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Sensory regulation of dopaminergic cell activity: phenomenology, circuitry and function

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Abstract - Dopaminergic neurons in a range of species are responsive to sensory stimuli. In the anaesthetised preparation, responses to non-noxious and noxious sensory stimuli are usually tonic in nature, although long-duration changes in activity have been reported in the awake preparation as well. However, in the awake preparation, short-latency, phasic changes in activity are most common. These phasic responses can occur to unconditioned aversive and non-aversive stimuli, as well as to the stimuli which predict them. In both the anaesthetised and awake preparations, not all dopaminergic neurons are responsive to sensory stimuli, however responsive neurons tend to respond to more than a single stimulus modality. Evidence suggests that short-latency sensory information is provided to dopaminergic neurons by relatively primitive subcortical structures – including the midbrain superior colliculus for vision and the mesopontine parabrachial nucleus for pain and possibly gustation. Although short-latency visual information is provided to dopaminergic neurons by the relatively primitive colliculus, dopaminergic neurons can discriminate between complex visual stimuli, an apparent paradox which can be resolved by the recently discovered route of information flow through to dopaminergic neurons from the cerebral cortex, via a relay in the colliculus. Given that projections from the cortex to the colliculus are extensive, such a relay potentially allows the activity of dopaminergic neurons to report the results of complex stimulus processing from widespread areas of the cortex. Furthermore, dopaminergic neurons could acquire their ability to reflect stimulus value by virtue of reward-related modification of sensory processing in the cortex. At the forebrain level, sensory-related changes in the tonic activity of dopaminergic neurons may regulate the impact of the cortex on forebrain structures such as the nucleus accumbens. In contrast, the short latency of the phasic responses to sensory stimuli in dopaminergic neurons, coupled with the activation of these neurons by non-rewarding stimuli, suggests that phasic responses of dopaminergic neurons may provide a signal to the forebrain which indicates that a salient event has occurred (and

possibly an estimate of how salient that event is). A stimulus-related salience signal could be used by downstream systems to reinforce behavioural choices.

Key words: Sensory stimuli; tonic; phasic; salience; reward

Contents

Abbreviations: DA, Dopaminergic; GABA, Gamma aminobutyric acid; PBN, Parabrachial nucleus; PPTg, Pedunculopontine tegnenatal nucleus; RMTg, Rostromedial tegmental nucleus; SC, Superior colliculus; SNc, Substantia nigra pars compacta; TH, Tyrosine hydroxylase; VTA, Ventral tegmental area;

INTRODUCTION

In 1979, Chiodo et al. reported that tail pressure, cervical probing and light flashes produced responses in dopaminergic (DA) neurons in the substantia nigra pars compacta (SNc) of anaesthetised Sprague Dawley rats. Since then, the finding that DA neurons respond to sensory stimuli has been extended to other stimulus types, to the awake preparation and to other species. Although perhaps a little premature to summarise, non-noxious sensory stimuli in awake animals tend to elicit short-latency, short duration 'phasic' responses in DA neurons whereas noxious stimuli in awake and anaesthetised animals (and non-noxious stimuli in anaesthetised animals) tend to elicit protracted 'tonic' responses which temporally track or even outlast the inducing stimulus. Tonic and phasic modulation of dopamine levels in the forebrain have been argued to subserve different functions (Grace, 1991; Floresco et al., 2003; Goto and Grace, 2005; Goto et al., 2007; Redgrave et al., 2008; Howe et al., 2013) and consequently the influence of sensory stimuli on these two modes of activity in DA neurons will be considered separately below. However, it is important at the outset to acknowledge a caveat with respect to the studies we are about to discuss – namely that the neurochemical identity of the neurons under consideration has usually not been firmly established. Hence, for 'DA neuron' below it is probably safest to read 'putative DA neuron' (unless identification has taken place) because of this uncertainty.

TONIC CHANGES IN DA CELL ACTIVITY IN RESPONSE TO NON-NOXIOUS AND NOXIOUS STIMULI

In the anaesthetised rat, non-noxious sensory stimuli do not typically elicit responses in DA neurons that are clearly time locked to the onset or offset of individual discrete stimuli. Instead, accounts suggest that sensory stimuli lead to a general elevation or reduction in firing rate, i.e. a tonic change in activity. In the rat, continuous tail or foot pressure, continuous

cervical probing, trains of light flashes, olfactory stimuli and trains of air puffs to the snout all produce long latency (~400 ms) activations and inhibitions in SNc DA neurons which last for the duration of the applied stimuli (Chiodo et al., 1979; Chiodo et al., 1980; likewise for tail and foot pressure, and cervical probing, in VTA DA neurons; Maeda and Mogenson, 1982). Not all cells respond, but responsive cells tend respond to more than a single stimulus modality, and individual cells can be activated and inhibited by different modalities. These tonic responses almost certainly reflect the temporally extended nature of the stimuli used by the authors (continuous, chemical, trains), and show that under certain conditions, the activity of DA neurons can track such prolonged stimuli. Indeed, in the anaesthetised preparation, it seems that stimuli have to be temporally extended for DA neurons to respond to them at all. In our hands, short duration, discrete light flash stimuli do not elicit responses in DA neurons in the anaesthetised rat (Dommett et al., 2005) and discrete somatosensory (whisker) stimuli are similarly ineffective (Overton, Vautrelle and Redgrave, unpublished observations). An important issue of course is the relevance of sensory-related tonic changes in the activity of DA neurons in the anaesthetised preparation to the regulation of DA neurons in the awake animal, where discrete non-noxious sensory stimuli can elicit phasic responses (see next section). However, tonic responses to sensory stimuli have been described in the awake restrained rat – to continuous tail pressure, trains of light flashes, olfactory stimuli and sound stimuli (Kiyatkin, 1988; Kiyatkin and Zhukov, 1988; Roesch et al., 1997), and to long duration light stimuli associated with chocolate milk reward (see Figure 2 of Miller et al., 1981), suggesting that tonic responses in DA neurons to non-noxious sensory stimuli are part of the 'natural' repertoire of responses in these cells.

So far we have been considering non-noxious stimuli, both conditioned and unconditioned. However, DA neurons also respond to noxious stimuli. In the anaesthetised rat, noxious

stimuli tend to induce responses which last for (and can outlast) the period for which the stimulus is applied. Hot water applied to the tail produces responses in SNc DA neurons (Tsai et al., 1980) and noxious tail pinch produces responses in both SNc and VTA DA neurons (Mantz et al., 1989; Ungless et al., 2004). Tsai et al. (1980) initially reported that all DA neurons are inhibited, an observation which was confirmed by Ungless et al. (2004) for neurochemically identified DA neurons in the VTA, and which fits with the accounts of short-latency (<100 ms) inhibitory responses in SNc and VTA DA neurons to protracted stimulation of the sciatic nerve (Tsai et al., 1980; Hommer and Bunney, 1980; Kelland et al., 1993). However, some DA neurons are activated rather than inhibited by noxious tail pinch, foot pinch or foot shock (Mantz et al, 1989; Coizet et al., 2006), and the most recent picture that has emerged is that there may be two populations of DA neurons in the VTA of the rat – one which responds with activation and one which responds with inhibition to noxious stimuli (Brischoux et al., 2009). Although the responses to long-lasting noxious stimuli tend to track the duration of the applied stimulus, there is evidence that the response is stronger towards the early phase of the stimulation, at least in the VTA (see Figure 1 of Mantz et al, 1989; Figure 2 of Brischoux et al., 2009).

These general findings in the anaesthetised rat also extend to the anaesthetised monkey. In the anaesthetised monkey, midbrain DA neurons are not responsive to a range of non-noxious sensory stimuli (such as rubbing of the skin, muscle taps and passive joint rotation; Schultz and Romo, 1987; Romo and Schultz, 1989). In contrast, noxious pinch is effective and the responses, which are more frequently inhibitions rather than activations, last for as long as the stimulus is applied (Schultz and Romo, 1987; Romo and Schultz, 1989). Presumably for ethical reasons, the majority of studies looking at the responses of DA neurons to noxious stimuli have been conducted under anaesthesia. However, in the awake restrained rat,

Kiyatkin (1988) and Kiyatkin and Zhukov (1988) report that a tail pricks or intense electrical stimuli to the tail produce responses (inhibitions or activations) in VTA DA neurons which temporally track the applied stimuli. Likewise, long duration tones associated by classical conditioning with electric shocks to the tail produce tonic inhibitory responses in neuro-chemically identified VTA DA neurons in the awake rat (see Figure 3 of Mileykovskiy and Morales, 2011), and tones associated with electric shocks to the pinnae produce tonic responses (this time most often activations) in VTA DA neurons in the awake rabbit (Guarraci and Kapp, 1999). Again, in both cases, these responses are greater at the beginning of the period of stimulation, but do persist throughout the stimulation, suggesting – in combination with the above - that tonic changes in activity are the standard, system-level response of DA neurons to both conditioned and unconditioned noxious stimuli. Phasic responses in DA neurons to noxious stimuli are of course possible. However, these responses - which tend to be short-latency (<100 ms) - only seem to occur when the inducing stimulus itself is of short duration (see Tsai et al., 1980; Hommer and Bunney, 1980; Kelland et al., 1993; Gao et al., 1996; Coizet et al., 2006; however see Mileykovskiy and Morales, 2011).

PHASIC CHANGES IN DA CELL ACTIVITY IN RESPONSE NON-NOXIOUS STIMULI

Dopaminergic neurons in the awake preparation in a range of species exhibit a highly stereotyped, short-latency (<100 ms), short duration (~100 ms) phasic change in activity in response to a variety of unpredicted conditioned and unconditioned stimuli. Perhaps the classic account of responses to unconditioned stimuli in the rat comes from Freeman and Bunney (1987), where they mention that 'manual stimulation of the rat's vibrissae…. elicited a burst of spikes' in VTA DA neurons, as did a 'whistle, hiss, [or] clap'. Bursts – packages of action potentials with short interspike intervals – appear to be a common response in DA

neurons to sensory stimuli in the awake preparation (Overton and Clark, 1997). Indeed, following more systematic testing of responses to unconditioned stimuli in the cat, Steinfels et al. (1983a; 1983b), Strecker and Jacobs (1985) and Horvitz et al. (1997) report that brief (1 ms) clicks and light flashes produce nonhabituating phasic responses (usually activations) in the majority of VTA and SNc DA neurons, with most cells responding to both stimuli. When activated by a stimulus, cells often show a burst response to stimulus presentation (Horvitz et al., 1997).

In the monkey, unconditioned phasic responses in midbrain DA neurons have been described to coloured, geometrically complex visual stimuli (Hollerman and Schultz, 1998) and combined auditory and visual stimuli (box opening; Ljungberg et al., 1992). These are usually considered to be 'novelty' responses, which tend to show habituation with repeated presentations. However, DA neurons in the food or fluid deprived monkey show nonhabituating unconditioned phasic responses to food when the food is touched (Romo and Schultz, 1989; 1990), and juice when delivered directly into the mouth (Mirenowicz and Schultz, 1996; Hollerman and Schultz, 1998; Fiorillo et al., 2013b), suggesting that DA neurons respond phasically not only to visual and auditory stimuli, but also to somatosensory and gustatory stimuli. Interestingly, unconditioned non-noxious aversive stimuli also elicit phasic responses in midbrain DA neurons. For example, air puffs to the hand produce activations in SNc DA neurons (Mirenowicz and Schultz, 1996) and air puffs to the face produce activations in some and inhibitions in other SNc and VTA DA neurons (Matsumoto and Hikosaka, 2009). The latter authors have argued that neurons exhibiting activations and inhibitions to aversive stimuli form two populations of neurons (Matsumoto and Hikosaka, 2009; Bromberg-Martin et al., 2010; cf Brischoux et al., 2009) – one of which signals salience (activated by all stimuli) and one of which signals value (activated by rewarding

stimuli and inhibited by aversive stimuli). However, this distinction has recently been challenged with the demonstration that an initial activation characterises the responses of many midbrain DA neurons to a range of non-noxious aversive stimuli, including air puffs to the face, saline and bitter tastes to the mouth (Fiorillo et al., 2013b). Value may be signalled by the phases of the response that follow the initial activation (Fiorillo et al., 2013b; see later).

In addition to exhibiting phasic changes in activity in response to non-noxious unconditioned stimuli, DA neurons in the awake animal also respond phasically to conditioned stimuli. Substantia nigra pars compacta and VTA DA neurons in the rat show activations in response to visual, auditory and combined auditory and visual stimuli, conditioned to food reward (Miller et al., 1981, Figure 2; Hyland et al., 2002; Pan and Hyland, 2005), with most neurons responding to both light and tone stimuli (Miller et al., 1981; Pan and Hyland, 2005). Likewise in the monkey, phasic responses in midbrain DA neurons have been described to auditory and simple visual stimuli which signal trial onset (Bayer and Glimcher, 2005; Bromberg-Martin et al., 2010), and to the opening of a food box following training with food (Romo and Schultz, 1989; 1990). They are also activated by simple visual stimuli (Schultz et al., 1993) and simple visual stimuli combined with auditory stimuli (Bayer and Glimcher, 2005) when associated with reward within a task. Auditory and simple visual stimuli associated with aversive air puffs to the hand also activate some midbrain DA neurons although they inhibit others (Mirenowicz and Schultz, 1996). However, most recent studies in the monkey have abandoned the use of simple visual stimuli in favour of coloured, geometrically complex visual stimuli, to which midbrain DA neurons respond with activation when the stimuli are paired with reward (Waelti et al., 2001; Morris et al., 2004; Fiorillo et al., 2003; Tobler et al., 2005; Joshua et al., 2008; Hudgens et al., 2009) or aversive outcomes

(Fiorillo et al., 2013a). Under rewarding conditions, responses to complex visual stimuli are modulated by the probability and magnitude of the reward they predict (Waelti et al., 2001; Morris et al., 2004; Fiorillo et al., 2003; Tobler et al., 2005; Joshua et al., 2008; Hudgens et al., 2009). Responses either follow unpredicted experimenter-driven stimulus presentation within task (Waelti et al., 2001; Morris et al., 2004; Fiorillo et al., 2003; Tobler et al., 2005; Joshua et al., 2008; Hudgens et al., 2009), or when the animal itself 'discovers' the stimulus during visual search (Matsumoto, 2013).

An important final question is the extent to which phasic responses in DA neurons are 'truly' phasic, rather than simply a reflection of the temporal properties of the stimuli researchers have employed. Many of the stimuli to which DA neurons exhibit phasic responses are themselves of short duration (clicks, light flashes, boxes opening, air puffs to the hand and face). However, other stimuli to which phasic responses have been reported are of a longer duration than the responses they elicit. For example, juice or saline/bitter tastes to the mouth are likely to result in a protracted sensory event. Likewise, the sensation associated with acquiring food by touch and bringing it to the mouth is again going to outlast the ~100 ms 'short burst of activity' (Romo and Schultz, 1989) associated with such an event. Finally, in much of the monkey work using food conditioned stimuli, the stimuli themselves are presented for >1 s, much longer than the responses elicited (e.g. Fiorillo et al. 2003; Tobler et al., 2005). As a consequence it appears that DA neurons (in the awake preparation) really do have two very different modes of responding to sensory stimuli – tonic responses to noxious stimuli and tonic, but more frequently phasic, responses to non-noxious stimuli.

ELUCIDATING THE CIRCUITRY

Whilst much is known about many aspects of the ascending DA systems, surprisingly little is known about the sensory inputs that modulate their activity. In the case of vision, the short latency of the phasic DA responses led us to investigate the possibility that a subcortical visual structure, the superior colliculus (SC), rather than a cortical relay, might be the critical source of afferent visual input (Comoli et al., 2003, Dommett et al., 2005). Visual response latencies of SC neurons (40-60 ms – Wurtz and Albano, 1980, Munoz and Guitton, 1986, Jay and Sparks, 1987, Peck, 1990, Stein and Meredith, 1993), are consistently shorter than those of DA neurons (70-100 ms – Schultz, 1998, Morris et al., 2004, Takikawa et al., 2004), whilst responses in cortical regions responsible for feature detection and object recognition are approximately the same or longer (80-130 ms; Thorpe and Fabre-Thorpe, 2001, Rousselet et al., 2004).

Our investigations led to the discovery of a significant, previously unreported direct projection from the SC to the SNc and VTA in the rat, which innervates both tyrosine hydroxylase (TH) positive (presumed DA) and negative (non-DA) neurons in these regions (Comoli et al., 2003). This tectonigral projection is a conserved feature of a wide range of species (rat: Comoli et al., 2003; cat: McHaffie et al., 2006; monkey: May et al., 2009). Associated electrophysiological experiments revealed that SC is a critical relay for short-latency visual evoked potentials recorded locally in the SNc (Comoli et al., 2003). Furthermore, we found that local disinhibition of the deep layers of the SC of anaesthetised rats is both sufficient and necessary for light stimuli to evoke short-latency phasic activations (including bursts) and inhibitions in DA neurons (Figure 1; Dommett et al., 2005), reflecting the excitatory and inhibitory components of the tectonigral projection (see Comoli et al., 2003). To our knowledge, this is the first demonstration of phasic responses in DA neurons to

non-noxious sensory stimuli in the anaesthestised animal, and in particular the first demonstration that such stimuli can produce burst firing under anaesthesia. Comparable disinhibition of the visual cortex had no effect, leaving midbrain DA neurons insensitive to the light stimulus. Hence it would appear that the SC is the primary, if not the exclusive, source of short-latency visual input to midbrain DA neurons, possibly mediated via the direct tectonigral projection.

However, the SC is a multi-sensory structure containing neurons which respond to visual, auditory and somatosensory stimulation (Drager and Hubel, 1975, Chalupa and Rhoades, 1977, Stein and Meredith, 1993, Wallace et al., 1996). As a consequence, it was natural for us to examine whether the SC is the primary source of sensory input to DA neurons for a modality other than vision. Given many studies have demonstrated that DA neurons respond to stimuli which are noxious, we chose to investigate whether the SC plays a critical role in signalling the occurrence of noxious events to DA neurons. The SC appears to play an important role in nociception, at least in the rodent. The intermediate and deep layers of the rat and hamster colliculus receive direct input from the nociceptive layers of the spinal cord (Rhoades, 1981, Almeida et al., 2004). These SC layers contain neurons that resemble spinal wide dynamic range and nociceptive specific (high threshold) cells, which respond with a short-latency tonic increase in activity to noxious mechanical and/or thermal stimulation (Stein and Dixon, 1979, McHaffie et al., 1989, Redgrave et al., 1996).

Interestingly, our studies with nociception suggest that the colliculus may not relay all short-latency sensory information to DA neurons (Coizet et al., 2006). Although the colliculus plays an important role in pain-related responses in the rat, suppression of collicular activity by the intracollicular application of the local anaesthetic lidocaine produces only minor

changes to the characteristics of the responses of DA neurons to noxious stimuli: the qualitative features of the responses are unaffected. Even though aspiration of the SC leads to an increase in the number of nonresponsive DA neurons encountered, some DA neurons are still responsive to noxious stimuli and the nature of the responses in these cells are indistinguishable from those in intact animals. So, the SC would appear to modulate the activity of DA neurons responding to nociceptive information from elsewhere, but does not supply this information.

Although the source of the afferent inputs which relay pain-related information to DA neurons was unknown at the time of our earlier work, during our retrograde anatomical work on the tectonigral projection, which involved the placement of tracer injections in the SNc, we noticed numerous retrogradely labelled cells in the mesopontine parabrachial nucleus (PBN). The PBN (especially the lateral part) is a major central target for ascending nociceptive information from the spinal cord (Hylden et al., 1989; Craig, 1995; Klop et al., 2005), which raised the possibility that the PBN may provide nociceptive signals to DA neurons. A more comprehensive study using parabrachial injections of anterograde tracers revealed robust projections to the SNc and VTA (Coizet et al., 2010). Axonal boutons were seen in close association with TH-positive and negative elements in these regions. Simultaneous extracellular recordings were made from parabrachial and DA neurons in the anaesthetized rat, during the application of noxious footshock. Parabrachial neurons exhibited short-latency, short duration activations to footshock while DA neurons exhibited short-latency inhibitions (Figure 2). Intra-parabrachial injections of lidocaine or the $GABA_A$ receptor agonist muscimol reduced the amplitude (and in the case of lidocaine, duration) of the phasic excitatory response to footshock in the PBN and reduced the amplitude of the phasic inhibitory response to footshock in DA neurons, in the case of lidocaine sometimes

abolishing it altogether (Figure 2). Attenuation or abolition of responses to footshock in DA neurons following PBN inhibition strongly suggests that the PBN is an important source of short-latency nociceptive input to DA neurons.

The direct projection from the PBN to the ventral midbrain may act in concert with the recently described nociceptive input to the VTA and SNc from the rostromedial tegmental nucleus (RMTg; Jhou et al., 2009a,b). The RMTg does not itself receive a direct nociceptive input from the spinal cord (Gauriau and Bernard, 2002), but does receive an excitatory input from the PBN (Jhou et al., 2009a), and projects to DA neurons in both the SNc and VTA (Jhou et al., 2009b). Since RMTg neurons projecting to the ventral midbrain - at least to the VTA - are primarily GABAergic (Jhou et al., 2009b), this may provide an additional route by which pain related information can inhibit DA neurons. Also, since RMTg neurons projecting to the VTA also terminate on non-DA (presumed largely GABAergic) neurons in the region (Jhou et al., 2009b), the inhibition of these cells following RMTg activation may produce some of the excitatory responses to noxious stimuli in VTA DA neurons (e.g. Brischoux et al., 2009). What functional need is subserved by having a direct and an indirect pain pathway from the PBN to the ventral midbrain is uncertain. However, the link in the RMTg provides a means by which the numerous brain regions which supply afferent inputs to the RMTg (see Jhou et al., 2009a) might modulate a component of the pain related signal going forward to DA neurons.

Other indirect routes of transmission for pain-related information from the PBN are of course possible. One potential component of a more indirect route is the lateral habenula, which contains nociceptive neurons (Benabid and Jeaugey, 1989) and has been hypothesized to provide nociceptive information to DA neurons (Brischoux et al., 2009). However, the fact

that nociceptive responses in DA neurons survive its destruction (Gao et al., 1990) suggests that the habenula may simply modulate pain related responses arriving from elsewhere (as with the SC, Coizet et al., 2006). Indeed, existing evidence suggests that the lateral habenula may provide information to DA neurons concerning aversive, non-noxious stimuli (Matsumoto and Hikosaka, 2007). If information about noxious stimuli is provided by the PBN (which does not receive an input from the lateral habenula, Tokita et al., 2009), this suggests that signals concerning these two types of negative outcome may be provided to DA neurons by different circuitry, an observation which is likely to be important for the debate about the neural separation of different classes of punishment signal (e.g. Boksem et al., 2008).

As well as receiving nociceptive information from the spinal cord, the PBN also receives inputs from widespread areas of the brain (Tokita et al. 2009), including the rostral part of nucleus of the solitary tract (Herbert et al., 1990), a brain area involved in the processing of gustatory information (Norgren and Leonard, 1973). Gustatory processing in the PBN is normally associated with an area which includes aspects of the lateral and medial subnuclei surrounding the superior cerebellar peduncle, as well as neurons within it (Karimnamazi and Travers 1998), all of which according to our retrograde anatomical results project to the SNc and VTA. Excitotoxic lesions of the PBN block the increased dopamine overflow in the forebrain produced by taste stimuli (Hajnal and Norgren, 2005), suggesting that the PBN may transmit gustatory information to DA neurons. The fact that both the lateral and medial medial subnuclei of the PBN also project to the RMTg (Jhou et al. 2009a; Kaufling et al., 2009), suggests that - once again – the direct pathway providing gustatory information to the ventral midbrain may operate in parallel with an indirect pathway acting via a link in the RMTg.

As well as visual, noxious and gustatory stimuli, DA neurons in the awake animal are strongly responsive to whisker stimuli (Freeman and Bunney, 1987), and auditory stimuli (e.g. Miller et al., 1981), as are neurons in the SC (Drager and Hubel, 1975, Chalupa and Rhoades, 1977, Stein and Meredith, 1993, Wallace et al., 1996). Despite this, we have not been able to produce (phasic) activations in DA neurons using whisker pad stimulation following $GABA_A$ antagonist injections into the SC. This may suggest that whisker-related information arriving at DA neurons does not use a collicular route. There is however one caveat: unlike the case with vision, $GABA_A$ antagonism in the SC does not lead to substantial phasic activation of neurons in that structure in response to whisker stimuli. That aside, preliminary anatomical work conducted in our laboratory suggests that at least part of the provision of auditory and somatosensory information to DA neurons may arise from non-collicular sources. Following injections of the retrograde anatomical tracer fluorogold into SNc, retrogradely labelled cells were found in the cochlear nucleus – the input station for incoming auditory information, and the trigeminal complex (principal sensory nucleus [Pr5] and spinal nucleus [Sp5]; Figure 3) – the input station for somatosensory information concerning the face and head. These are all non-collicular sources of sensory information, however once again they are primary sub-cortical sensory relays, only one synapse away from the sensory periphery.

Again subcortical, but further along the stimulus processing chain, Watabe-Uchida et al. (2012) identify inputs to SNc DA neurons from the auditory inferior colliculus, and to SNc and VTA DA neurons from the pedunculopontine tegmental nucleus (PPTg). Local inhibition of the latter structure attenuates responses to visual and auditory stimuli in SNc/VTA DA neurons in awake rats (Pan and Hyland, 2005). Whilst the fact that neurons in the PPTg respond to sensory stimuli in the awake rat (Pan and Hyland, 2005) and awake monkey

(Okada et al., 2009) possibly suggests that sensory information is routed to DA neurons via the PPTg, the PPTg is part of the cholinergic arm of the reticular activating system (Garcia-Rill, 1991), and as such may provide excitatory tone (arousal) to the ascending dopamine systems. Removing this arousing influence may blunt responses non-specifically, and may account for the difficulty of eliciting sensory responses in DA neurons in anaesthetised animals. By the same token, the reticular formation itself, identified as afferent to both SNc and VTA DA neurons (Watabe-Uchida et al., 2012), could also play a non-specific role in the sensory responsiveness of these neurons.

A PROBLEM AND A SOLUTION

Our investigations up to this point had suggested that DA neurons are supplied with short-latency sensory information by comparatively primitive primary subcortical sensory structures. The SC for example is a primitive sensory structure with limited perceptual processing capabilities (Schiller and Koerner, 1971; Goldberg and Wurtz, 1972; Schiller and Malpeli, 1977). Visual neurons in the primate colliculus are sensitive to the onset, offset and movement of stimuli, but the majority are insensitive to shape, contrast, orientation, velocity and direction of movement (Schiller and Koerner, 1971; Goldberg and Wurtz, 1972). Furthermore, the SC does not receive an input from colour opponent cells in the retina (Schiller and Malpeli, 1977).

However, in spite of a lack of apparent processing complexity in the colliculus, DA neurons in the primate have been shown to be able to distinguish between complex visual stimuli and indicate their value (Fiorillo et al., 2003; Tobler et al., 2005). Closer analysis however suggests that the response of DA neurons to these complex visual stimuli is actually biphasic. The truly discriminatory phase of the DA response comes after an earlier, more invariant

response feature (Hudgins et al., 2009; Nomoto et al., 2010). Given the rather primitive processing capabilities of the SC, the natural assumption would be that the shorter latency component of the DA response is of collicular origin whilst the longer latency discriminatory phase has its origin elsewhere in the brain (Hudgins et al., 2009). The sophisticated visual processing required to discriminate between complex stimuli most likely involves the visual cortex (Zeki, 1993; Thorpe and Fabre-Thorpe, 2001; Orban, 2008), although cortical inputs to DA neurons are relatively sparse (Frankle et al., 2006; Watabe-Uchida et al., 2012). In contrast, our work and that of others has shown that the cortical mantle projects heavily to the SC in a wide range of species (Fries, 1984; Harting et al., 1992; Comoli et al., 2012). Furthermore, cortically-dependent responses in the SC are temporally delayed with respect to those arising via more direct retinotectal activation (White et al., 2009). The large cortical projection to the SC suggests that the cortical information which may be signalled by the later phase of the sensory response in DA neurons could arise via a relay in the SC.

On the basis that there are robust projections from the cortex to the SC, we examined whether cortical information could reach DA neurons via a relay in the colliculus. The whisker barrel cortex – which projects directly to the SC (Comoli et al., 2012) – was stimulated electrically (0.3 ms pulses, 0.5 Hz, 600-800 μA) in anaesthetised rats. Single pulse electrical stimulation of the barrel cortex produced small phasic activations in the colliculus, but did not elicit responses in the majority of DA neurons (Figure 4). However, following disinhibitory intra-collicular injections of bicuculline, electrical stimulation of the barrel cortex now elicited phasic activations in the SC and previously unresponsive DA neurons now exhibited phasic activations or inhibitions (Figure 4; Bertram et al., 2013). We have obtained similar results using stimulation of the primary visual cortex cortex (Vautrelle et al., 2011), which also projects to the SC (Comoli et al., 2012). Pulse trains applied to the barrel cortex lead to

phasic changes (excitations to inhibitions) in the activity of DA neurons at baseline. These can be blocked or attenuated by the intracollicular administration of the $GABA_A$ agonist muscimol. Taken together, the results indicate that the cortex can communicate with DA neurons via a relay in the SC, at least for visual and somatosensory information. The possibility that other cortical sensory areas can also access the DA systems via the SC has yet to be determined, as has the potential modulating impact of the numerous non-sensory cortical afferents to the SC (Comoli et al., 2010) on the throughput of sensory information.

FUNCTIONAL IMPLICATIONS

Dopaminergic neurons in the awake animal have two different modes of responding to sensory stimuli – tonic responses to noxious stimuli and tonic, but more frequently phasic, responses to non-noxious stimuli. Tonic responses to non-noxious stimuli are typically activations (Kiyatkin, 1988; Kiyatkin and Zhukov, 1988; Roesch et al., 1997), which almost certainly lead to a net increase in dopamine levels in the striatum (Keller et al., 1983; Keefe et al., 1993). The neurochemical outcome in the forebrain following noxious stimuli is a little harder to predict. Noxious stimuli can lead to either activations or inhibitions, at least in the rat VTA (Mantz et al, 1989; Brischoux et al., 2009). In our earlier work using collicular disinhibition, visual stimuli led to activations and inhibitions in midbrain DA neurons, yet the net effect of those changes was to increase (albeit phasic) dopamine levels in the striatum (Dommett et al., 2005). Evidence suggests that noxious stimuli also lead to an elevation of dopamine levels in the dorsal and ventral striatum (Keller et al., 1983; Young et al., 1993). Hence the net effect of all tonic sensory responses in DA neurons may very well be an increase in striatal dopamine levels and the extent to which the pauses in activity seen in a subpopulation of DA neurons in response to noxious stimuli are 'visible' in the dorsal and ventral striatum is uncertain. The functional consequence of raising tonic dopamine levels

(which may rise rapidly, given the intensity of the early phase of many tonic responses) – at least in the nucleus accumbens – appears to be a shift in the balance of influence in afferent regulation away from the cortex and towards the limbic system (Goto and Grace, 2005; Goto et al., 2007). It could be that under certain circumstances, especially with noxious stimuli, the selection of appropriate actions in relation to particular stimuli are more adaptively guided by the affective nature of the stimuli than by cortical, cognitive processes.

As far as short-latency phasic responses to unpredicted sensory stimuli in DA neurons are concerned, convergent evidence suggests that at least some component of the short-latency phasic response is mediated by inputs which arise from primary subcortical structures. Evidence with vision suggests that the shortest latency responses arise from activation of the SC, but longer latency responses may have a cortical origin, although these cortical signals may themselves be routed through the colliculus. This duality maps nicely onto convergent evidence from monkey studies which suggests that the earliest phase of the response of DA neurons to all non-noxious stimuli – which are universally activations – reflect sensory intensity (salience; Fiorillo et al., 2013b; Bromberg-Martin et al., 2010), whereas the later phase(s) may reflect value. Both phases are comparatively short. The second phase of the response of DA neurons to complex visual stimuli reported in the monkey has a peak latency of around 160 ms (Morris et al. 2004; Hudgins et al. 2009; Nomoto et al. 2010). Given that saccades take 180-200 ms to initiate (Becker, 1989) and then last for 3-100 ms/degree depending on amplitude (Bahill et al., 1975), both the second phase and the initial shorter latency phase of the response to complex visual stimuli are pre-saccadic under conditions of experimenter-driven stimulus presentation, i.e. they occur before the animal has had a chance to move its eyes to foveate the stimulus concerned. Indeed, the second phase of the visual response described by Nomoto et al. (2010) is often co-incident with saccade generation.

Somatosensory information reaches the somatosensory cortex more quickly than visual information reaches the visual cortex (somatosensory, ~10 ms; Di et al. 1990; Ahisser et al. 2001; Martin et al. 2006; Zhu et al. 2009; visual 30-50 ms; Maunsell and Gibson, 1992; Thorpe and Fabre-Thorpe, 2001), and so cortically driven responses to somatosensory stimuli have the capacity to be even faster than those to visual stimuli. Given dopamine's critical role in reinforcement learning (Wise, 2004), we have argued that the short latency of the dopamine signal is particularly well suited to reinforce the discovery of agency – those events in the world for which the agent is responsible (Redgrave and Gurney, 2006; Redgrave et al. 2008). According to this view, the advantage of having DA reinforcement occur before any behaviour evoked by the sensory event itself is that the record of behavioural output (motor efference copy) will remain uncontaminated by non-causal components of behaviour. This would greatly simplify the problem of assigning credit to appropriate causal components of immediately preceding behaviour (Izhekevitch, 2007).

If the second (potentially cortical) phase of the DA response to complex visual stimuli in the monkey can be pre-saccadic (but may not always be – see Matsumoto, 2013), under these circumstances it cannot report the results of a fine-grained analysis of the inducing stimuli, as this would require foveation. This conclusion has important implications for the widely accepted view that sensory-evoked DA responses signal information (prediction errors) specifically related to rewards (e.g. Montague et al., 1996, 2004; Schultz, 2006). Reward-related stimuli can take any form, potentially requiring the full processing power of the sensory systems to discriminate them. The fact that the DA signal can be pre-saccadic suggests that rather than a specific role in reward, the response is more consistent with a system which signals a 'sensory predication error' (signalling for example that something salient or important but unpredicated has happened; Redgrave et al., 2011), thus

incorporating those studies which have found phasic excitatory responses of DA neurons to novel (Ljungberg et al., 1992), intense (Horvitz et al., 1997) and noxious stimuli (Gao et al., 1996), i.e. stimuli which are not clearly rewarding. If it is the case that DA neurons signal a sensory prediction error, then this raises an important question about why DA responses (the second phase at least) are modulated by reward. Numerous studies have demonstrated that sensory processing in the cortex can be potentiated when associated with reward (e.g. Mogami and Tanaka, 2006; Hui et al., 2009; Franko et al., 2010; Hickey et al., 2010; Serences and Saproo, 2010; Weil et al., 2010). Our finding that the cortex can transmit information to DA neurons via the SC thus provides a mechanism by which short-latency sensory signals relayed to DA neurons can reflect stimulus value. However, the signal will be 'dirty', in the sense that it will be contaminated by responses to non-rewards. It may thus be more useful as a signal which indicates how salient an event is, rather than something about its value. Furthermore, reward related modulations have only ever been shown in the constrained environment of the laboratory, usually following many hundreds or thousands of trials with a restricted stimulus set (e.g. Fiorillo et al., 2003), and so the extent to which this modulated signal is likely to be available in the wild is uncertain.

CONCLUSION

There have been numerous demonstrations that DA neurons in a range of species are responsive to sensory stimuli. Under anaesthesia, responses to non-noxious and noxious sensory stimuli are usually tonic in nature, although long duration changes in activity have been reported in the awake preparation as well. However, in the awake preparation, short latency, phasic changes in activity are most common. These phasic responses can occur to both unconditioned aversive and non-aversive stimuli, as well as to the stimuli which predict them. Evidence suggests that short-latency sensory information is provided to DA neurons by

relatively primitive subcortical structures – including the SC for vision and the PBN for pain and possibly gustation (Figure 5). Auditory and somatosensory information may also be provided by subcortical structures, and future work should be directed at definitively elucidating the source of such information. Although short-latency visual information is provided to DA neurons by the relatively primitive SC, DA neurons can discriminate between complex visual stimuli (outwith the apparent processing complexity of the colliculus) – a paradox which can be resolved by the recent discovery of a route of information flow through to DA neurons from the cortex, via a relay in the SC (Figure 5). Evidence so far suggests that visual and whisker-related cortical areas can influence DA neurons via the SC. However, given the widespread projections from the cortex to the SC, other sensory areas may also utilise this route of information flow and again future work should examine this possibility and the potential interaction between sensory and non-sensory cortical inputs to the SC in the transmission of information to the dopamine systems. Furthermore, the possibility that DA neurons acquire their ability to reflect stimulus value by virtue of reward-related modification of sensory processing in the cortex should also be explored. At the forebrain level, sensory-related changes in the tonic activity of DA neurons may regulate the impact of the cortex on forebrain structures such as the nucleus accumbens. In contrast, the short latency of the phasic responses to sensory stimuli in DA neurons, coupled with the activation of these neurons by non-rewarding stimuli, suggests that phasic responses of DA neurons may provide a signal to the forebrain which indicates that a salient event has occurred (and possibly an estimate of how salient that event is). A stimulus-related salience signal could be used by downstream systems to reinforce behavioural choices.

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Figures

Figure 1: Disinhibition of collicular deep layers induces phasic visual responses locally and in DA neurons. (A) Initially, raster displays and peri-stimulus histograms show that collicular neurons and a simultaneously recorded DA neuron were unresponsive to a regular (0.5Hz) light flash (vertical dotted line) (top graphs). After a collicular microinjection of bicuculline, both local neurons and the DA neuron were excited at short latency by visual stimulation (bottom graphs). (B) Example of a light-evoked inhibitory response of a DA neuron after collicular disinhibition. (C) DA neurons remained insensitive to light following bicuculline-induced facilitation of the flash-evoked field potential in visual cortex.

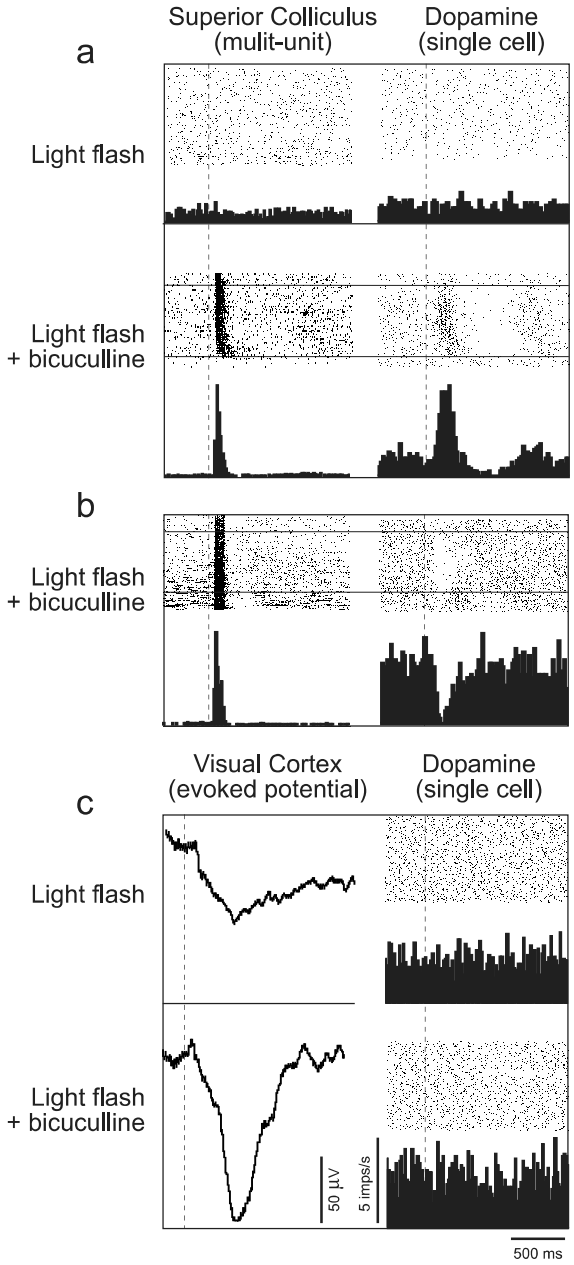
Figure 2: Effects of local intraparabrachial injections of lidocaine on footshock-evoked multi-unit responses in the parabrachial nucleus (PBN) and in a single dopaminergic (DA) neuron. The graphs present raster displays and peri-stimulus histograms of single case data aligned on the presentation of 120 stimuli (0.5 Hz; vertical dotted line; stimulus artifacts have been removed for clarity – these did not overlap with responses in the PBN or in DA neurons). Prior to the injection of lidocaine, both the PBN and the DA neuron (A and B) were responsive to the footshock. Following the injection of lidocaine into the PBN, local neurons became unresponsive to the footshock (C) and so did the DA neuron (D).

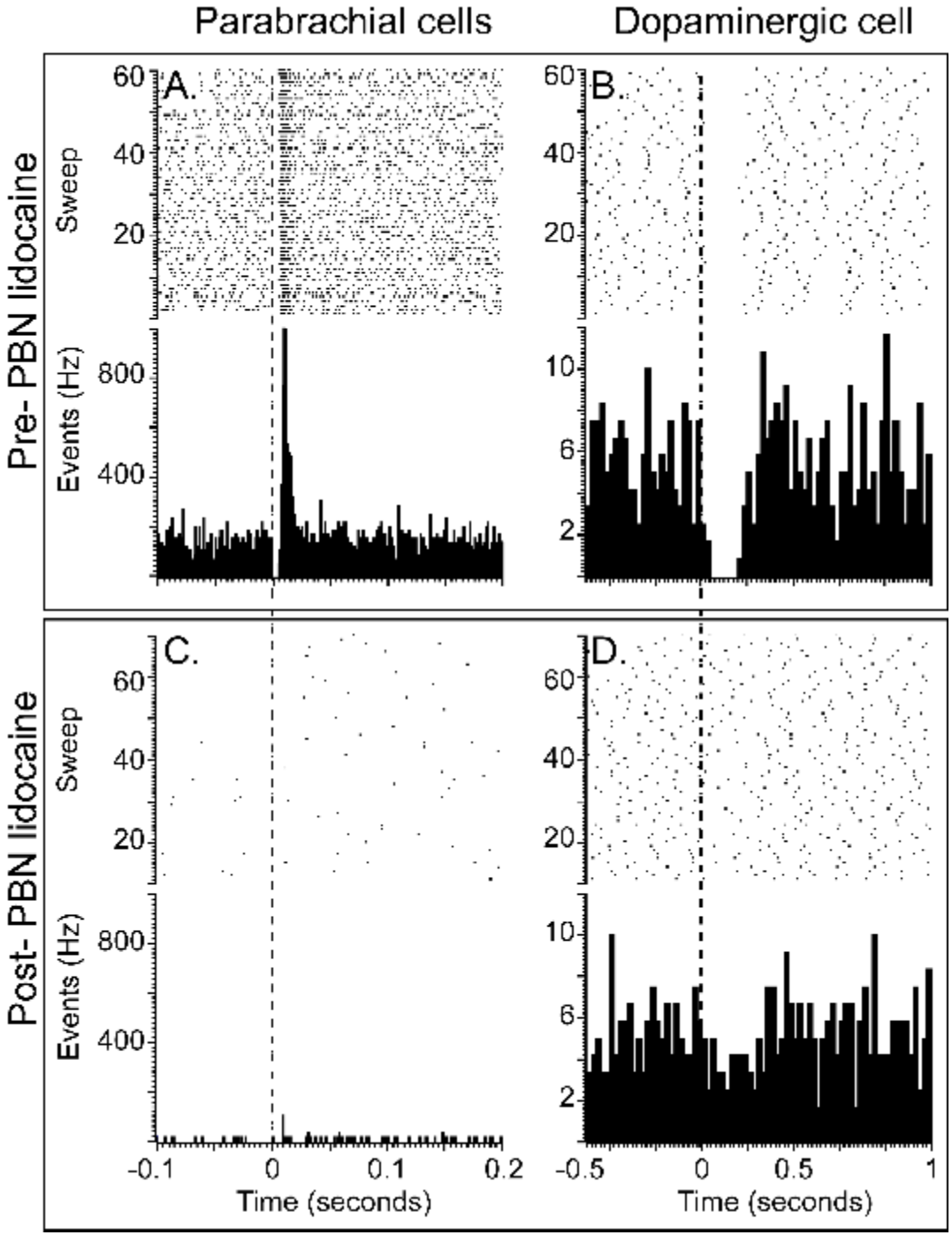
Figure 3: Retrogradely labelled cells in the trigeminal complex following pressure injection of the fluorescent tracer fluorogold (20 nl) into the substantia nigra. (A) Injection site (outlined in red) in substantia nigra pars compacta (SNc), extending into subjacent pars

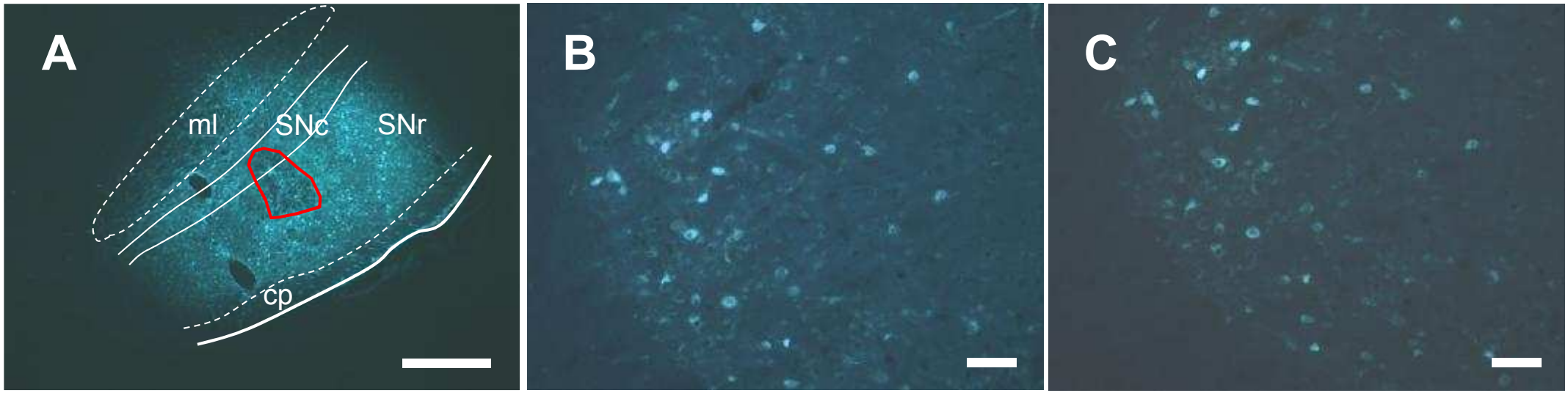
reticulata (SNr). ml = medial lemniscus; cp = cerebral peduncle. (B) Retrogradely labelled cells in the principal sensory nucleus (Pr5). (C) Retrogradely labelled cells in the spinal trigeminal nucleus (Sp5). Scale bar = 1 mm (A); 50 μm (B, C).

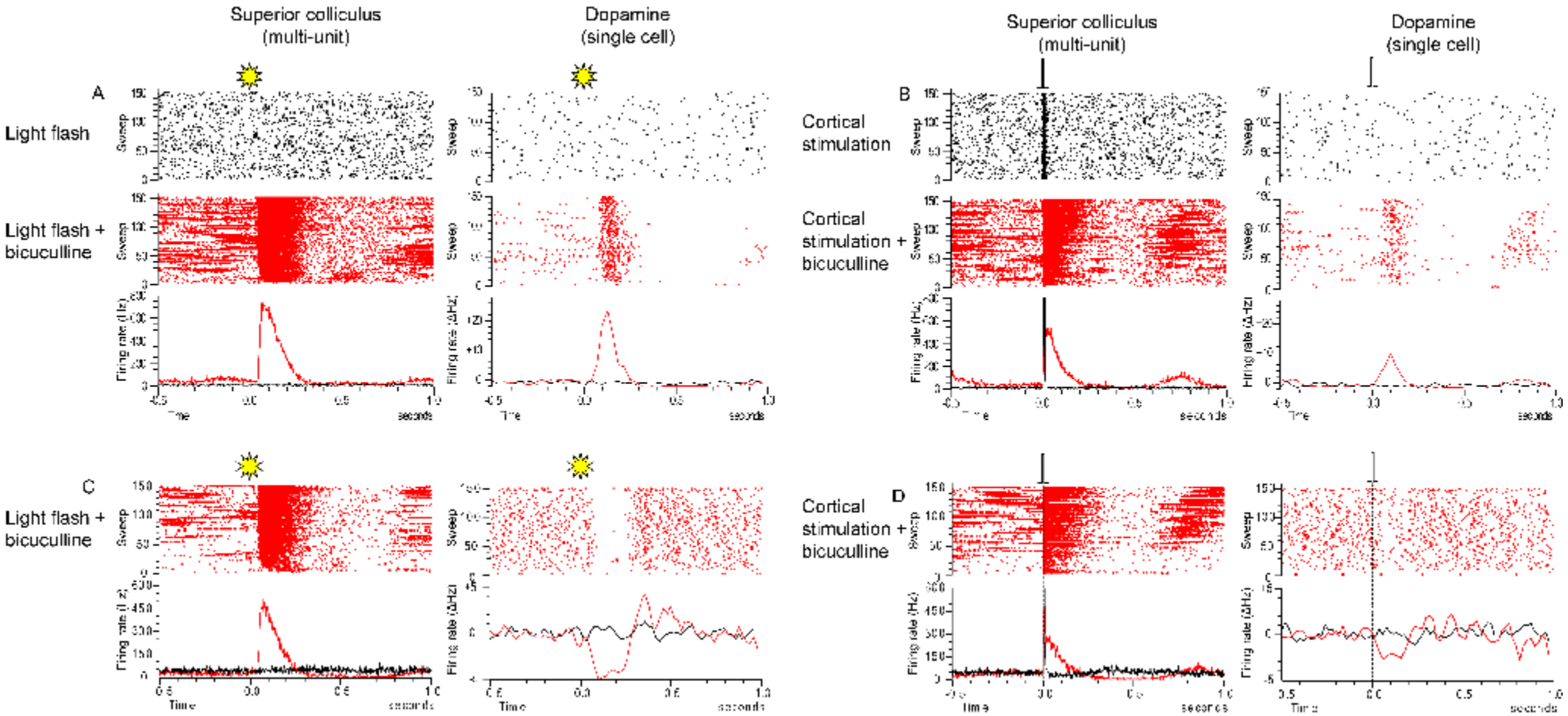
Figure 4: Response of the superior colliculus and dopaminergic neurons to light flash stimuli and electrical stimulation of the barrel cortex. (A) Raster displays (top) and peri-stimulus time interval histograms (PSTHs; bottom) show that deep layer collicular neurons (SC) and a simultaneously recorded dopaminergic (DA) neuron in this animal were initially unresponsive to regular (0.5 Hz) wholefield light flash stimuli (vertical dotted line). After a collicular microinjection of bicuculline, both collicular neurons and the DA neuron were excited at short latency by visual stimulation; (B) Raster displays and PSTHs show that collicular neurons exhibited a short latency excitatory response to single pulse electrical stimulation of the barrel cortex (0.1 ms, 1 mA 0.5 Hz; vertical dotted line), whereas (in common with the majority of DA neurons), a simultaneously recorded DA neuron in this animal was unresponsive. After a collicular microinjection of bicuculline, the collicular response to cortical stimulation was enhanced and the DA neuron was now excited at short latency by the stimulation. As well as short latency excitations, light flash stimuli (C) and single pulse electrical stimulation of the barrel cortex (D) could also induce short latency inhibitions.

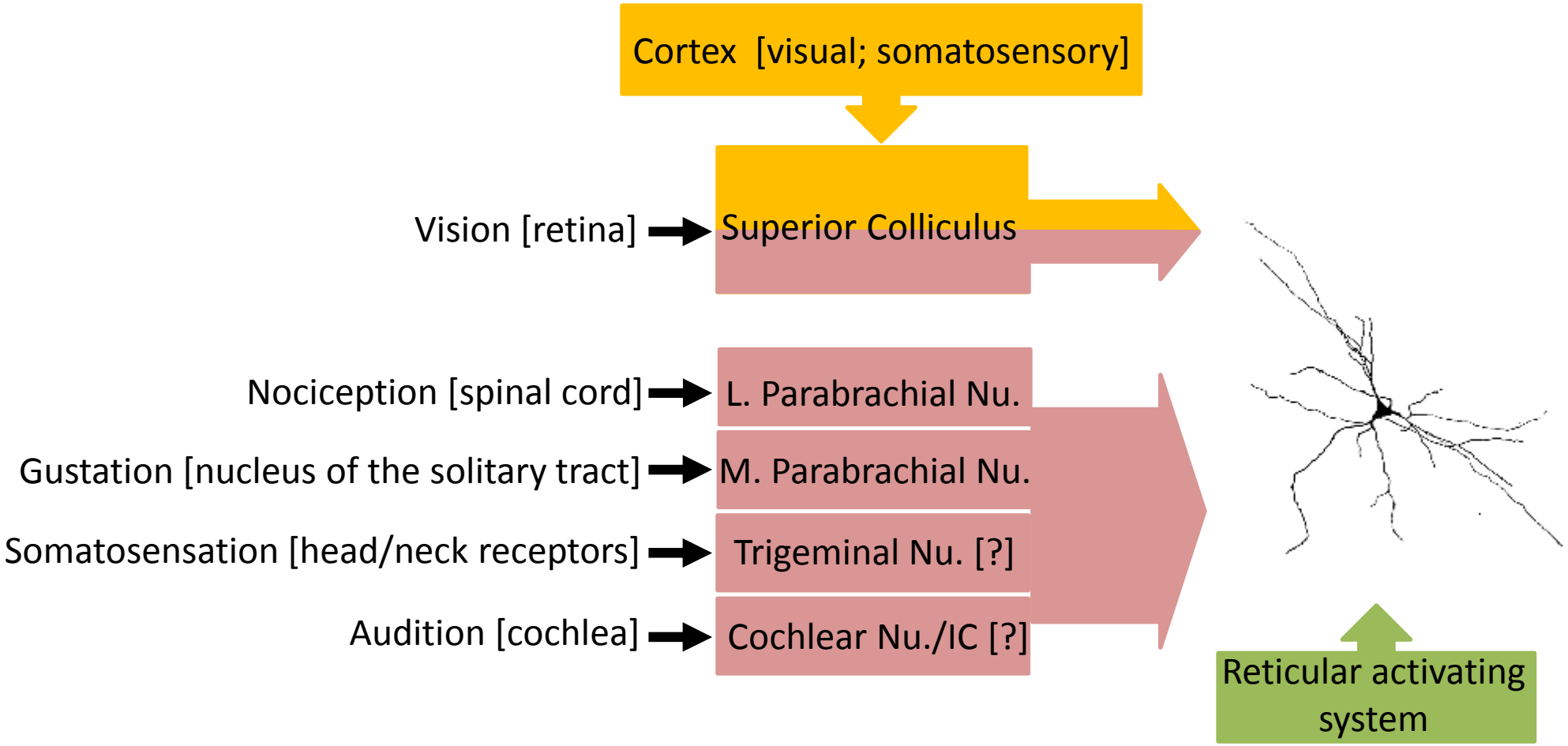
Figure 5: Circuitry providing sensory information to dopaminergic neurons. Current evidence suggests that visual information is provided to midbrain dopaminergic (DA) neurons (single cell illustrated on far right) by the superior colliculus (which receives an input from the retina), nociceptive information by the lateral (L) parabrachial nucleus (which receives an input from the nociceptive layers of the spinal cord), gustatory information by the medial (M) parabrachial nucleus (which receives gustatory information from the nucleus of the solitary tract), and possibly with head/neck somatosensory information by the trigeminal nucleus and with auditory information by the cochlear nucleus and inferior colliculus (IC; the cochlear nucleus receives auditory in formation from the cochlea). These short latency sensory inputs (in pink) stand in contrast to the slower sensory regulation (in yellow) provided by the cortex, thus far identified to arise from the visual and somatosensory cortices. In the awake animal, these short and longer latency sensory influences are facilitated by an excitatory (arousal) drive from the reticular activating system.


a
Superior Colliculus
(mulit-unit)
Dopamine
(single cell)
Light flash
Light flash
+ bicuculline
b
Light flash
+ bicuculline
c
Visual Cortex
(evoked potential)
Dopamine
(single cell)
Light flash
Light flash
+ bicuculline
50 µV
5 imps/s
500 ms


Parabrachial cells
Dopaminergic cell
Pre- PBN lidocaine
Post- PBN lidocaine
A.
B.
C.
D.
Sweep
Events (Hz)
60
40
20
800
400
10
6
2
-0.1
0
0.1
0.2
-0.5
0.5
1
Time (seconds)


A
ml
SNc
SNr
cp
B
C


Superior colliculus
(multi-unit)
Dopamine
(single cell)
A
Light flash
Light flash +
bicuculline
B
Cortical
stimulation
Cortical
stimulation +
bicuculline
C
Light flash +
bicuculline
D
Cortical
stimulation +
bicuculline
Sweep
Firing rate (Hz)
Time
seconds


Cortex [visual; somatosensory]
Vision [retina]
Superior Colliculus
Nociception [spinal cord]
L. Parabrachial Nu.
Gustation [nucleus of the solitary tract]
M. Parabrachial Nu.
Somatosensation [head/neck receptors]
Trigeminal Nu. [?]
Audition [cochlea]
Cochlear Nu./IC [?]
Reticular activating system