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METHODS
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Computer Vision Evidence Supporting Craniometric Alignment of Rat Brain Atlases to Streamline Expert-Guided, First-Order Migration of Hypothalamic Spatial Datasets Related to Behavioral Control

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The rat has arguably the most widely studied brain among all animals, with numerous reference atlases for rat brain having been published since 1946. For example, many neuroscientists have used the atlases of Paxinos and Watson (*PW*, first published in 1982) or Swanson (*S*, first published in 1992) as guides to probe or map specific rat brain structures and their connections. Despite nearly three decades of contemporaneous publication, no independent attempt has been made to establish a basic framework that allows data mapped in *PW* to be placed in register with *S*, or vice versa. Such data migration would allow scientists to accurately contextualize neuroanatomical data mapped exclusively in only one atlas with data mapped in the other. Here, we provide a tool that allows levels from any of the seven published editions of atlases comprising three distinct *PW* reference spaces to be aligned to atlas levels from any of the four published editions representing *S* reference space. This alignment is based on registration of the anteroposterior stereotaxic coordinate (*z*) measured from the skull landmark, Bregma (β). Atlas level alignments performed along the *z* axis using one-dimensional Cleveland dot plots were in general agreement with alignments obtained independently using a custom-made computer vision application that utilized the scale-invariant feature transform (SIFT) and Random Sample Consensus (RANSAC) operation to compare regions of interest in photomicrographs of Nissl-stained tissue sections from the *PW* and *S* reference spaces. We show that *z*-aligned point source data (unpublished hypothalamic microinjection sites) can be migrated from *PW* to *S* space to a first-order approximation in the mediolateral and dorsoventral dimensions using anisotropic scaling of the vector-formatted atlas templates, together with expert-guided relocation of obvious outliers in the migrated datasets. The migrated data can be contextualized with other datasets mapped in *S* space, including neuronal cell bodies, axons, and chemoarchitecture; to

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generate data-constrained hypotheses difficult to formulate otherwise. The alignment strategies provided in this study constitute a basic starting point for first-order, user-guided data migration between *PW* and *S* reference spaces along three dimensions that is potentially extensible to other spatial reference systems for the rat brain.

Keywords: stereotaxic, stereotactic, atlas, data migration, registration, computer vision, subject matter expert, behavioral control

INTRODUCTION

Following the 1930s, when the design for the original Horsley-Clarke stereotaxic instrument (Horsley and Clarke, 1908) underwent modifications (Ranson and Ingram, 1931; Harrison, 1938) and was later diversified for performing intracranial surgery in the laboratory rat (Clark, 1939; Beattie, 1952; Stellar and Krause, 1954; Greer et al., 1955; Andreas and Legler, 1969; Krieg, 1975; also see Hillarp, 1947 for an alternate technology), several investigators published various stereotaxic coordinate systems to aid in the precise manipulation of small brain structures in this animal model, beginning with Krieg's atlas of 1946 (Krieg, 1946) (see Table 4 in Khan, 2013). Such manipulations have included ablation or stimulation of brain structures (Sheer, 1961; Myers, 1974; Thompson, 1978), tissue microdissection for biochemical analyses (Palkovits and Brownstein, 1988), chemical sampling of brain extracellular space via microdialysis or electrochemistry (Parada et al., 1998; also see Carter and Shieh, 2015), delineation of neural circuits using tracers (Heimer and Robards, 1981; Zaborszky and Heimer, 1989; Zaborszky et al., 2006), or molecular neurobiological techniques involving antisense, RNA interference, or viral-based vector delivery of various constructs to activate or silence activity in a cell-specific manner (Khan, 2013). More recently, such manipulations have also included optogenetic studies in rats (e.g., Gradinaru et al., 2009; Witten et al., 2011), including studies involving *in vivo* stimulation of hypothalamic cell bodies, their axonal projections, or their axonal inputs (Larson et al., 2015; Gigante et al., 2016), a structure that we also focus on in this study. Stereotaxic-based methods to manipulate brain structures to control behavior in the rat have contributed richly to our collective understanding of structure-function relations in the brain.

However, an inevitable outcome from these efforts—which collectively now span over seven decades of research using rat brain stereotaxic atlases—has been that anatomical data have been mapped within several different stereotaxic coordinate systems, hampering our abilities to interrelate formally the hard-earned and valuable results published in numerous studies. For example, the locations of injection sites published by a laboratory using a particular stereotaxic rat brain atlas may be difficult to place in register with corresponding locations, *within the same physical space*, of neuronal populations that might lie underneath such injections, but which have been mapped by another laboratory using a different stereotaxic atlas. This is because of several variables that will differ between such atlas reference spaces: plane of section, intervals between sections, originations of various "zero" points for Cartesian coordinates calibrated to landmarks on the skull surface, and strains and body weights of the animals used to create the atlases (Kruger et al., 1995; Khan, 2013). Indeed, the idea of "interoperability" between different software and hardware systems in computer science is now being extended to describe similar needs for anatomical reference frameworks of the brain (Zaslavsky et al., 2010; Hawrylycz et al., 2011), which have also been represented digitally in three-dimensional space (Toga et al., 1989, 1995; Timsari et al., 2001; Hjornevik et al., 2007).

The problem of poor interoperability is compounded further by the progression of time. Older editions of brain atlases fall out of fashion, go out of print, or are supplanted by more popular coordinate systems of other atlases, or by newer editions of the same atlas. Take, for instance, a laboratory that published critical data about a neural system two decades ago, using what were then state-of-the-art techniques to map their anatomical data to what was then a current edition of a specific rat brain stereotaxic atlas. Today, data from that study may no longer be so useful to laboratories that routinely use a different atlas reference space and entirely different coordinates based on a radically different plane of section. Thus, the high quality data from this 20 year-old study are now "trapped" within an old reference space, effectively sealed by coded locks that no longer have appropriately registered keys. The consequence of this is that if no other laboratory has taken up the same problem, those trapped data continue to represent all that is known about that particular structure-function relation in the brain, but our abilities to interpret that information continue to decrease with time. A related consequence is that current investigators may have to repeat the same experiment because they cannot contextualize such data with their own observations. These issues are similar to those envisioned over 75 years ago (Asimov, 1942), and also discussed in relation to the "Digital Dark Age(s)," in which older information may not be obsolete, but simply locked or uninterpretable, similar to software or hardware that no longer is accessible due to modernization of digital standards (Sanders, 1997; Rosenzweig, 2003; Lima, 2011; also see Lepore, 2015). The locked data may still be useful and relevant if there was a living key. Also, even if neuroanatomical data from a study are not yet "trapped," migrating or registering them to additional anatomical reference spaces ensures their continued widespread use, lasting preservation, and broader contextualization with other (both older and newer) datasets [see, for example, the GitHub methods package release (https://github.com/RittmanResearch/maybrain) from Whitaker et al. (2016) to contextualize human brain MRI data with human brain gene expression data collected by the Allen Institute for Brain Sciences]. If supported by a durable and upgradable infrastructure, an extant anatomical reference space