01/14/19

NON-SYNAPTIC TRANSMISSION AND THE FOUNDATIONS OF

AFFECT

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ABSTRACT

Neuroscience has overwhelmingly and understandably focused on the synaptic modality of signal transmission. There is evidence, however, that from an evolutionary perspective, non-synaptic transmission (NST) preceded synaptic signaling. Moreover, in modern nervous systems, NST coexists and extensively interacts with synaptic transmission modifying neuronal dynamics. In fact, NST remains widespread in complex animals, especially within the interoceptive system where the dearth of insulating barriers such as myelin sheaths and the blood-brain barrier enhances the communication between neural and non-neural tissues mediated by NST. We suggest that this physiological arrangement makes a fundamental contribution to interoception—the process of sensing visceral states—which is an essential underpinning of the capacity to feel and the foundation of affective processing.

1

01/14/19

I.   THE DAWN OF SIGNAL TRANSMISSION

Synapses mediate and finely regulate nerve impulse conduction throughout the nervous system, playing a central role in physiological responses, movement and thought. Not surprisingly, synapses are commonly regarded as biological marvels and fundamental pillars of neural function. Nonetheless, several lines of evidence suggest that the intricately sophisticated synapse stems from comparatively humble beginnings, and that, no less importantly, exemplars of these earlier forms continue to play crucial roles in modern nervous systems. [1]

Signal transmission can be found in rudimentary and ancient organisms. In fact, most modern neurotransmitters arose and functioned as signaling agents long before the appearance of neurons in evolution. For example, in the sponges that make up the phylum Porifera, GABA, glutamate, acetylcholine and serotonin operate in paracrine[*] mode, in the absence of synapses and neurons [2]. Genetic, anatomical and biochemical analyses indicate that the paracrine pathways of Porifera are evolutionarily related to certain synaptic elements present in metazoans, although it remains unclear whether sponges preceded the evolutionary appearance of neurons or underwent a loss of neural cell types [2]. The origin of the molecules commonly referred to as "neurotransmitters" dates even farther back than Porifera or even the animal kingdom. In fact, most of the main neurotransmitters found in the mammalian nervous system play a central role in organisms

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*The term **Paracrine** designates signaling involving a molecule secreted by a cell and interacting with receptors on neighboring cells; the term **Intracrine** refers to intracellular signaling by a molecule acting in the cell where it is produced; **Autocrine** signaling involves a molecule secreted by a cell and interacting with receptors on that same cell; **Endocrine** signaling involves a molecule secreted by a cell and interacting with receptors on distant cells.

01/14/19

devoid of nervous systems, such as unicellular eukaryotes and even bacteria [3,4]. Acetylcholine, for example, may date as far back as 3 billion years [5] while animals are only thought to have arisen ~600 million years ago and nervous systems even later [6]. Neurotransmitters were not "neuro" for the vast majority of their existence.

One theory that has been advanced to account for the evolution of signal transmission proposes that metabolites initially functioned in an autocrine or intracrine manner, in bacteria. Later, in unicellular eukaryotes, they operated as messengers within and between unicellular organisms [2,7-9]. Even later, in multicellular organisms, these messengers continued to fulfill their inter-cellular function, but now within the perimeter of a single organism [10,11]. Thus in early animals inter-cellular communication was largely mediated by signals released into the extracellular matrix (i.e. paracrine signaling). During the development of Metazoa, evolutionary forces may have favored more direct and faster communication modalities, leading to changes in cellular morphology — the development of axons and dendrites — and to the compartmentalization of the neurotransmitter release channels. These changes would have facilitated a gradual transition from dispersed release to an open synaptic architecture, and, finally, to closed synapses, thus effecting a transition from paracrine to electrochemical signal transduction [2]. This conceivable evolutionary path would have substantially increased channel selectivity and speed in point-to-point transmission, an obvious advantage in the case of movement and, eventually, of perception and cognitive abilities such as memory and the manipulation of percepts, actual or recalled. In this perspective, synapses are an evolutionary specialization of nonsynaptic transmission (NST) offering refinement and efficiency.

01/14/19

II.   NST IN MODERN NERVOUS SYSTEMS

In spite of the advantages conferred by the synapse, the rudimentary NST precursor was not replaced and has remained prevalent. NST is prominent in numerous invertebrate phyla, including species where it coexists with synaptic signaling, and remains widespread in the vertebrate nervous system [11,12-14], where nonsynaptic receptors may actually outnumber synaptic ones [15,16]. In fact, most neurotransmitters can act nonsynaptically, and in many cases do so predominantly [15,17,18]. For example, a large fraction of acetylcholinergic, serotonergic and noradrenergic varicosities are nonsynaptic; in some areas of the nervous system, as many as 80-90% do not show the structural specializations that characterize synapses and are therefore thought to release the neurotransmitters for diffusion in the extracellular compartment, thereby activating more or less remote receptors [19,20-23]. This scenario is supported by fact that the monoaminergic (dopamine, noradrenaline and serotonin) fiber terminals from which the transmitters are released are often not adjacent to the respective receptors [24-26], indicating that following their release the molecules must diffuse in the extracellular space. The numerous examples of monoamine involvement in NST include the vertebrate retina (where dopamine may play a role in light-dark adaptation [28]) and the amygdala [27]. Dopamine is also believed to operate non-synaptically in the spinal cord and in the cortical microvasculature where it helps regulate blood flow [26,29,30]. Even neurotransmitters typically associated with synaptic transmission, such as glutamate and GABA, have been shown to operate less conventionally and signal via extrasynaptic pathways, e.g. in the cerebellum and hippocampus (34, 35).

01/14/19

The scope of NST extends far beyond canonical neurotransmitters. ATP and neuropeptides also have a well-established non-synaptic role (31, 32, 33). Examples of peptide signaling include cytokines such as interleukin-1b(IL-1b) (42), and ß-endorphin, which can be detected in cortical areas distant from the cell bodies where it originates and is thought to migrate long distances via diffusion in the extracellular fluid and cerebrospinal fluid (36). In fact, all hormones, peptide and otherwise, can be said to function via nonsynaptic signaling. Endocrine signaling, the diffusion of signaling molecules via the bloodstream, can be seen as a modality of NST.

ATP and neuropeptides also have a well-established role in NST [31,32,33]. Even neurotransmitters typically associated with canonical synaptic transmission, such as glutamate and GABA, have been shown to play less conventional roles and signal via extrasynaptic pathways, e.g. in the cerebellum and hippocampus [34,35]. Yet another example of a diffusing substance in the CNS is β-endorphin, which can be detected in cortical areas distant from the cell bodies where it originates; it is thought to migrate long distances via diffusion in the extracellular fluid and cerebrospinal fluid [36].

Gases and ions can also mediate NST. For example, nitric oxide (NO) is a widespread paracrine transmitter (neuro- and otherwise) with well-established roles in a plethora of physiological and pathological phenomena such as vasodilation, gastro-intestinal smooth muscle relaxation, learning and memory, and the immune response [37]. Carbon monoxide (CO) is another example of a gas involved in non-synaptic signaling. CO is produced in vascular smooth muscle cells and plays a role in the regulation of blood vessel tone. It may also function as a

01/14/19

neurotransmitter [38]. NO and CO can cross cell membranes and diffuse away from their

production sites, ultimately acting on cell surface and intracellular targets alike [35]. As for ions,

extracellular potassium (K^+) produced as a result of impulse transmission and synaptic currents

can also modulate neuron signal transmission and glial function [39]. Additionally, protons (H^+)

modulate membrane excitability, synaptic function and gap-junction conductance — for

example, H^+ can bind NMDA receptors [40]. Finally, receptors for Ca^{2+} are present in the cell

membranes of nerve terminals in several brain regions [41].

NST is prevalent across most areas of the nervous system. In the CNS, instances of NST can

be found at virtually every level of the neuraxis, especially in subcortical regions, namely the

spinal cord, brain stem, basal ganglia and some hypothalamic nuclei. NST may play a

particularly prominent role in limbic structures [11]. In the peripheral nervous system,

chemosensitivity has been widely documented along the axonal trunks of peripheral sensory

fibers and of the vagus nerve [43-47], strongly pointing to a role for NST in

interoception/visceroception. NST also seems widespread in peripheral ganglia. It can be

observed in roughly 90% of spinal ganglion neurons [48] and has also been reported in the nodose

ganglion of the vagus [49]. Yet its physiological roles and mechanisms have remained unclear.

NST in peripheral ganglia is thought to be neurotransmitter-mediated, although the specific

transmitter in question has not been identified [49-51]. The extensive crosstalk observed among

neighboring cell bodies elicits changes in membrane potential and firing threshold, which in turn

control the likelihood of action potential propagation along sensory axons [52]. Thus DRG somas

have the potential to act as sensory pathway gatekeepers and may operate as a synchronization

mechanism.

01/14/19

NST is also prevalent in the autonomic nervous system. Examples include 1) autonomic neuroeffector junctions [53] and 2) the enteric nervous system, where noradrenaline released from sympathetic nerves acts on neighboring cholinergic terminals to prevent acetylcholine release, in spite of the fact that no synaptic contacts exist between the two types of fibers [35].

Given its ubiquity in modern nervous systems, NST is increasingly recognized as a major modality of neurotransmission on a par with the canonic synaptic variety [15].

Of note, the physiological role of NST extends far beyond the nervous system. Unlike synapses, which connect neurons to each other or to cells such as myocytes or glia, NST has virtually no cell type restriction. Examples of NST between non-neuronal cells abound [26]. Certain endocrine hormones, such as insulin or cortisol, are obvious examples. A paracrine role in the pancreas has also been described for glutamate, acetylcholine and GABA. The latter is secreted by pancreatic β-cells and binds membrane receptors on the surface of neighboring islet cells, possibly regulating insulin and glucagon secretion[54,55]. Acetylcholine is thought to be a nearly universal signaling molecule, playing a paracrine, non-neuronal role in the lung bronchial epithelium, in erythrocytes, in ovarian endocrine cells and the immune system, among others [5,56,57]. These observations demonstrate that NST establishes communication pathways involving neuronal and non-neuronal cells alike.

01/14/19

III.   THE DISTINCTIVE PHYSIOLOGY OF NST

By comparison to synaptic transmission, NST presents a number of striking differences. NST entails an agent (neurotransmitter, neuropeptide, ion or gas) being released by a cell, diffusing across the extracellular space and exerting its effects by reaching one or more target cells where it can act by e.g. binding to extra-synaptic membrane receptors. However, unlike the case of synapses, where the point of communication is physically well defined, NST does not require terminal varicosities or boutons and the two or more cells involved in the communication need not be adjacent. The signaling agent diffuses three-dimensionally in the extracellular space, predominantly in the intercellular interstitium but in some instances also in the cerebrospinal fluid and even in the blood stream. Signals travel over variable distances as a consequence of energy gradients [58,59]. For example, the monoamines dopamine, noradrenaline and serotonin are prominent NST messengers involved mostly in short-range transmission, on the order of micrometers [60]. Dopamine gets released into the extracellular fluid, where its receptors are often located in the non-synaptic regions of dendrites, axons and cell somas [61,62]. These receptors have an effective radius of 2-8μm [63], i.e. 2-3 orders of magnitude larger than the typical synaptic cleft width of ~12-20nm [64]. In sharp contrast, neuropeptides (beta-endorphin, oxytocin, etc) are typical long-distance signalers, covering millimeters or even meters in the extreme cases of ghrelin, leptin and insulin, which are produced in the gastro-intestinal system and can act as far away as the CNS [65].

NST is affected by the myriad physicochemical factors that have an impact on extracellular diffusion. These include electrical potentials and concentration, pressure, and temperature

01/14/19

gradients [66,67]. Extasynaptic neurotransmitters are also more vulnerable to inactivating

mechanisms such as degrading enzymes present in the extracellular fluid and plasma membrane

transporters. The latter play an especially intriguing role, since in addition to their uptake of

extracellular transmitters —which reduces the concentration of diffusing molecules — they can

operate in "reverse mode" by releasing transmitters from the neuronal cytoplasm into the

surrounding extracellular space and thereby enabling NST [35]. Together these elements determine

the clearance and half-life of non-synaptic agents and therefore effectively and dynamically

regulate NST.

01/14/19

IV. THE FUNCTIONAL ADVANTAGES OF NST

The widespread distribution of NST in the nervous system and its role in myriad biological processes, from synaptic plasticity to behavior, strongly indicate that NST is more than a mere evolutionary relic. Another powerful argument in favor of the physiological relevance of NST is its remarkable structural conservation. For example, the architecture of central monoaminergic neurons (with its neurotransmitter-releasing terminals typically distant from the receptor sites) is identical across several mammalian species, indicating functional relevance [67].

The persistence of NST suggests a substantial evolutionary benefit. In fact, although at first glance it may appear metabolically wasteful compared to the targeted and geographically confined synapse, NST may provide advantages in specific circumstances. While synapses clearly are a more direct and faster way to transmit a signal between two specific cells i.e. "one-to-one" transmission, NST becomes energy-efficient in instances of "one-to-many" communication, in which one cell can potentially influence hundreds or thousands of others without the need for the elaborate wiring network of axons that synaptic signaling would require to achieve the same effect [68,69]. NST may also allow faster regulation[70]. For example, in a local context where one cell secretes a messenger, e.g. a neuropeptide, hundreds of neighbors are potentially exposed to it, but their receptivity to the signal is determined individually by the expression of the respective membrane receptor. An unresponsive subpopulation of cells can be rapidly turned "on" merely by upregulating the expression of one protein, the membrane receptor in question (Fig. 1). Conversely, switching the cell "off" requires only that the receptor be internalized or downregulated. In contrast, synaptic transmission requires entire axons/synapses

01/14/19

to be built anew, a far more energy- and time-consuming process [34]. Thus NST may allow a

population of cells exposed to one or many signals to regulate signal transmission quickly and

with energetic efficiency [71]. Synapses and NST are thus likely to be complementary, context-

dependent methods of signal transmission [68]. Synaptic signaling provided an evolutionary

advantage in cases in which specific information is relayed between two well-defined points in a

time-sensitive manner (e.g.movement, reflexes, perception), while its predecessor, NST,

remained the approach of choice for instances of one-to-many transmission, with fewer time

constraints.

01/14/19

V.   SYNAPTIC AND NONSYNAPTIC TRANSMISSION: COMPLEMENTARY

APPROACHES TOWARD A COMMON GOAL

Synapses and NST coexist in an intricate interactive balance of extensive crosstalk and

mutual regulation. How are these two signal transmission modes integrated and translated into

neural function? What are the molecular mechanisms of their crosstalk? Transmembrane

receptor heteromers appear to play a central role. Ion channels and G-protein coupled receptors

(GPCRs) act as sensors of synaptic and non-synaptic signals, and exhibit direct, allosteric

interactions which integrate distinct extracellular signals into common downstream molecular

pathways [60,72,73].

Another integration mechanism involves the diffusion of neurotransmitters from the synaptic

compartment to the surrounding extracellular space. Leaked synaptic transmitters can (a) activate

nonsynaptic membrane receptors, effectively merging synaptic transmission and NST, or (b)

diffuse back into the synaptic compartment of neighboring synapses, a phenomenon known as

intersynaptic "spillover" (Fig. 2). All different permutations of this scenario have been reported

[34]. Whether of synaptic or nonsynaptic origin, neurotransmitters can affect membrane potential,

thereby modulating the likelihood of action potential firing. In the context of the synapse these

ionic changes are known as post-synaptic potentials (PSPs) and can be excitatory or inhibitory,

depending on whether the post-synaptic membrane undergoes depolarization or

hyperpolarization, respectively increasing or decreasing the likelihood of the neuron reaching

threshold [74]. Nonsynaptic transmitters can have similar effects [48]. In fact, nonsynaptically

generated PSPs can have exceptionally long durations [35], probably due to the longer-lasting and

01/14/19

slower nature of NST. Since such changes in membrane potential are graded and potentially additive, this represents a potential mechanism for synaptic/non-synaptic signal integration. Thus a given neuron's likelihood of firing is determined by the integration of the mechanisms acting upon it and those mechanisms are both synaptic and non-synaptic, both excitatory and inhibitory.

In addition to serving parallel and complementary functions, there is some evidence that ST and NST can, on occasion, fulfill overlapping roles. For instance, in Parkinson's disease, which is due to loss of dopaminergic neurons in the substantia nigra, one physiological compensatory strategy involves a potentiation of NST [26]. Moreover, the therapeutic effect of L-Dopa, the key treatment of Parkinsonism, is attributable to NST since L-Dopa is converted to dopamine by non-dopaminergic neurons and released non-synaptically, allowing it to reach its target cells by diffusion [26,75].

01/14/19

VI.   THE BRAIN-BODY INTERFACE, NST AND THE PHYSIOLOGY OF AFFECT

There is a striking affinity between NST and unmyelinated neuronal fibers. Unmyelinated

axons were followed by an evolutionary specialization—the myelin sheath—that enhanced the

speed of signal transmission, but as is the case with NST, unmyelinated fibers were not simply

replaced by the more modern, faster variety. They remain widely represented in complex

nervous systems, including those of humans. Myelination is a metabolically costly process but

that fact alone is unlikely to explain the less than universal adoption of myelin [76]. The

topographical overlap of NST and unmyelinated axons is another sign of their affinity. For

example, unmyelinated, tightly packed fibers are more prone to ephaptic interactions, which

depend on NST [77]. Moreover, unmyelinated axons of the peripheral nervous system are sensitive

to extrasynaptic neurotransmitters such as acetylcholine, serotonin, norepinephrine and ATP,

even if these molecules only reach the axonal trunk, away from the nerve terminals [44-46,78]. In the

CNS, the subcortical nervous system is home to a substantial proportion of unmyelinated

structures, and is also the origin of many nonsynaptic transmitters [22]. Specifically, medial

structures of the neuraxis such as those in the limbic system and brain stem, which are

prominently involved in the regulation of homeostasis and affect (drives, emotions, feelings), are

especially rich in unmyelinated fibers and monoaminergic/peptidergic neurons and are thought to

signal prominently via NST [79,80]. In contrast, the more lateral domains of the mammalian brain

(including the main sensorymotor systems, the association cortices and the cerebellum) are

especially rich in well myelinated axons [11,81]. Finally, the interoceptive nervous system— a key

physiological contributor to the phenomena of feeling—exhibits a high concentration of

unmyelinated fibers, as well as numerous instances of NST [45,49,50,78]. The structures where NST

14

01/14/19

is prevalent tend to have abundant denuded axons, whereas structures relying mostly on synaptic communication—those involved in movement, cognition, sensory perception—appear to be predominantly served by myelinated fibers. This bimodal distribution matches the contrasting temporal scales of the related neural process. Myelination is an improvement that mainly serves time-sensitive synaptic transmission, whereas unmyelinated fibers and NST pertain largely to processes that can afford slower and less precise transmission, which is the case with certain aspects of interoceptive information and feelings [76,82].

The conspicuous overlap between NST and unmyelinated fibers is likely to have functional relevance. In effect, myelin is a physical obstacle to NST, the myelin sheath acting as a potential block to both secretion and reception of the messenger [83-85]. Unmyelinated fibers are comparatively exposed and thus able to sense and emit circulating molecules, including neurotransmitters.

Another striking feature of the interoceptive nervous system are the localized gaps in the blood-brain barrier (BBB)—or blood-nerve barrier, as it is commonly designated in the peripheral nervous system. The BBB exhibits particularly conspicuous gaps in spinal ganglia. Each ganglion is divided into two regions, one housing most cell bodies and another containing mainly nerve fibers. The former is greatly enriched for vascularization, with a dense network of capillaries intimately wrapped around the sensory neuron somas. In contrast, the nerve fiber-rich area of the ganglion, as well as the adjacent nerves, are almost entirely devoid of blood vessels [86]. Moreover, the endothelium of the capillaries supplying the ganglia shows large fenestrations and is permeable to blood-borne agents of high molecular weight, properties reminiscent of areas

01/14/19

of the CNS lacking a BBB, such as the area postrema, and also observable in autonomic sympathetic ganglia and the enteric nervous system [87]. In sharp contrast, the capillaries present within nerve trunks tend to be impermeable. Presumably as a result of this selective vulnerability, blood-borne toxins preferentially affect the sensory pathways, and indeed can accumulate in spinal ganglia, whereas motor pathways are comparatively spared [86]. This selectivity is revealed by intra-venous administration of labeled albumin, subsequently found to accumulate in the extravascular, peri-neuronal space of the cell body-rich, but not the nerve fiber-rich area of spinal ganglia. This strongly indicates that the dense network of capillaries enveloping the sensory cell bodies bear a specific and topographically conscribed gap in the BBB, presumably a result of the epithelial fenestrations and molecular differences in tight junction composition [88]. The trigeminal ganglion is also devoid of BBB [89,90], suggesting that this feature is a general characteristic of peripheral sensory ganglia.

Stripped of a BBB and thus constitutively exposed to blood-borne factors, spinal ganglia may operate as chemosensors, responding to blood pH or concentration of metabolites or neuroactive substances [91], thereby serving as major sites of convergence of neural and humoral signals originating in the body, a role that has typically been associated with more rostral structures in the CNS. Blood-borne chemical signals crossing blood vessel walls and gaining direct access to neuronal somas may bind surface receptors and trigger changes in membrane potential, thereby impacting cellular excitability and action potential propagation, effectively governing the function of spinal ganglia and, consequently, interoceptive processing.

01/14/19

The three characteristic features of the interoceptive nervous system highlighted above—predominant use of NST, lack of myelin sheath and presence of gaps in the BBB—are structurally and functionally connected. The dearth of physical barriers such as BBB and myelin effectively exposes the denuded neuronal structures to chemical factors present in the blood stream (in the case of spinal ganglion neuronal cell bodies) and the internal milieu (in the case of unmyelinated axonal trunks of the PNS), providing them with an unparalleled ability to sense circulating molecules and detecting metabolic changes. These denuded, highly sensitized regions of the nervous system constitute an interface between neural and non-neural tissue, akin to the circumventricular organs but peripheral and dispersed throughout the organism rather than central. In all likelihood these regions are more capable of detecting subtler, incipient and localized chemical changes, potentially placing these structures at the very root of interoceptive sensing and, ultimately, of the feelings that allow us to become cognizant of varied states of homeostasis.

The contrasting anatomical and physiological features of synapses and NST (Table 1) suggest a theoretical framework. NST appears ideal to operate the molecular and visceral phenomena expressed in affective experiences [15,92,93], in full agreement with the previously proposed role for unmyelinated axons in the processing of affect [76]. Whereas movement and perception require precision and gain from speed, the world of affect—moods, and plenty of feelings—can tolerate some vagueness and slowness, perhaps even benefit from them. Affective experiences originate in the graded, modulated transitions from one visceral configuration to another. This would be in keeping with the fact that NST occurs over relatively long timescales—seconds, minutes or even longer—, as opposed to the milli- or even microsecond

17

01/14/19

range involved in synaptic transmission [94,26]. Also in support of this notion, the neurotransmitters

involved in volume transmission originate mainly in subcortical structures [11,22], which have been

implicated as primary central neural substrates of feeling and subjectivity [76]. Thus synapses may

mediate the "what" of neural function (consisting of processes such as sensory perception,

skeletal muscle contraction and higher cognition) and NST leads in "how" functions such as

affect and arousal [15,70,81,95]. This view has notable implications for the elucidation of the

neurophysiology of feelings and, ultimately, for a comprehensive understanding of human

mental processes.

01/14/19

	Synaptic Transmission	Nonsynaptic Transmission
Predominant fibers	well myelinated (Aα/Aβ)	poorly myelinated or unmyelinated (Aδ/C)
Cell types connected	neuron-to-neuron, neuron-to-glia, neuron-to-myocyte	any
Time scale	Very fast (μs-ms)	Slow (seconds/minutes/hours)
Neural processes supported	movement, fine perception, learning, reasoning, calculation, verbal language	interoception/visceroception, affect (moods, emotions, feelings)
Main areas of the nervous system	cerebral cortex, main motor and sensory pathways	limbic system, brain stem, autonomic nervous system, nociceptive pathways
Blood-brain barrier	continuous	localized gaps
Main neurotransmitters and neuromodulators	glutamate, GABA	monoamines (dopamine, noadrenaline, serotonin), ACh, neuropeptides

Table 1. General characteristics of synaptic and nonsynaptic transmission modes.

01/14/19

Figure legends

Fig. 1. Synaptic and non-synaptic transmission involve different regulatory mechanisms. A, Synaptic transmission connects neurons via cellular projections (axons/dendrites) and their associated terminal varicosities or synaptic boutons (in red). Establishing a new connection (right, blue neuron) thus involves de novo production of the axon/varicosities/synaptic structures (dashed line). B, Non-synaptic transmission is effected via messenger diffusion. Cells exposed to the messenger can be receptive (black neurons, left) or not (blue neuron, right) depending on the expression of the appropriate surface membrane receptor (in green) recognizing the messenger. A new connection can be established acutely by upregulation of the receptor molecule, without the need for any additional cellular structure.

Fig. 2. Synaptic and non-synaptic transmission interact to achieve signal integration. Neurotransmitters can 'spill' out of the synaptic cleft and into the surrounding extracellular space (left). Such leaked signaling molecules can activate extrasynaptic membrane receptors (A) or leak into neighboring synapses and modulate intra-synaptic receptors ('intersynaptic spillover', B). Similarly, transmitters released non-synaptically (right) can leak into synaptic compartments and modulate their function (C) or interact with nonsynaptic receptors (D).

01/14/19

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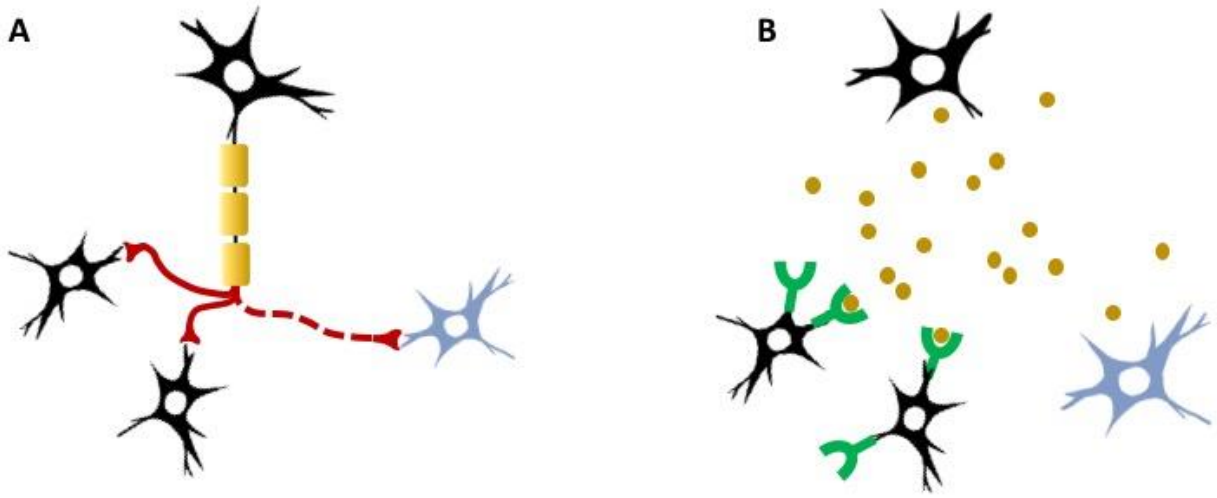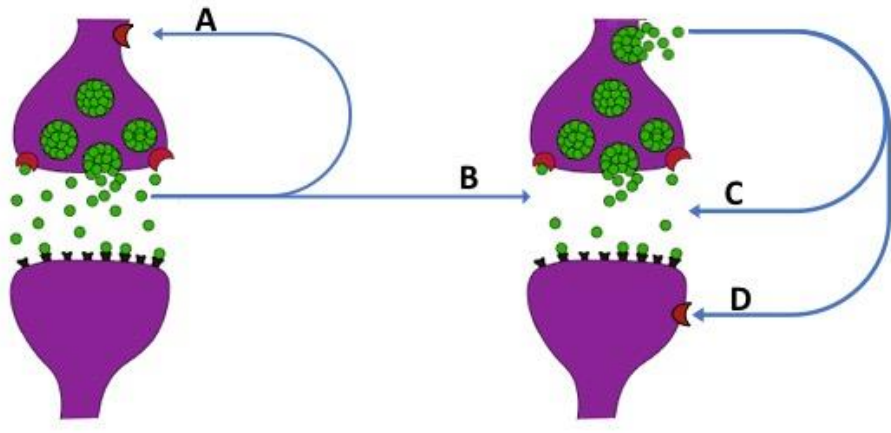
01/14/19

Fig. 1

01/14/19

Fig. 2