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Detecting the unexpected

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Sensory input is inherently dynamic and redundant. Humans and animals alike show a remarkable ability to extract regularities from the sensory scene and dynamically update their responses to the environment. This type of short-term plasticity occurs on time scales ranging from seconds to minutes (and possibly longer). Mismatch Negativity (a component of the human event-related potentials, MMN) and Stimulus Specific Adaptation (a single-neuron analogue, SSA) are two examples of this form of short-term plasticity. Conceptually, both are thought to express a form of surprise and to represent predictive processing. MMN and SSA therefore provide us with handles for investigating this important time scale of short-term plasticity.

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Introduction

To survive in an ever-changing environment, humans and animals alike rely on their capacity to extract rules and patterns from their dynamic surroundings. It is often suggested that sensory cortices generate predictions of future events based on statistical regularities of the past sensory stream. One particularly important class of such predictions are dynamic predictions: they are generated online and have a short life span, because they are specific to the current sensory landscape. The occurrence of such predictions should be reflected in brain signals and should affect neuronal responses in a context-dependent manner. The best-studied examples of such changes are related to the responses to unexpected stimuli: the same sensory stimulus evokes one response when it is expected, and another (often a larger response) when it is not.

In this review we will discuss possible neural processes underlying the capacity of brains to highlight relevant sensory information based on the statistical analysis of sound sequences over time scales of seconds to minutes. This is an intermediate time scale that neither fits standard experimental models of long-term nor of short-term memory. After a survey of human electrophysiology, we will discuss in details a single-neuron example of context dependent responses: SSA in the auditory system.

Sensitivity to deviance in human subjects

Arguably the best-known brain response to unexpected events is MMN [1]. MMN is usually studied using oddball sequences — sequences that contain a standard sound, repeated often, and a deviant sound, repeated rarely. MMN occurs as a negativity that peaks around 150 ms after deviance onset. MMN does not occur when the same stimulus is presented in neutral conditions, for example, when it occurs as one of many rare stimuli [2].

Deviance affects auditory event-related potentials even before the MMN time window. In particular, consistent (although small) deviance effects have been shown to occur as early as the mid-latency responses (peaks ~40 ms after sound onset), associated with early responses in auditory cortex [3–6]. Deviance effects have not been consistently found in the even earlier wave V of the auditory brain responses (peaks <10 ms after sound onset), associated with responses in the inferior colliculus [4,5,7]. Thus, regularities in a tone sequence affect neuronal responses in the human brain at least as early as the primary auditory cortex and potentially as early as the auditory midbrain.

One possible mechanism that may produce MMN is simple adaptation. In adaptation schemes, the repeated presentation of the standard adapts the neuronal elements responsive to the standard, but not (or less) those responsive to the deviant. Thus, the deviant evokes a larger response simply by virtue of its lower presentation rate [8,9•]. Adaptation-based models of this type do not show true deviance sensitivity, since the larger responses to the deviant are not related to the regularity set by the standard [10]. While the adaptation account for MMN has not been falsified, mounting evidence suggests that the model of simple adaptation is at least incomplete [10,11•,12]. For example, a number of MMN studies explored sensitivity to regularity in the responses to the standard. Baldeweg and co-workers [13–15] demonstrated 'repetition positivity', a slow potential that becomes more positive as the number of standard repetitions increases, and that contributes to the size of the

MMN. Similarly, Costa-Faidella *et al.* [16] showed a positivity that was associated with the standard when the oddball sequence was isochoronous but not when sound onsets were jittered so that sounds were temporally less predictable. However, these positive potentials accounted only for a small part of the MMN.

Paradigms that explore responses to deviance abound in human research, and span a large range of experimental setups and response latencies. Responses sensitive to deviance/rarity include the P3 family (evoked by rare events that require attentional processing [17]), the N400 (classically evoked by semantic incongruity [18]) or the P600 (evoked for example by 'garden path' sentences that require re-interpreting syntactic structure [19]). Because these responses occur with long latencies, they are not often considered in the context of short-term plasticity. Rather, they are most commonly described in terms of the evoking perceptual or cognitive mismatches. Mechanistically, however, the underlying neuronal processes require the brain to be in a state where certain stimuli are expected and others are not; the transition into this state is the short-term plastic effect discussed here.

The phenomenology of SSA

On the neuronal level, the phenomenon of selective attenuation of neuronal responses to standard tones in oddball sequences has been studied over the past 10 years or so in the auditory system under the name of SSA. Despite the name, recent work suggests that — as in the case of the MMN — adaptation of excitation is not sufficient to fully account for SSA, at least not at the level of auditory cortex.

SSA, like MMN, is most often studied using oddball sequences and describes the selective attenuation of neuronal responsiveness to a sound when common relative to the responses to the same sound when rare. Most studies of SSA use sequences consisting of pure tones of two frequencies, one of which is commonly, the other one rarely presented. Importantly, single and multiple unit responses along the auditory pathway are frequency selective. In order to disambiguate effects of tone probability from those due to frequency selectivity, the roles of the two frequencies are also reversed. SSA is then presented as the difference in the response to the same sound presented with different probabilities (Figure 1; [20•,21]). SSA has been documented in single and multi-unit recordings, using intracellular and extracellular recordings, and for many species, including mice [22], gerbils [23], rats [24–37], cats [20•,21], bats [38] and primates [39], and even in non-mammalian species such as barn owls [40–43]. Cortical SSA is mostly sensitive to frequency deviance. While there is contradictory evidence for cortical sensitivity to intensity deviance, duration deviants do not seem to give rise to SSA [20•,44]. There is initial evidence for SSA to spectro-temporal structure [45]. Moreover, recent evidence suggests a stunningly accurate sensitivity of cortical neurons to stimulus sequence and sequence structure [46•].

In spite of the substantial similarities, SSA is not a direct neuronal correlate of MMN [44,47]. SSA seems to occur significantly earlier in the processing hierarchy than MMN and may therefore be related to deviance sensitivity of the mid-latency responses (which in rats occur at ~20 ms) [48]. Furthermore, SSA has not been found to a subset of deviants evoking MMN, such as duration deviants (SSA [44], MMN [49]). Finally, while MMN is disrupted by NMDA antagonists [50], SSA appears to be insensitive to NMDA antagonists [44]. Considering the evidence, it is plausible to assume that SSA in auditory cortex is one of several mechanisms that lie upstream of MMN generation.

Functional anatomy of SSA

While the phenomenology of SSA is extremely robust, its site of origin and mechanism of generation are still under discussion. Initially demonstrated in primary auditory cortex [20•], SSA to pure tone frequency has been elicited as early as the auditory midbrain [23,24,28•,29]. Two parallel pathways originate in the IC, project to the MGB and from there to auditory cortex, the lemniscal or core pathway and the non-lemniscal pathway [51–53]. The lemniscal pathway originates in the central nucleus of the IC (ICc), which projects to the ventral division of the MGB (MGv) and from there to A1 [54]. Neurons in ICc and MGv are tonotopically organized and exhibit robust responses to tones, sharp frequency tuning, and short response latencies. Projections from MGv terminate exclusively in A1 and mostly in deep layer III and layer IV [55]. The non-lemniscal pathway originates in the external cortices of the IC, synapses onto dorsal and medial MGB neurons [53], and projects to all layers of primary and secondary auditory cortex [56]. Neurons in both ICc and MGv show a minor amount of SSA if any, whereas SSA in the non-lemniscal pathway is strong and robust [27,28•,29,57]. By contrast, neurons in A1 layer III and IV, which are considered a part of the lemniscal pathway, show strong and robust SSA [33,58]. Consequently, A1 is the first lemniscal station to exhibit a significant amount of SSA.

Given the prominent cortical projections to non-lemniscal MGB and IC [52,53,59], non-lemniscal SSA could be generated cortically and projected to subcortical stations. However, the corticofugal origin of SSA has been excluded experimentally by reversible deactivation of auditory cortex through cooling while recording from MGB [23,30•] and IC [60]. Cortical deactivation did not abolish SSA in these structures. Instead, cortical input provided a gain that was independent of whether a sound was standard or deviant. Interestingly, at least in MGB,