Anticipatory Changes in Regional Cerebral Hemodynamics: A New Role for Dopamine?

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Target Article


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Abstract

Recently, adaptively timed, anticipatory changes in hemodynamic responses, independent of neural activity, were described in primate primary visual cortex. Task-related properties of these responses point to a possible link between regional cerebral microcirculation and dopaminergic signaling. In this paper, this link is elaborated on the basis of known physiological data, and further experiments are proposed to test the possible role of dopamine in task-dependent, “on-demand” allocation of metabolic resources.

Animals are by nature opportunistic. An unexpected encounter with a reward-predicting stimulus leads to a fast redirection of behavior. As with the behavior, at the neural level, it is conceivable that this encounter may also yield an anticipation of an increased demand for neural processing necessary to facilitate the (potential) task in service of collecting the predicted reward. However, in bipeds, cerebral perfusion is maintained constant over a wide range of systemic pressures (termed “cerebral autoregulation”). Autoregulation is critical to neurophysiologic health since too little flow could cause ischemia whereas too much could raise intracranial pressure. Therefore, an “on-demand” allocation of regional blood volume without changing the overall perfusion pressure is likely to be among the key biological abilities. Indeed, in a recent paper, Sirotin and Das(14) described a new, trial-locked hemodynamic signal in visual cortex in response to anticipation of expected tasks. In their experimental paradigm, two monkeys are trained to perform a “dark-room fixation task”, in which the visual input was minimized compared to standard, periodic, visual tasks while the trial timing was preserved. After training, Sirotin and Das(14) observed a robust hemodynamic signal (indicative of increased regional blood volume, thus, oxygenation) before the onset of the next trial, comparable in magnitude to stimulus-evoked signal, and tightly linked to trial onset. This hemodynamic signal arose despite the virtual absence of a visual stimulus, and was not related to any local neural activity, as confirmed by simultaneous recordings of multi-unit spiking activity (though there appeared to be a
non-significant modulation of the high-frequency local field potential with the task structure). To verify the timing properties of these hemodynamic signals, the authors manipulated the temporal course of the fixation task so that the inter-trial interval switched unexpectedly between “short” and “long” trials every 10-20 trials. Interestingly, during such reversals of temporal contingency, anticipatory hemodynamic responses entrained to these slow and fast “rhythms” to conform to the new temporal contingency, although the “switch” in hemodynamic response was slower that the switch in the monkey’s behavior. The authors concluded their paper with the remark that the mechanism driving this **adaptively-timed anticipatory signal** remains to be elucidated. Both the authors and a recent commentary on the study(10) discussed the significance of this finding mainly from the point of view of imaging methods, in particular, functional magnetic resonance imaging. However, as Sirotin and Das(14) noted, it is important to explicate the physiologic substrate of this anticipatory behavior.

Another conspicuous population of neurons that exhibit adaptively-timed anticipatory responses (among others) is the dopaminergic neurons of the substantia nigra pars compacta and ventral tegmental area. These neurons are part of an adaptive system that uses learned expectations to filter reward-related signals. In particular, their firing patterns are related to learned cues that predict reward.(12) The genesis of the dopamine responses have been investigated by numerous researchers, and the effects of anticipatory increases in dopamine release on target sites have been discussed only in terms of its effects on learning (and partly on behavioral performance). Thus, though a wealth of data are available on the role of dopamine on learning, performance, and cognitive processes in general, its role in regulation of regional blood flow and oxygenation has attracted very little attention from neuroscientists. Historically, it is known that dopamine has both vasodepressor and vasopressor effects on vasculature.(6) More recently, it has been shown that the dynamics of striatal dopamine release, induced by stimulation of median nerve, correlates well with regional cerebral blood volume changes.(3) Furthermore, this relation appears to be a direct effect of dopamine on the
microvasculature, mediated partially through D1/D5 receptors (increasing regional blood volume) and through astroglial D3 receptors (reducing regional blood volume). (4) This role of dopamine is also indirectly supported by studies in animal models of Parkinson’s disease (marked by a significant degeneration of substantia nigra pars compacta dopaminergic neurons) where a strong relation between the loss of dopamine and changes in regional blood volume has been documented.(2) In fact, the effects of dopamine on regulation of cerebral blood flow, perfusion pressure, and oxygenation is well studied in pediatric literature (see, for example, Tyszczuk et al.(17)). Therefore, it should not come as a surprise that anticipatory dopaminergic responses may elicit regional hemodynamic changes in the target structures.

Indeed, though most of the dopaminergic innervation is directed to the frontal and limbic cortical areas, a specific dopaminergic innervation of primary visual cortex that arises from the ventral tegmental area is described in several species, including rats and humans.(11) Furthermore, it appears that the dopamine released in primary visual cortex acts via D1 receptors,(15) increasing regional blood volume.(4) These considerations do not eliminate the possibility that anticipatory hemodynamic responses may be brought about by different neurotransmitter systems that may influence regional blood flow, namely norepinephrine, acetylcholine, and serotonin (among others; see, for example, (1)). Nevertheless, though novel stimuli and reversals in task contingency may induce transient changes in norepinephrine release, these changes disappear once the (new) task contingency is established(5) (in contrast to the observation of Sirotin and Das(14) that hemodynamic responses entrained to rhythms conform to the new temporal contingency even after reversal); activation of basal forebrain cholinergic pathway is mostly driven by visual stimuli, rather than being an anticipatory response(9); and, serotonin reduces regional cerebral blood flow, at least in rats(7). Furthermore, additional indirect support for involvement of dopamine is provided by the recent report that neural responses in primary visual cortex can accurately predict reward timing,(13) and by entrainment of hemodynamic responses
to reversals in temporal contingency (14); described above), two functions mostly attributed to
dopaminergic responses (12). Therefore, given the anticipatory responses of ventral tegmental area
dopamine cells, the most parsimonious explanation of the findings of Sirotin and Das (14) appears to
be the dopaminergic innervation of primary visual cortex.

Two major implications should be noted. First, it may be necessary to reinterpret of results from
functional imaging of the basal ganglia, particularly of the striatum, a major recipient of dopaminergic
afferents from substantia nigra pars compacta. In such imaging studies, several research groups
attributed task-related activations of the striatum to striatal neurons. If dopaminergic signaling links
directly to striatal hemodynamics, the observed activation may be secondary to task-dependent
dopamine release, rather than (or perhaps in addition to) striatal cell responses. In fact, a close
relation between dopamine release and local blood oxygen level dependent (BOLD) signal has
recently been documented in the ventral striatum (8). Because this point was already discussed by
Sirotin and Das (14) and Leopold (10) it will not be elaborated here. A second implication of the
dopaminergic account of the observation of Sirotin and Das (14) is that dopaminergic signaling plays a
heretofore overlooked role that is nevertheless consistent with the optimization function of its role in
reinforcement learning.

As already mentioned, the firing patterns of midbrain dopaminergic neurons are related to learned
cues that predict reward. Also important, the magnitude of the dopamine release in response to such
cues is shown to be proportional to the expected reward value, and its magnitude during the delay
period between the predictive cue and predicted (rewarding) event is proportional to the uncertainty of
the expected event (12). Furthermore, if the expected (rewarding) event is omitted, dopamine cells
respond with a pause in their firing rate (12). Such a multitude of response properties, coupled to
different phases of the task, makes these neurons a suitable candidate for task-dependent regulation
of regional blood volume, thus, oxygenation (Figure 1). For example, a selective increase in dopamine release in response to an anticipated stimulus would facilitate the blood flow to the relevant region to meet the demands of (expected) activity. Similarly, gradual increase in the dopamine release during a delay period can ensure sustained regional blood flow during the delay period, when a sustained activation (therefore, sustained metabolic demand) of several cortical regions is anticipated. An example is persistent activation of prefrontal cortical neurons during delay or trace conditioning paradigms, commonly associated with working memory processes. Remarkably, when the expected event fails to occur, pauses in dopamine release may ensure an ad-hoc reduction in regional blood flow, perhaps in an attempt to facilitate redirection of blood volume to other regions, without the requirement of changing overall cerebral perfusion. Therefore, regulation of regional microcirculation by dopaminergic signaling may constitute an important, but overlooked, function of dopaminergic innervation of the brain.

Nevertheless, though the study by Sirotin and Das(14) provides a first hint towards this function, further experiments are required to prove or refute this hypothesis. For example, a simple test would be to utilize the fact that the magnitude of dopamine release depends on the expected value of reward. In a typical reinforcement learning paradigm, wherein both the intensity of the predictive cue and the animal’s behavior are minimized (similar to the “dark-room fixation task”, but minimizing the feature(s) of the stimulus that are relevant to the task deployed) a relation between the hemodynamic signals and (expected) dopamine release (bursts vs. pauses) would provide an evidence (though indirectly) for the linkage hypothesis. The aforementioned study by Knutson and Gibbs(8) provides such evidence for ventral striatum, but for other areas a possible link between task-dependent variations in regional cerebral microcirculation and anticipatory dopamine signals awaits verification.
References


Figure Captions

Figure 1: Task-dependent regulation of regional blood volume by dopaminergic neurons. Left panel: a specific dopaminergic projection from ventral tegmental area (VTA) modulates regional blood flow in primary visual cortex via D1 dopamine receptors (D1-R). Right panel: Illustration of the hypothesized mechanism. Bottom panel shows the phasic responses of dopaminergic cells during a typical reinforcement learning paradigm (black trace) and corresponding dopamine release (red trace) after learning (simulated using the model of Tan and Bullock.(16)) Upper panel shows hypothesized modulation of regional blood flow by dopamine released.
Regional blood flow

DA Cell firing rate (normalized)

Trial onset
(Anticipatory dopamine response)

Trial offset
(Dopamine response to primary reward)