Published in final edited form as:

Brain Res. 2012 December 3; 1487: 140–149. doi:10.1016/j.brainres.2012.05.061.

Bursts modify electrical synaptic strength

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Abstract

Changes in synaptic strength resulting from neuronal activity have been described in great detail at chemical synapses, but the relationship between natural forms of activity and strength at electrical synapses had previously not been investigated. The thalamic reticular nucleus (TRN), a brain area rich in gap junctional (electrical) synapses, regulates cortical attention, initiates sleep spindles, and participates in shifts between states of arousal. Plasticity of electrical synapses in the TRN may be a key mechanism underlying these processes. Recently, a novel activity-dependent form of long-term depression was described at electrical synapses in the TRN [29]. Here we provide an overview of those findings and discuss them in broader context. Because gap junctional proteins are widely expressed in the mammalian brain, modification of synaptic strength is likely to be a widespread and powerful mechanism at electrical synapses across the brain.

Introduction

Gap Junctions

Electrical (gap junctional) synapses are extensively expressed throughout the mammalian brain [4,5,10,11] and predominantly couple GABAergic neurons of similar biochemical subtype [9,11,25,26]. Mature mammalian neuronal gap junctions are formed by paired hexomers of connexin36 proteins; these hexomers form a ring with a central pore ~2 nm in size, which pass charged ions as well as small molecules. Functionally, electrical synapses contribute to synchrony in coupled neuronal networks [2,3,5,6,19,22,24,26,43,47,49,74], although some studies suggest that the precise role of gap junctions in synchrony can be more complex [8,45,61,77] or firing state-dependent [30].

Electrical synapses are important components of intra-neuronal signal integration. Interactions between electrical synapses and intrinsic neuronal currents, such as the persistent sodium current, have been described [15,19,30,49], wherein the membrane currents act to amplify signals transmitted by electrical synapses. Modulation of electrical synapses by other synapses [66] and by chemical transmitters and neuromodulators [79], including dopamine [44,53,59,62], glutamate [42] and noradrenaline [81], occurs as well.

Activity-dependent forms of plasticity, which are widely thought to underlie the brain's encoding and memories, have been extensively described at excitatory (glutamatergic)

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chemical synapses [21,48], and to a lesser extent, at inhibitory (GABAergic) chemical synapses [31,41,56]. However, the possibility of activity-dependent modulation of electrical synapses had received far less attention. In one study, a short-term effect of tetanic activity was shown at the goldfish Mauthner mixed synapse [60]. In mammals, electrical synaptic strength has been shown to be altered by efferent input: activation of metabotropic glutamate receptors, by agonist application or by tetanizing efferent cortical-feedback fibers, induces long-term depression (LTD) of electrical synapses in the TRN [42].

The Thalamic Reticular Nucleus

The thalamic reticular nucleus (TRN) is a shell comprised of a homogenous population of parvalbumin (PV)-positive GABAergic neurons laterally surrounding the dorsal thalamus [33,57,58]. It provides powerful inhibition to thalamocortical relay neurons [63] upon integration of their corticothalamic and thalamocortical inputs. In addition to its proposed role in focusing the “neural spotlight of attention” [14,51], the TRN is strongly involved in regulating states of arousal [65,73] by altering its firing patterns between burst and tonic modes. Burst firing in TRN is a prominent component of sleep spindles [16,69,71,72,78] and the sharp wave discharges (SWDs) that characterize absence seizures [17,36,37,52,67,69,78]. Glutamatergic input from both thalamocortical and corticothalamic fiber terminals in the TRN is thought to generate its bursts [28,34,55,70,73]. The TRN is considered to be the seat of spindle-rhythm generation [32,72]. Both sleep spindles and absence seizures are marked by dramatic changes in cortical attention and by a loss of behavioral responsiveness to sensory input.

Cells in the TRN are densely and powerfully connected by electrical synapses [43,47] that persist into adulthood [7]. As in other brain areas, these electrically coupled neurons participate in synchronous activity [47]. The experimentally isolated TRN can generate spindles in the absence of other inputs [72], suggesting that electrical synapses are likely to be key players in maintaining TRN synchrony in that state and in behavioral switching between firing states.

Because electrical synapses are likely to play a major role in coordinating TRN activity, including bursting, we sought to investigate the effects of bursting activity in coupled neurons on the strength of the electrical synapse between them. We summarize these results here, which were published previously [29], and discuss the implications of electrical synaptic plasticity across the brain.

Methods

Experimental details are as described in [29].

Results

Recordings were made from pairs of gap junction-coupled TRN neurons embedded in conventional thalamocortical brain slices (Fig. 1A). Electrical synaptic strength was measured with hyperpolarizing current injections into one neuron (cell 1) and voltage responses were recorded in both neurons, which were maintained at a baseline $V_m = -65$ mV (Fig. 1B). These deflections determined the directional coupling coefficient $cc_{12} = \Delta V_{\text{cell } 2} / \Delta V_{\text{cell } 1}$, and from current injection into cell 2, $cc_{21} = \Delta V_{\text{cell } 1} / \Delta V_{\text{cell } 2}$. Coupling conductance G_C was also calculated from each direction of current injection. From 313 paired recordings of coupled TRN neurons, the average cc was 0.12 ± 0.08 and G_C was 0.80 ± 0.63 nS (mean $\pm$ SD; Fig. 1C), in line with the values for previous reports in TRN [42,43,47], and similar to cc values reported in cortex and other areas [18,27,49,76].

Gap junction channels formed by pairs of homogenous hexomers of connexin36, the dominant protein underlying gap junctions in the mammalian brain, are voltage-independent and generally thought to be non-rectifying for physiological ranges of voltage differences across the gap [68]. However, asymmetry of electrical synapses has been previously reported [18,49]. In the present data, cc was rarely symmetrical, which was reflected by the spread of values when plotting cc_{21} against cc_{12} for each pair (Fig. 1D). Asymmetry can be quantified by the ratio of directional cc s (cc_{21}/cc_{12}) for each pair; over all pairs, the mean ratio of directional cc s was 1.6 ± 0.6 (Fig. 1E, $n = 313$ pairs). Ratios of directionally measured G_C (G_{21}/G_{12}), which account for differences in input resistance R_{in} , had a mean of 1.2 ± 0.27 (Fig. 1E, $n = 313$ pairs).

Electrical coupling strength was examined before and following 5 min of synchronous bursting in pairs of coupled TRN neurons. Bursts were driven by simultaneous current injections of 100 - 300 pA for 50 ms at 2 Hz through the recording electrodes of both neurons. Resting potentials were held between -65 and -70 mV by steady-state current injection (Fig. 2A). In this activity paradigm, cc was reduced by $12.0 \pm 3.6\%$ and G_C was depressed by $13.2 \pm 1.8\%$ ($p < 0.05$, 2-tailed unpaired t-test, $n = 7$ pairs; Fig. 2B) compared to baseline. This synaptic depression outlasted the activity that drove it and persisted for the length of recordings (for at least 30 min after paired bursting), with no apparent signs of diminishing (Fig. 2B). The lack of significant changes in input resistance or membrane resting potential (Fig. 2C) indicated that the observed changes in electrical synaptic strength were unique to the electrical synapses and did not reflect changes in the intrinsic properties of the neurons at the whole-cell level. Pathological changes in internal calcium concentration affect gap junction strength [12,60,64], but the calcium influx due to the slow rate of bursting used here was much smaller. Bursting *in vivo* is usually faster than the stimulation used here [22,72].

Several manipulations were used to determine which components of paired bursting – the calcium event and the sodium spikes crowning it in both cells – contributed to the induction of LTD. To determine whether bursting in one neuron alone was sufficient to induce LTD, the bursting was induced in only one neuron of a pair (Fig. 2E) while the coupled cell was maintained at ~ -70 mV to prevent it from bursting. Following single-cell bursting, cc was reduced by $15.0 \pm 3.4\%$ and G_C was reduced by $13.0 \pm 2.3\%$ (Fig. 2F, $p < 0.05$, $n = 11$ pairs). To determine the contribution of sodium spikes to LTD, the bursting paradigm was repeated in both cells using a bath application of 1 μ M TTX, which completely and reversibly blocked the barrage of sodium-mediated action potentials crowning the calcium-mediated bursts (Fig. 3A). Following paired bursting in TTX, cc decreased by $12.3 \pm 3.2\%$ and G_C decreased by $11.7 \pm 2.6\%$ (Fig. 3B, $p < 0.05$, $n = 9$ pairs). Bursts were also induced in one cell alone in TTX (Fig. 3E). Following single-cell activity in TTX, cc decreased by $6.5 \pm 2.3\%$ and G_C was reduced by $6.0 \pm 2.0\%$ (Fig. 3F, $p < 0.05$, $n = 11$ pairs). Of these four activity paradigms, the amount of depression from single-cell bursting in TTX was significantly weaker than the LTD from the other three bursting paradigms (Fig. 3H, $p < 0.05$); the other three paradigms were not significantly different from each other. Thus, sodium-mediated action potentials in both cells are necessary for the full extent of LTD measured, while the calcium-mediated LTS is sufficient for a smaller amount of depression of electrical synapses.

The activity paradigms in which only one cell was active allowed for characterization of the time course of changes in electrical synaptic strength, by measurement of the amplitude of the postsynaptic burstlet in the coupled cell during the 5 min. of activity. For both single-cell bursting and single-cell bursting in TTX, changes in synaptic strength (measured by burstlet amplitude) reached steady-state depressed values within 2 min of activity (Fig. 3D).

Like many thalamic neurons, TRN neurons spike in two modes: conventional fast sodium-based tonic spikes, and slower, all-or-nothing low-threshold calcium-based spikes (LTS) known as a bursts that are crowned by a barrage of fast sodium spikes. Bursts often result from activation of T-type calcium conductances, which in the TRN are based on CaV 3.2 and CaV 3.3 [35]. In many pairs in the current study, bursts elicited by positive current injection into one neuron were sufficient to drive bursts in its coupled neighbor, even with baseline membrane resting potentials maintained at $V_m \approx -65$ mV (Fig. 4A1, B1). After induced depression of the electrical synapse between these pairs, bursts were no longer effective in driving activity in the coupled cell (Fig. 4A2, B2). Thus, the order of magnitude of changes shown here is a relevant change and can fundamentally alter the coordinated bursting spread by gap junctions, which is a prominent and relevant feature of coupled TRN neurons.

In two of the activity paradigms, the activity of the coupled pair, and thus the use of the synapse, was also asymmetrical (Fig. 3A, E). That is, one neuron was active while the other was quiescent, resulting in largely unidirectional current flow across the gap junction during activity. These asymmetric stimuli allowed for investigation of whether the observed LTD of gap junctional strength was also expressed in an asymmetric manner. First, a convention for quantifying the effects of activity on each direction of coupling was established, with respect to the active cell. Coupling measured by current injection into cell 1 (the active cell during pairing), or outbound coupling, is denoted as cc_{12} , while coupling measured by current injection into the quiet cell 2 and relayed by the gap junction back to the active cell 1, or inbound coupling, is cc_{21} (Fig. 5A). For full bursting in one neuron (Fig. 5B), the inbound coupling cc_{21} decreased by $16.0 \pm 3.4\%$, while outbound coupling, cc_{12} , decreased by $8.6 \pm 3.7\%$ (Fig. 5C and D; $p < 0.05$ for both directions; $n = 11$ pairs). The change in cc_{21} was significantly different from that of cc_{12} ($p < 0.05$). Directionally measured conductances decreased similarly; G_{21} decreased by $10.8 \pm 3.2\%$ and G_{12} decreased by $6.8 \pm 3.2\%$ ($p < 0.05$). For single-cell LTS bursting in TTX (Fig. 5D), inbound coupling, cc_{21} , decreased by $10.0 \pm 3.0\%$ ($p < 0.05$, $n = 10$ pairs), while the change in outbound coupling, cc_{12} , was not significant (Fig. 5G and H; $-5.5 \pm 2.7\%$, $p = 0.07$, $n = 10$ pairs). In TTX, G_{12} decreased by $7.5 \pm 2.0\%$ ($p = 0.04$) and G_{21} decreased by $6.6 \pm 2.5\%$ ($p = 0.09$). Thus, the effects of activity on an electrical synapse depend on the direction of its use; inbound signals to a spiking neuron are, on average across pairs, depressed more than outbound signals from it.

In principle, asymmetric use of a gap junction could decrease, increase, or preserve the pre-activity asymmetry of coupling in any given pair; these changes could happen independently of the average asymmetry mentioned above. To examine the systematic effects of unidirectional synapse use on asymmetry within pairs, the ratios of directional cc s and G_C s (cc_{21}/cc_{12} and G_{21}/G_{12}) were examined for each pair following unidirectional activity (y-axis) against the initial value (x-axis). The identity line corresponds to coupling asymmetry that was unaffected by asymmetrical use of the synapse. For full bursts in one cell, ratios of cc s increased on average by $9.1 \pm 2.4\%$ after activity (Fig. 5E, $p < 0.01$, $n = 11$); this shift represents a systematic trend of greater change in the coupling of inbound communication, cc_{21} , relative to outbound communication, cc_{12} . Ratios of G_C increased by $5.0 \pm 2.2\%$ ($p < 0.05$). Changes in asymmetry were not due to coordinated shifts in input resistance; R_1/R_2 decreased by $3.1 \pm 2.6\%$ ($p = 0.25$). For LTS bursts without sodium spikes in one cell, ratios of cc s and G_C s fell along the identity line after activity, with an insignificant change in rectification from initial values (Fig. 5I, ratio of cc s: $6.0 \pm 4.2\%$, $p = 0.6$; ratio of G_C s: $-0.6 \pm 2.0\%$, $p = 0.76$; R_1/R_2 : $-5.3 \pm 3.4\%$, $p = 0.07$; $n = 10$ pairs), indicating that the changes in rectification in ACSF may be due to sodium spikes. As expected, ratios of coupling coefficients also did not change significantly for symmetrical synapse use (paired bursting). Therefore, the direction of current flow through a gap junction can affect the rectification of the synapse.

Discussion

Although activity-dependent changes have been extensively described and characterized at chemical synapses, long-term modification of electrical synapses by precise patterns of activity of coupled cells themselves was previously unexplored. The results described here represent a new perspective for gap junctions across the brain, wherein the strength of electrical connections is not a fixed property but can be modified in a long-lasting manner by natural activity.

Electrical synapses have been shown to interact with other membrane currents, such as the persistent sodium current [15,19,30,49]. These interactions, as well as others, play important roles in regulating synchrony in networks of coupled neurons. The present data indicate that spiking activity is easily transmitted through gap junctional networks, even for coupled neurons close to their resting potentials. Thus, modification of electrical synapses can dynamically exert large effects on synchrony.

The changes we measured, ~15%, are somewhat small in comparison to the magnitudes of changes often measured at chemical synapses. However, neurons receive thousands of individual chemical synaptic inputs, which are each very small, often distant from the soma, and of short and stereotyped timecourses. Any given chemical synaptic input is typically ineffective as a single voice in driving a cell to spike. In contrast, electrical synaptic signals are fundamentally different signals. Because electrical synaptic signals are proportional to the voltage difference between cells, they are often larger than chemical synaptic inputs. Further, electrical synaptic inputs persist for the duration of the voltage difference, whether that is a spike, a burst, or an overall state change. The average coupling we measured ($\kappa = 0.12$) applied to the average presynaptic burst (~50 mV) yields a several-mV burstlet in a postsynaptic cell that lasts for the entire ~50 ms of the burst (Fig. 1F, 2E, 3E). Indeed, as we described, bursts are often large enough to individually drive bursts or spikes directly in quiescent coupled neighbors (Fig. 4). Thus a reduction by 15% is a considerable effect, given the efficacy of the synapses; and this weakening of electrical synapses can eliminate the ability of a single cell to drive its neighbor(s) to spike.

Plasticity of an electrical synapse could provide a single cell with the ability to adjust its input sensitivity between a mode in which intra-TRN electrical-synaptic connections are strongest and dominate cellular responsiveness, to a different mode in which incoming corticothalamic and/or thalamocortical chemical afferents primarily control TRN responsiveness. In the latter scenario, individual cells would then act more as independent gates of thalamocortical exchange, after tuning out the messages from their closer neighbors within the TRN.

Plasticity of individual electrical synapses could also serve to reorganize small syncytia or sub-networks of synchronously active neurons, effectively switching the TRN between spatially broad network-wide synchrony to a set of locally related but independent “neighborhoods” of fewer, more tightly coupled neurons whose synapses are able to maintain synchrony. Membership or behavior within a neighborhood could also be tuned by plasticity of electrical synapses. Other forms of electrical synaptic plasticity in different brain areas are likely to provide different effects according to their physiological and computational requirements. In the cortex, for example, plasticity of electrical synapses might similarly switch cells within a coupled network between modes of independent processing and intrinsic rhythm generation.

Activity-dependent LTD could be a mechanism used by a single bursting cell to unplug from an overly active or overly synchronous neighbor or network. Overall, hypersynchrony

of coupled cells in the TRN would drive depression of most of its electrical synapses, thereby desynchronizing the nucleus. Thus, burst-driven LTD has a stabilizing, homeostatic influence. Regulation of coupling strength may play a key role in the balance between healthy and pathological rhythms, both in the TRN and elsewhere in the brain; epilepsy may arise at least in part from a lack of an ability to modify electrical synaptic strength. The LTD we observed may be just one component of a homeostatic regulatory process, in which electrical synaptic strength has a physiological set point.

What cellular and structural processes might underlie the observed LTD? A single gap junction plaque is comprised of hundreds to thousands of individual gap junction channels clustered together in an organized lattice-like fashion. Insertion and deletion – recycling – of gap junction channels is a normal component of cellular function and is a candidate mechanism for permanent changes in gap junction strength — that is, either a reduction or increase in the rate of surface-protein recycling. However, for the two types of activity in which one cell was quiescent, significant changes took place within the first minute of activity. This timescale suggests phosphorylation of the connexin36 proteins forming gap junction pores. Indeed, connexin36 proteins have multiple phosphorylation sites [1,39], and phosphorylation-related changes in coupling [40,75] or hemi-channel conductance [54] have been described. Changes in channel phosphorylation states could, in principle, underlie both depression and potentiation of electrical synapses.

Our experiments with single-cell activity indicate that electrical synaptic strength is asymmetric at baseline, and can be further modified in a directional manner. The measured baseline asymmetry may be a result of spatial filtering of signals from gap junctions located at various dendritic distances from the soma, where our electrodes were located; for example, a synapse might be somatic in one neuron, but distally dendritic in the coupled counterpart. Another possibility is that these neuronal gap junctions are not comprised of strictly connexin36 protein. Results in the connexin36 knockout mouse indicate that electrical synapses comprised of non-connexin36 proteins are more asymmetrical [80]; connexin45 is one possible candidate member of a heterotypic gap junction [46,50].

Our results also demonstrate that coupling asymmetry can be shifted according to activity; that is, neurons can fine-tune their relative proportion of input they send and/or receive from coupled neighbors via electrical synapses. Increased expression or activation of already-present non-connexin36 proteins could account for this activity-dependent increase in asymmetry. Recent work has shown that calcium bursts can be independently activated in dendrites and/or somatic compartments [13], which could result in independent phosphorylation of one side of a gap junction, and provide a possible explanation for activity-dependent shifts in asymmetry.

Despite evidence of gap junctional rectification in mammalian systems, the canonical symbol for electrical synapses has remained the simple resistor (R_C). Our observations of baseline conductance asymmetry, in addition to activity-dependent shifts in asymmetry (Fig. 5A), led us to reconsider the standard model, as a linear resistor cannot account for asymmetry or increases in asymmetry. We suggest a model of a gap junction as two branches in parallel (Fig. 5J): one branch carries the common resistance (R_C), or the maximum resistance (minimum of conductance) as measured from both directions. A parallel branch consists of a resistor (R_D) in series with a diode, representing the increase in conductance (or decreased resistance) observed in one direction. Diodes have been used to model heavily rectifying invertebrate gap junctions [20,23,38], but have not yet been considered as part of a mammalian gap junctional circuit. The combination of asymmetrical synapses and activity-dependent, asymmetrical changes renders a fine degree of dynamic

flexibility to networks of coupled neurons, which we have now incorporated into the mammalian gap junction model.

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Figure 1.

A) 60x IR image from patch recordings of a coupled pair of TRN neurons. **B)** Current injection into cell one (I_1) of a coupled pair drives a direct response in that cell (V_1) and a gap junction-relayed response in the second cell (V_2). The ratio of the voltage deflections is the coupling coefficient, cc . Scale bar 5 mV, 0.1 s. **C)** Mean gap junction conductance (G_C ; see Methods) plotted against mean cc (dots). Open circles are a binned averages, with a slope of 7.9 (bin width 0.02; $R^2 = 0.77$, $n = 313$ pairs). The coefficient of variation, $\sigma(G_C)/\text{mean}(G_C)$, was ~ 0.3 for all well-sampled bins. **D)** Directional cc (purple, scaled by 10) and G_C (orange) for each pair; $1 \rightarrow 2$ represents coupling measured by current injection into cell 1, as in (B). **E)** Coupling asymmetry was quantified by distribution of ratios (cc_{12}/cc_{21} and G_{12}/G_{21}). Asymmetry as measured by cc ratio had a mean of 1.6 ± 0.6 (purple, mean $\pm$ SD, $n = 313$ pairs) and by G_C ratio 1.2 ± 0.26 (orange; mean $\pm$ SD). Bin width was 0.05. With permission from [29].

Figure 2.

A) Paired bursting was driven by simultaneous current injections into both cells of a coupled pair. Scale bars: 20 mV, 50 ms. Inset: zoom of paired burst event. **B)** Following 5 minutes of paired bursting at 2 Hz, cc depressed by $12.0 \pm 3.6\%$ and G_C depressed by $13.2 \pm 1.8\%$ ($p < 0.05$, $n = 7$ pairs). **C)** Average input resistance (R_{in}) and resting membrane potential (V_m) for the neurons summarized in (B). **D)** Measurements of coupling coefficients in one pair before and after activity pairing, measured as in Fig. 1B. Scale bar is 100 ms, 2.5 mV (coupled response, in black), 7.5 mV (direct response, in gray). **E)** Bursting was driven by injections of current into one cell of a coupled pair (black trace) while the other neuron was quiescent (grey trace). Scale bars: 20 mV, 50 ms. Inset: zoom of burst event and burstlet in quiescent neuron. **F)** Following 5 minutes of paired bursting at 2 Hz, cc depressed by $15.0 \pm 3.4\%$ and G_C depressed by $13.0 \pm 2.3\%$ ($p < 0.05$, $n = 11$ pairs). **G)** Average input resistance (R_{in}) and resting membrane potential (V_m) for the neurons summarized in (E). **H)** Measurements of coupling coefficients in one pair before and after activity pairing. Scale bar is 100 ms, 2.5 mV (coupled response, in black), 7.5 mV (direct response, in gray). With permission from [29].

Figure 3.

A) Paired bursting was driven by simultaneous current injections into both cells of a coupled pair in the presence of 1 μ M TTX to block sodium spikes. Scale bars: 10 mV, 50 ms. Inset: zoom of paired burst event. **B)** Following 5 minutes of paired bursting at 2 Hz in TTX, cc depressed by $12.3 \pm 3.2\%$ and G_C depressed by $11.7 \pm 2.6\%$ ($p < 0.05$, $n = 9$ pairs). **C)** Average input resistance (R_{in}) and resting membrane potential (V_m) for the neurons summarized in (B). **D)** Burstlet amplitude during single-cell activity plotted against elapsed time during activity and normalized to final values. **E)** Bursting was driven by injections of current into one cell of a coupled pair (black trace) while the other neuron was quiescent (grey trace), also in TTX. Scale bars: 10 mV, 50 ms. Inset: zoom of burst event and burstlet in quiescent neuron. **F)** Following 5 minutes of paired bursting at 2 Hz, cc depressed by $6.5 \pm 2.3\%$ and G_C depressed by $6.0 \pm 2.0\%$ ($p < 0.05$, $n = 11$ pairs). **G)** Average input resistance (R_{in}) and resting membrane potential (V_m) for the neurons summarized in (E). **H)** Summary of changes in G_C for the four paradigms: paired bursting (2B), single-cell bursting (1B), paired bursting in TTX (2B + T), and single-cell bursting in TTX (1B + T). With permission from [29].

Figure 4.

Gap junction-relayed activity before and after LTD. **A₁**) For one pair of neurons ($cc_{12} = 0.2$, $G_{12} = 2.2$ nS), spikes driven by current injection into cell 1 (grey traces, I_1) elicited a burst in cell 2 (blue traces, V_2). Scale bar 20 mV, 100 ms, 400 pA. **A₂**) After paired bursting resulting in LTD ($\Delta G_c = -13\%$; $\Delta cc_{12} = -11\%$), the same stimulus and resulting spike train in cell 1 failed to elicit a burst in cell 2. **B₁**, **B₂**): Same paradigm as in (A) for a pair with initial $cc_{12} = 0.18$ and $G_{12} = 1.3$ nS, $\Delta G_c = -9\%$; $\Delta cc_{12} = -8\%$. Scale bar 20 mV, 100 ms, 400 pA. With permission from [29].

Figure 5.

A) For activity in cell 1, cc_{12} (blue) represents the ‘outbound’ coupling measured by current injection into cell 1, and cc_{21} (green) represents ‘inbound’ coupling. B) Single-cell bursting in cell 1 with postsynaptic burstlets in cell 2. Scale bars: 20 mV, 50 ms. C) Inbound cc_{21} before and after full bursts in cell 1. D) Outbound cc_{12} before and after full bursts in cell 1. E) Ratios of directional cc (black filled circles; division of the changes in C divided by the changes in D for each pair) and G_C (open circles, $p < 0.05$ for both cc and G_C) following full bursts in cell 1, plotted against initial values. F) Bursts in cell 1 in 1 μ M TTX. Scale bars: 20 mV, 50 ms. G) Inbound cc_{21} before and after bursts in cell 1 in TTX. H) Outbound cc_{12} before and after bursts in cell 1 in TTX. I) Ratios of directional cc (red filled squares; $p = 0.6$) and G_C (open squares; $p = 0.76$) following bursts in cell 1 in TTX, plotted against initial values. J) Model of an asymmetrical gap junction as two parallel branches. R_C represents the minimum conductance (maximum resistance) common to both sides of the gap junction and R_D represents additional, asymmetrical conductance in one direction. With permission from [29].