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Review Article

Positional information in neural map development: Lessons from the olfactory system

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Positional information is fundamental in development. Although molecular gradients are thought to represent positional information in various systems, the molecular logic used to interpret these gradients remains controversial. In the nervous system, sensory maps are formed in the brain based on gradients of axon guidance molecules. However, it remains unclear how axons find their targets based on relative, not absolute, expression levels of axon guidance receptors. No model solely based on axon–target interactions explains this point. Recent studies in the olfactory system suggested that the neural map formation requires axon–axon interactions, which is known as axon sorting. This review discusses how axon–axon and axon–target interactions interpret molecular gradients and determine the axonal projection sites in neural map formation.

Key words: axon sorting, neural map, neuropilin-1, odorant receptor, positional information.

Introduction

In the nervous system, sensory information detected by the peripheral nervous system is spatially represented in the brain. In the visual system, visual information detected and processed in the retina is spatially represented in the tectum (or its mammalian equivalent, superior colliculus) maintaining the relative spatial order in the retina (known as retinotopy). A similar map is known for the somatosensory system (known as somatotopy). For example, in the primary somatosensory cortex, each body part is spatially represented forming the ''cortical homunculus.'' Non-spatial sensory information is also represented by spatial maps in the brain. Auditory information is detected by the cochlea in the inner ear, where hair cells are aligned according to receptive frequencies of sound. As a result of topographic projection from the cochlea, a tonotopic map can be formed, which represents the frequency of the stimulus. All of these maps are known as topographic maps, where the nearest-neighbor relationships in the peripheral sensory organ are maintained in the map. Olfactory information is detected by approximately 1000 types of olfactory sensory neurons (OSNs), and each of these neurons only expresses a single type of odorant receptor (OR) out of a repertoire of approximately 1000 OR genes. Olfactory sensory neurons expressing a given type of OR are scattered throughout the olfactory epithelium. However, their axons converge onto a specific pair of glomeruli in stereotypical locations in the olfactory bulb (Fig. 1). As a result, the OR activation pattern is spatially represented in the olfactory bulb (reviewed by Mori *et al.* 2006). Although the olfactory map is not a classical type of continuous topographic map, it is also referred to as a topographic map in that the map is stereotyped and receptor-topic.

Sensory maps have fascinated many neurobiologists that study the molecular bases of neuronal wiring. Specifically, the visual map has been extensively studied for more than a half century, and it is now accepted that the map topography is established by chemical gradients (reviewed by Huberman *et al.* 2008; Feldheim & O'Leary, 2010). However, the exact mechanism used by axons to interpret the chemical gradient still remains controversial. Recent studies in olfactory map formation provided a new concept of neural map formation: axon–axon interactions. This review discusses how sensory maps are formed using graded chemical cues, focusing on recent studies in the mouse olfactory system. Neural activity is another

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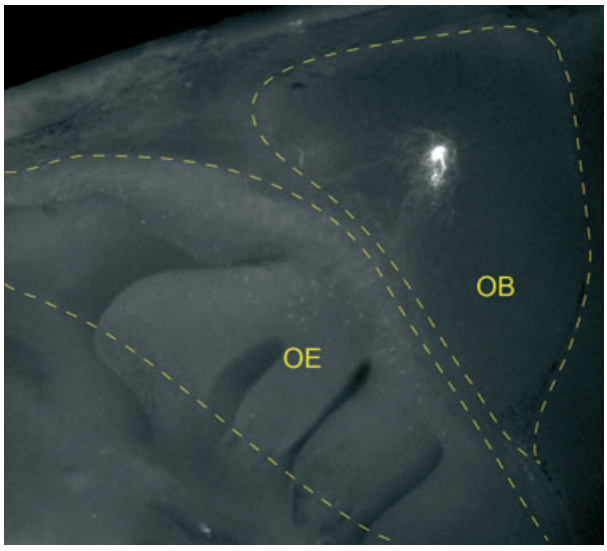

Fig. 1. Axonal projection of olfactory sensory neurons (OSNs) expressing the *I7-IRES-gapEYFP* transgene under the control of the *MOR23* promoter (Imai *et al.* 2006). EYFP fluorescence in the olfactory epithelium and olfactory bulb is shown (medial view of sagittally-transected sample). OSNs expressing the same type of odorant receptor (OR) converge their axons to a specific pair of glomeruli in the olfactory bulb. A, anterior; D, dorsal; OB, olfactory bulb; OE, olfactory epithelium; P, posterior; V, ventral.

important mechanism in neural map formation (Huberman *et al.* 2008); however, this will not be discussed in the review. For a more comprehensive review on olfactory map development, see Imai *et al.* (2010). More general roles of axon–axon interactions are discussed in Imai & Sakano (2011).

Purpose of neural maps

Although the scope of this review is to discuss the molecular logic of neural map formation, it would be equally interesting to discuss the purpose of the map, because form and function are two sides of the same coin. Why does our brain use neural maps for sensory perception?

One possible purpose of neural maps is for the functional classification of output pathways. In fish and mammals, different parts of the tectum (or superior colliculus) are tightly coupled to different sets of reflex motor circuits (Herrero *et al.* 1999; reviewed by Dean *et al.* 1989). The somatosensory map is also known to be linked to motor circuits (Matyas *et al.* 2010; Mao *et al.* 2011). In the mouse olfactory system, only the dorsal part of the olfactory bulb mediates innate avoidance behavior toward threatening predator odors, although the ventral bulb can also sense and distinguish the same odors (Kobayakawa *et al.* 2007). It is assumed that in these cases, activation of specific glomeruli leads to specific behavior.

A second purpose of neural maps is that they may be useful for information processing, particularly in pattern extraction and sharpening based on lateral inhibition. For example, the inhibitory circuit is thought to help generate orientation selectivity in the primary visual cortex (Bock *et al.* 2011; reviewed by Shapley *et al.* 2003). Similarly, the olfactory bulb is not simply a relay station; inhibitory bulbar circuits are assumed to sharpen odor responses (reviewed by Wilson & Mainen 2006; Murthy 2011). Thus, sensory maps may be arranged such that the lateral inhibition is most effective. The geometry of dendrites may also play important roles in information processing (reviewed by Branco & Hausser, 2010).

In the olfactory system, neural maps allow common sensory inputs to converge, increasing the sensitivity and signal-to-noise ratio (i.e., the ratio of spike frequencies during odor sensing versus resting). In the mouse, approximately 1000 OSNs expressing the same type of OR converge their axons onto a single glomerulus. Because the noise level is given by a square root of n, a simple estimation of the signal-to-noise ratio at the level of a glomerulus would be approximately 30 ($=1000^{1/2}$)-fold higher than a single OSN, allowing for sensitive detection of odors.

Neural map organization can also be considered in the context of wiring strategy and wiring cost (reviewed by Chklovskii & Koulakov 2004). Assume an altered map in which the neuronal positions in the map are randomized but the entire connection diagram is maintained. This altered circuit might possess a similar function as the original one to a certain extent. However, in this altered map, it would be much more difficult to make and maintain the correct connections. The total length of axons and dendrites would be much larger, and many more guidance molecules would be required to correctly establish the same connection diagram. In reality, an extremely large number of connections in the neural maps are established with a surprisingly small number of graded guidance molecules, as discussed below. Thus, the map layout of the neural circuits might be an economical wiring strategy. The wiring economy principle has successfully explained neuronal placement in the *Drosophila* optic lamina (Rivera-Alba *et al.* 2011).

Axon–target interactions in the visual map formation

The retinotectal projection has been a classical model of neural map formation. In the retinotectal system, retinal ganglion cells in the retina project axons in a

topographic fashion, such that the nasal-temporal (anterior-posterior) and dorsal-ventral orders in the retina are maintained in the tectum along the posterior-anterior and ventral-dorsal axes, respectively. Sperry (1963) performed eye rotation experiments and a series of regeneration experiments, and proposed that axons are guided by chemical cues either in the target or along the pathway, which is known as the ''chemoaffinity hypothesis''. Sperry postulated that graded chemical cues existed along two axes on the target and assumed that complementary gradients of receptors on the axons could be used to interpret this information. Although Sperry assumed a ''lock-and-key'' matching mechanism between axons and targets, later studies suggested that repulsion, rather than attraction/adhesion, is a primary (though not the sole) mechanism. For example, in an *in vitro* axon guidance assay (stripe assay), temporal axons were repelled by a posterior tectal membrane and grew toward an anterior membrane (Walter *et al.* 1987). Later studies revealed that this interaction is mediated by the ephrin-A ligand in the tectum and the Eph-A receptor in retinal axons (Drescher *et al.* 1995; Cheng *et al.* 1995). However, theoretical studies suggested that a repulsive mechanism alone cannot form the map because all of the axons would be repelled to the extreme end of the map (Gierer 1983). As a counterbalance, attraction (McLaughlin *et al.* 2003; Schmitt *et al.* 2006) and adhesion (Hansen *et al.* 2004) have been proposed.

In theory, a combination of repulsive and attractive/adhesive mechanisms between axons and targets might explain the precise mechanism of map formation. However, this model cannot explain several observations suggesting that relative, rather than absolute, expression levels of guidance receptors determine axonal projection sites. Ablation of half of the tectum results in a compression of the visual map into the remaining half of the tectum (Yoon 1976; Finlay *et al.* 1979). Conversely, when the retina is half-ablated, the remaining retinal axons expand to cover the entire tectal region (Yoon 1977). Such plasticity is also observed naturally during fish development: as the number of retinal ganglion cells expands during development, the projection area slides to fit the limited tectal size (Gaze *et al.* 1974; Easter & Stuermer 1984). More recently, it was shown that overexpression of the EphA3 receptor in a mosaic population of retinal ganglion cells resulted in duplicated visual maps in the superior colliculus; one resulting from the original EphA levels and the other from elevated EphA levels (Brown *et al.* 2000). Thus, relative but not absolute expression levels of guidance receptors determine axonal projection sites (Reber *et al.* 2004). When the number of retinal ganglion cells was dramatically reduced using Math5 mutant mice, most of the retinal axons terminated at the anteromedial superior colliculus, rather than filling the entire target (Triplett *et al.*, 2011). Based on these observations, axonal competition has been proposed, although the underlying molecular mechanisms remain unknown. A detailed history of our understanding of visual map formation has been described in Holt & Harris (1993) and Flanagan & Vanderhaeghen (1998). For the most recent reviews, see Huberman *et al.* (2008) and Feldheim & O'Leary (2010).

Olfactory map formation by axon sorting

Compared with the visual map, studies of the olfactory map have a very short history. Odor-specific map organization has been suggested by electrophysiological studies (Mori *et al.* 1992), and became more evident after molecular cloning and subsequent histological analyses of ORs (Buck & Axel 1991; Ressler *et al.* 1994; Vassar *et al.* 1994). Genetic tagging of OR genes clearly demonstrated that OSNs expressing the same type of OR converge their axons onto a pair of glomeruli in stereotyped locations in the olfactory bulb (Mombaerts *et al.* 1996).

Transgenic experiments using OR gene promoters have also contributed to our understanding of olfactory map formation (Fig. 1). The first insight into the mechanisms of olfactory map formation came from a finding that OR proteins affect the axon guidance process: when an OR coding sequence was swapped with that of another OR, axonal projection sites shifted along the anterior-posterior axis of the olfactory bulb (Mombaerts *et al.* 1996; Wang *et al.* 1998). Based on thorough mutagenesis of ORs *in vivo*, Feinstein & Mombaerts (2004) proposed a contextual model in which the map is formed based on OR type-specific homotypic axon sorting.

Although it was initially believed that OR proteins might function as axon guidance or adhesion molecules, a later study demonstrated that OR proteins indirectly regulate axon guidance through the cAMP signaling pathway (Imai *et al.* 2006). This study proposed that each OR generates a unique level of cAMP signals and that the levels of OR-derived cAMP signals determine the anterior-posterior axis of the map (reviewed by Imai & Sakano 2007). The cAMP signals transcriptionally regulate an axon guidance receptor, Neuropilin-1 (Nrp1), in a positive manner. Nrp1-high axons project to the posterior region of the olfactory bulb. Thus, the logic of olfactory map formation is similar to that of the visual system in that the expression level of the guidance receptor determines the coarse targeting of axons. The only difference is the transcriptional regulation of axon guidance molecules: in the

visual system, expression levels are determined based on neuronal positions in the retina. However, in the olfactory system, the expression level of Nrp1 is determined by the intracellular cAMP level.

When Nrp1 was overexpressed in olfactory sensory neurons expressing transgenic OR-I7, all of the OR-I7-positive neurons converged to a posterior glomerulus relative to the control. In contrast, when Nrp1 was conditionally knocked out in transgenic OR-I7-expressing OSNs, the transgenic OR-I7 OSNs converged their axons onto an anterior glomerulus relative to the control. Thus, Nrp1 determines the anterior-posterior axis in a dose-dependent manner. Curiously, however, when Nrp1 was knocked out in all OSNs including OR-I7 OSNs, OR-I7 OSNs projected diffusely onto multiple glomeruli along the A-P axis of the olfactory bulb (Fig. 2). If absolute Nrp1 levels determine glomerular positioning, all glomeruli should form in the anterior olfactory bulb in the OSN-specific knockout, and the results for OR-I7 OSNs should be the same between the OR-I7-specific knockout and OSN-specific knockout. Thus, relative, not absolute, expression levels of Nrp1 determine the axonal projection sites, which is similar to that of the EphA receptor in the visual system. How do relative levels of Nrp1 determine the anterior-posterior positioning of glomeruli in the axonal projection of OSNs?

It has been shown that OSN axons that project to distinct destinations are presorted within axon bundles (Satoda *et al.* 1995). Nrp1-high axons that project to the posterior olfactory bulb and Nrp1-low axons that project to the anterior olfactory bulb are presorted in the bundles. Axon sorting occurred in *Gli3* mutant mouse, where the olfactory bulb is completely absent. In the *Gli3* mutant, OSN axons were arrayed in the cranial cavity, showing an anterior-low and posterior-high gradient of Nrp1, which supports the notion that the anterior-posterior map can be formed, at least in part, without axon–target interactions. It was found that pre-target sorting of anterior- and posterior-targeting axons is in part regulated by repulsive interactions among axons: Semaphorin-3A (Sema3A), which is expressed by anterior-targeting axons, repels posterior-targeting axons expressing Nrp1, thereby

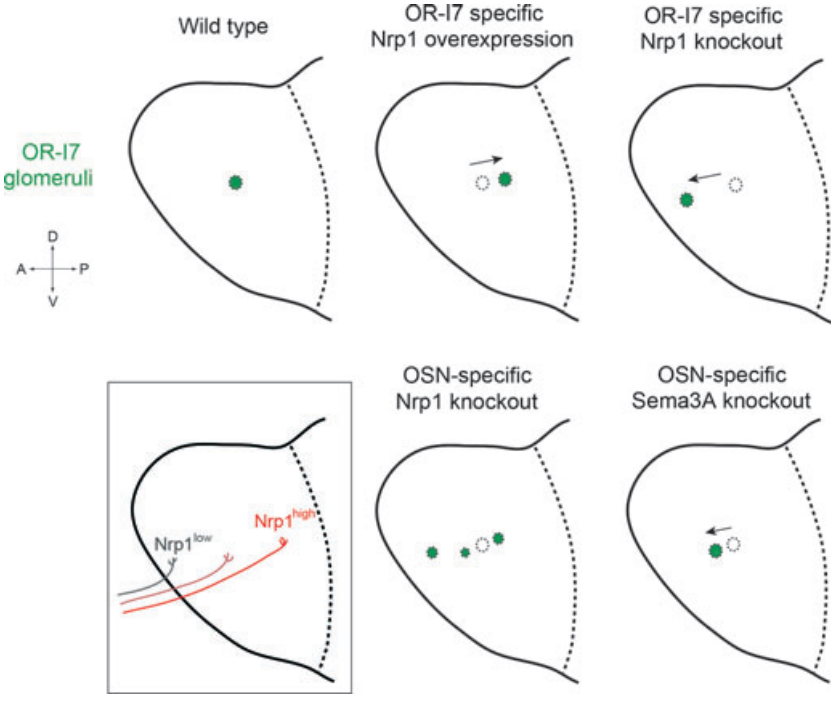

Fig. 2. Summary of gain and loss of function experiments for Nrp1 and Sema3A in the mouse olfactory system (Imai *et al.* 2009). As shown in the inset, the Nrp1 expression level in olfactory sensory neurons (OSNs) determines the anterior-posterior targeting of OSN axons: $Nrp1^{high}$ axons project posteriorly, and $Nrp1^{low}$ axons project anteriorly. Gain and loss of function of Nrp1 in OR-I7 expressing OSNs resulted in posterior and anterior shifts of projection sites, respectively. However, in OSN-specific Nrp1 knockout mice, OR-I7 axons project to diffuse multiple glomeruli along the anterior-posterior axis, rather than all projecting to the anterior olfactory bulb (OB). OSN-specific knockout of Sema3A changes the olfactory map, suggesting that trans-axonal Sema3A-Nrp1 signaling is involved in olfactory map formation.

segregating these heterotypic axons (Imai *et al.* 2009). OSN-specific knockout of *Sema3A* caused an alteration in axon sorting and olfactory map formation.

However, with the axon sorting mechanism alone, the map would easily rotate. How are presorted axons arrayed along the anterior-posterior axis of the olfactory bulb in a reproducible manner? This array probably requires cues derived from the target and intermediate targets; *Sema3A* is transiently expressed during embryonic stages in the anterior olfactory bulb and along the pathway. In fact, total knockout of *Sema3A* caused a more severe phenotype than the OSN-specific knockout (Schwarting *et al.* 2000; Imai *et al.* 2009). However, as mentioned above, the target does not provide the ''positional cue'' that determines the absolute positions of axons. The gradient in the target likely functions as a ''directional cue'' that determines the axis of the map. Axonal projection sites are determined based on the relative expression levels of guidance molecules that are expressed by axons, i.e., Nrp1 and Sema3A for anterior-posterior targeting of OSNs. A similar strategy is used for dorsal-ventral targeting of OSNs; Nrp2 and Sema3F are expressed by OSN axons to determine the dorsal-ventral map in the olfactory bulb (Takeuchi *et al.* 2010).

Axon–axon interactions in the visual map formation?

Pre-target axon sorting has been well described in the visual system, especially in fish and amphibians (Sperry 1963; Scholes 1979; Plas *et al.*, 2005). Although axon sorting (fiber–fiber interactions) was proposed as one possible mechanism of visual map formation (Scholes 1979), several later studies favored the axon–target model (reviewed by Holt & Harris 1993). Pre-target axon sorting in the bundle was less evident in the chick and mouse (Plas *et al.*, 2005; reviewed by Feldheim & O'Leary, 2010). In these organisms, final projection sites are determined by axon branch remodeling rather than the directional guidance process in the axon bundle. Furthermore, in regeneration experiments in the newt (Fujisawa 1981), and heterochronic projection experiments in *Xenopus* (Holt 1984), retinal axons reached the correct target area even though the pathway in the axon bundle was altered from the original pattern. Based on these observations, it has been widely accepted that only the target provides the positional information. However, the axon-sorting model can also explain the above observations: retinal axons on the surface of the target may provide graded chemical cues. For example, in the mammalian visual map formation, axon branch remodeling might be controlled not only by the target cues, but also by cues on the neighboring axons.

Indeed, axon–axon repulsion has also been demonstrated for retinal axons *in vitro*: temporal retinal axons are repelled not only by the posterior tectum but also by nasal retinal axons (Bonhoeffer & Huf 1985; Raper & Grunewald 1990). A recent study demonstrated that when a single retinal axon was allowed to project to the tectum in the zebrafish, the solitary axon terminated at a larger area on the target than in the control (Gosse *et al.* 2008). Similarly in the mouse, retinal axons failed to project to topographically correct positions on the target when the number of retinal ganglion cells was dramatically reduced, contradicting the models solely based on axon–target interactions (Triplett *et al.*, 2011). Because ephrins and Ephs are both expressed in the retina in a complementary manner, ephrins/Ephs may act not only between axons and targets but also among axons in the axon bundle and/or on the surface of the target. Indeed, recent studies clearly demonstrated that adhesion and repulsion between sensory and motor axons are regulated by trans-axonal ephrin-A/EphA reverse and forward signaling, respectively (Gallarda *et al.* 2008; Wang *et al.* 2011). A similar finding was also reported for callosal axon projections (Nishikimi *et al.* 2011). It will be interesting to study, ideally using mosaic conditional mutagenesis, whether the trans-axonal ephrin/Eph signals observed in the sensory and motor axons are also involved in visual map formation.

A revised model: axon sorting and directional guidance by the target

As mentioned above, models solely based on axon–target interactions contradict a number of experimental observations demonstrating that the ''relative'' levels of guidance receptors determine the projection sites. Furthermore, the axon–target model based on absolute levels of molecules should be highly sensitive to environmental and genetic fluctuations. In contrast, mechanisms based on axon sorting should be robust in neural map formation because axon sorting occurs based on relative levels of signals among axons. In the mammalian olfactory system, OR genes have dynamically evolved by gene duplications and gene losses to adapt to the changing environment. Because the olfactory map is formed by axon sorting, the target does not need to change when an OR gene is gained or lost during evolution. In fact, it has been demonstrated that the acquisition of a new OR gene is sufficient to generate new glomeruli in the olfactory bulb (Belluscio *et al.* 2002). Thus, neural map formation by

axon sorting is economical from an evolutionary point of view.

Cell sorting seems to be important not only in neural map formation but also in developmental patterning in general. It is generally believed that morphogenesis and patterning are controlled by the morphogen gradients (reviewed by Wolpert 2011). However, again, mechanisms based on ''absolute'' concentration of morphogens should be highly sensitive to perturbations and fluctuations. Recent studies demonstrated that cell position has no role in patterning in some systems. For example, in the multicellular state of the social amoeba *Dictyostelium*, one of the most primitive multi-cellular organisms, patterning occurs through random differentiation in a salt-and-pepper fashion and subsequent cell sorting without a morphogen gradient (reviewed by Kay & Thompson 2009).

Concluding remarks

In this review, the axon sorting model for neural map formation was discussed: the relative positions of axon terminals in neural maps are determined by axon sorting in the pathway and/or on the surface of the target after the axons have arrived. Target-derived guidance cues serve as directional cues rather than positional cues, and help arrange the sorted axons along the correct axis of the target (Fig. 3). Although the experimental evidence is available only in the mouse olfactory system, similar mechanisms are also likely involved in the neural map formation in other systems, including the visual system. Furthermore, similar cell sorting mechanisms may also explain developmental processes in non-neuronal systems.

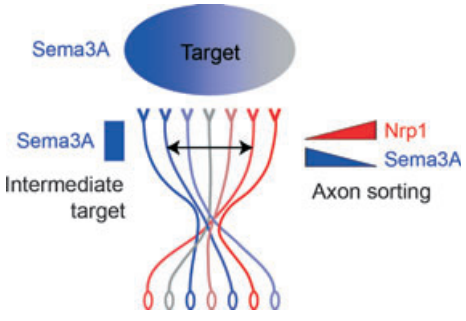

Fig. 3. A model of neural map formation in the mouse olfactory system (Imai *et al.* 2009). In the olfactory sensory neurons (OSNs), an axon guidance receptor Nrp1 and its repulsive ligand Sema3A are expressed in a complementary manner. The relative positions of axon terminals are determined by axon sorting based on relative expression level of Nrp1. The target and/or intermediate target provides directional cues and helps to arrange the sorted axons along the correct axis.

In the olfactory system, trans-axonal Sema3A-Nrp1 and Sema3F-Nrp2 signals are involved in axon sorting and neural map formation. However, they are most likely parts of trans-axonal signals, and attraction and/or adhesion may counterbalance these repulsive actions. In one scenario, adhesion mechanisms that fasciculate all OSN axons might be sufficient to counterbalance the repulsion. To fill the entire target region, axonal tiling (or axonal competition, Triplett *et al.*, 2011), which probably require both axon–axon and axon–target interactions, may also play an important role. It will be important to determine how the repulsive trans–axonal interactions are counterbalanced by attractive/adhesive and tiling/competition mechanisms.

An emerging view of olfactory map formation is that the map is largely self-organized by peripheral axons. However, odor-evoked behavior is sometimes robust and stereotyped, suggesting ''hard-wired'' olfactory circuits (reviewed by Stowers & Logan 2010). This may indicate that some additional molecules determine the precise matching between OSNs and second-order neurons, mitral and tufted cells. Alternatively, mitral/tufted cells may be naïve without inputs, and OSN-derived signals may instruct the wiring specificities of mitral/tufted cells (Belluscio *et al.* 2002). These are important issues for future studies.

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