humans, cooperativeness, trainability, and advances in awake, non-invasive measurement of neural processes make the domestic dog a promising model of human neuro-cognition, one that complements traditional models
- for the dog to contribute to comparative neuroscience in a relevantly comparative, reliable, and valid manner, methods that allow for *functional comparability* to human methods are key
- differences between breeds and species as well as between design of canine and human studies confer both methodological advantages and disadvantages
- dogs permit examination of
  - a range of socio-cognitive skills that share key behavioural and functional characteristics with those of human's
  - within-species (1) relation between brain structure and function, and (2) the effects thereof on neuro-cognition, as well as
  - within-subject (3) temporal stability of neural measures, and (4) correspondence of neural correlates with performance across social, emotional, and cognitive paradigms

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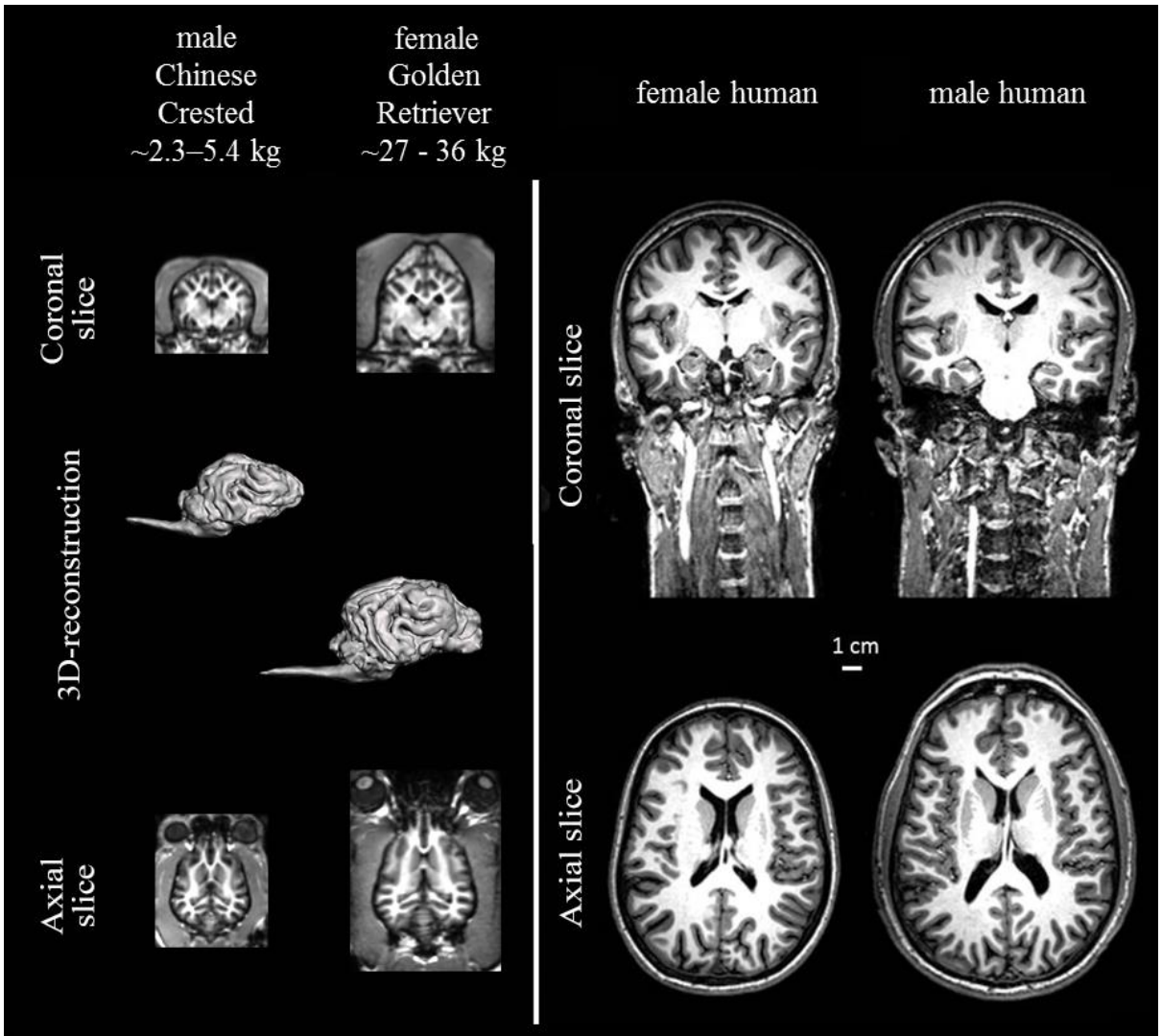

Figure 1. *Example images depicting differences in skull formation and brain anatomy across two adult dogs and two adult humans.* There are within- and between-species differences in skull formation and brain anatomy across dogs and across dogs and humans. These differences have implications for comparative cognitive neuroscience research with the dog. First, they present a natural opportunity to examine within-species relation among brain structure, function, and behaviour in dogs and the within-species effects thereof on neuro-cognition. In addition, they pose methodological challenges for fMRI (e.g., use of an atlas and template) and EEG/ERP research (e.g., large variation in absolute EEG power across dogs calls for use of relative EEG spectrum data and ear and eye movement introduces artefact for which correction techniques need to be improved). Finally, the named differences highlight need for future research on the degree to which certain anatomical structures and circuits correspond across dogs and between dogs and humans, including for purposes of source localisation of electrocortical signal.

Table 1.

Differences in method and experimental design across adult human, child human, and canine neuroscience studies

	Normalization – template	Methods for correction for multiple comparisons including FDR and FWE on voxel and cluster levels	Anatomical atlas for ROI analyses	# of Scalp electrodes	Paradigm	Length of training
adult human	Montreal Neurological Institute (305) T1 template	Bonferroni, Cluster-Level Inference/Spatial Extent Methods (e.g., Alphasim via Monte Carlo simulations), FDR, small volume	If used, then Montreal Neurological Institute with Anatomical Automatic Labeling	16-256	several examples of studies using active, passive, and resting state	none
child human ≥ 2 weeks old	mainly Montreal Neurological Institute (305) T1 template but also [41] and [42]	Bonferroni, Cluster-Level Inference/Spatial Extent Methods (e.g., Alphasim via Monte Carlo simulations), FDR, small volume	If used, then Montreal Neurological Institute with Anatomical Automatic Labeling	16-64 (head size displayed in cap ≥34 cm ≤46 cm)	several examples of studies using active, passive, and resting state	maximum two-occasion, 30-60-min familiarization with a mock-scanner and recordings of scanner noise
dog	- none: 3, 5, 6, 7, 10; - a selected individual: 1, 2, 13, 14, 17; - Datta et al., 2012: 4, 8, 9	- none: 1, 4, 5, 6, 9, 10; - Alphasim: 7, 8, 11, 12; FDR: 3; - small volume: 2 - N/A: 17	- no atlas, sample/study-specific anatomical localization: 2, 3, 4, 5, 6, 7, 8; - anatomical localization based on a common template; none - no atlas, functional localization: 1, 2, 4; - N/A because whole-brain: 9, 10, 13, 14, 17	- 3 (needle electrodes): 11, 12; - 4 (scalp electrodes): 15; - 5 (scalp electrodes): 19; - 7 (scalp electrodes): 16, 18	- active inhibitory: 7; - passive auditory: 1, 2; - passive olfactory: 4, 13, 14; - passive visual: 3,5, 8, 9, 10; - passive auditory and visual: 6; - resting state: 17	- none (exploration for polysomnography 5-10 min): 15, 19; - none (relaxation 40-60 min pre-semi-invasive measurement): 11, 12; - 18 months: 16, 18 - 5-20 sessions pre-scanner and 5-9 in scanner (length of sessions not reported): 1 - ~2-3 months: 3, 4, 5, 6, 7, 8, 10 - ~1-4 months: 9 - 30 min clicker training and 20, 60 min sessions MR training: 13, 14 - not specified: 2, 17

Table 1 continued

Note. MNI = Montreal Neurological Institute; ROI = region of interest.

1 = Andics et al. 2014, *Curr Biol*;
2 = Andics et al. 2016, *Science*;
3 = Berns et al. 2012, *PLoS One*;
4 = Berns et al. 2015, *Behav Process*;
5 = Berns et al. 2013, *PLoS One*;
6 = Cook et al. 2016, *SCAN*;
7 = Cook et al. 2016, *Anim Cogn*;
8 = Cook et al. 2014, *PeerJ*;
9 = Cuaya et al. 2016, *PLoS One;*
10 = Dilks et al. 2015, *PeerJ*;
11 = Howell et al. 2011, *J Neurosci Methods*;
12 = Howell et al. 2012, *Behav Process*;
13 = Jia et al. 2014, *PLoS One*;
14 = Jia et al. 2015, *Chem Senses*;
15 = Kis et al. 2014, *Physiol Behav*;
16 = Kujala et al. 2013, *PLoS One*;
17 = Kyathanahally et al. 2015, *Brain Struct Funct*;
18 = Tornqvist et al. 2013, *Anim Cogn*;
19 = Kis et al. 2017, *Sci Rep*.