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The brain on the beat: How music may heal schizophrenia

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"Music and rhythm find their way into the secret places of the soul"

(Plato)

Music is a universal human behaviour with biological underpinnings and is more than mere form of entertainment or socio-cultural behaviour. Music and rhythm perception play important role in human adaptive functions involving a complex set of neural networks including the basic auditory, music-syntactic, prefrontal-executive, episodic memory, motor, emotion and reward networks. Over the last three decades, neuroscientific investigations on deficits in music and rhythm perception and production in various clinical conditions has contributed to a deeper understanding of the neural substrates of music and rhythm (Koelsch, 2011; Zatorre, 2005). These findings have in turn contributed to better understanding of the functioning of the human brain in health, and in neuropsychiatric disease (Sihvonen et al., 2017). Two recent articles in *Schizophrenia Research* shed further light on this topic and suggest some future directions for research (Takahashi et al., 2023; Honda et al., 2023).

Glutamate, an excitatory neurotransmitter plays a vital role in brain development and neuroplasticity and is strongly implicated in the pathogenesis of schizophrenia (SZ) (Keshavan, 1999; Keshavan et al., 2015). Glutamatergic dysfunction has been implicated in the core features of SZ such as neurocognitive deficits, and negative symptoms such as amotivation and anhedonia (Hatada et al., 2014). There is evidence that glutamatergic metabolites levels are higher in treatment resistant schizophrenia (TRS) patients (Mouchlianitis et al., 2016). Capitalizing on these observations, Takahashi and colleagues reported impaired mismatch negativity (MMN) to be an indicator of impairment in perceiving beat interval in SZ (Takahashi et al., 2023). Impaired MMN is a putative marker of glutamatergic function (Harms et al., 2021). Honda et al. (2023) examined rhythm perception and production in TRS and non-TRS vs. healthy controls. SZ had impaired ability to synchronize to musical beat. TRS and non-TRS differed on the beat finding and

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interval test. This test included tasks like discriminating tempo of a given rhythm pattern and tapping to quarter note beat with rhythm patters with changing tempo. Interestingly, rhythm perception and production were worse in patients with TRS compared with non-TRS and healthy controls. Beat finding, and interval test correlated with negative symptoms and both perception and production of rhythm were associated with severity of neurocognitive functions. Clearly, the Takahashi and Honda studies highlight how music rhythm perception may be related to glutamatergic pathways in the brain, and can help us understand why musical deficits are closely associated with other neurocognitive deficits such as executive functions as well as negative symptoms. Engaging with music actively or passively such as listening or playing an instrument or singing engages a host of neurocognitive functions. Neuroscientific investigations on neural correlates of music have contributed to deeper understanding of neural plasticity as well as emotion (Chatterjee et al., 2021).

Another well-known hypothesis explaining the pathophysiology of SZ is dopaminergic dysfunction. Dopamine is related to how brain constructs music as a pleasure inducing and rewarding experience. Music is a very strong elicitor of emotion and music represents a dynamic form of emotion as music is something that unfolds in time. There is evidence that that levodopa increases the hedonic experience and music-related motivational responses, while risperidone, a dopamine antagonist leads to a reduction of both (Ferreri et al., 2019). While dopaminergic overactivity is related to psychosis, decreased dopaminergic tone is thought to characterize persistent features such as negative symptoms. Dopaminergic pathways also mediate cognitive functions by modulating pre-frontal executive function and working memory circuits. Dopaminergic reward circuitry is strongly associated with music, given that music is a highly pleasurable and rewarding experience (Ferreri et al., 2019). In addition to musical components such as pitch, melodic contour, rhythmic aspects of music is intimately associated with emotional experience. Rhythmic and musical expectation and entrainment play a pivotal role in engaging musical affect, and music reward responses. Music reward is in turn known to engage extensive neural network of subcortical and cortical regions (Salimpoor et al., 2015). In fact, nigrostriatal pathway /network are implicated in time perception, in processing musical rhythm (Fung et al., 2021). It is possible that negative symptoms in SZ which may reflect reduced dopaminergic activity could potentially benefit from music.

Thus, music and rhythm perception and production as well as the musical experience may involve a synergistic interaction between glutamatergic and dopaminergic systems. Music with its strong predictive components, such as rhythmic sequences have a very strong impact on both dopaminergic and glutamatergic function (Weigmann, 2017). Dopaminergic activations occur when rewarding events are better than predicted. Music is very a highly rewarding experience given its predicted and often superior unpredicted experiences. The experience of ‘goose bumps’ that often accompanies musical experience is due to the surge of dopamine release related to prediction error. Activation of dopaminergic circuits by music as well as activation of sensory and cognitive areas impacts the emotional intensity, arousal, hedonic and rewarding experience (Salimpoor et al., 2015).

Music and rhythm perception akin to other neurocognitive and motivational functions is perhaps at the core of this debilitating illness reflecting the underlying pathophysiology of

both dopaminergic and glutamatergic pathways (Keshavan, 1999). Music inherently taps into predictive coding and predictive timing aspect. Music and rhythm may facilitate brain's anticipation of future sensory events based on experience and content (Weigmann, 2017). Given this background, studies using music and rhythm can provide us with newer and deeper understanding of the complex nature neurocognitive deficits, sociocognitive and emotional deficits as well as the underlying pathophysiology in SZ.

Taken together, the Takahashi et al. (2023) and Honda et al. (2023) studies suggesting glutamate-mediation of music rhythm deficits as well as the association between dopamine pathways and musical experience point to a dysfunction in two key neurochemical systems in SZ (Fig. 1). This model points to some needed next steps in SZ research. First, future studies could perhaps investigate music and rhythm perception deficits as potential endophenotypes of psychotic disorders. Second, in light of known deficits in auditory processing in certain phenotypes of psychotic disorders (Narayanan et al., 2015), music and rhythm-based interventions could be developed as a way to enhance neurocognitive functions in the non-musical domains with far transfer effect coming to play. Third, given evidence for reduced neural plasticity in SZ and youth at clinical high risk for psychosis (Keshavan et al., 2015) it is worth asking whether musical perception deficits and cognitive impairments reflect impaired neural plasticity processes. If confirmed, the effect of music on brain plasticity can be harnessed in neuropsychiatric disorders (Chatterjee et al., 2021). Indeed, music-based interventions have been gaining prominence in various clinical conditions including SZ (Geretsegger et al., 2017). However, there is debate on the method and type of music therapy that may be beneficial in this clinical condition to address both neurocognitive deficits as well as negative symptoms. Finally, recent studies suggest that tetanic auditory stimulation (i.e. trains of quickly repeating auditory stimuli) alter the electroencephalogram similar to electrical stimulation and induce glutamatergically mediated long-term potentiation. We suggest that such tetanic sensory stimuli, if combined with rewarding music, perhaps via dopaminergic mechanisms, could enhance such plasticity benefits (Sanders et al., 2018).

In summary, music can has a multi-pronged impact on the functioning of the human brain. We hereby propose this via the model which can direct future research in this direction for SZ and SZ like disorders (Fig. 1). Multimodal effects of music on neurocognitive, emotion and reward systems can be harnessed to address unmet treatment needs of SZ i.e., neurocognitive deficits, sociocognitive deficits, negative symptoms and treatment non-adherence.

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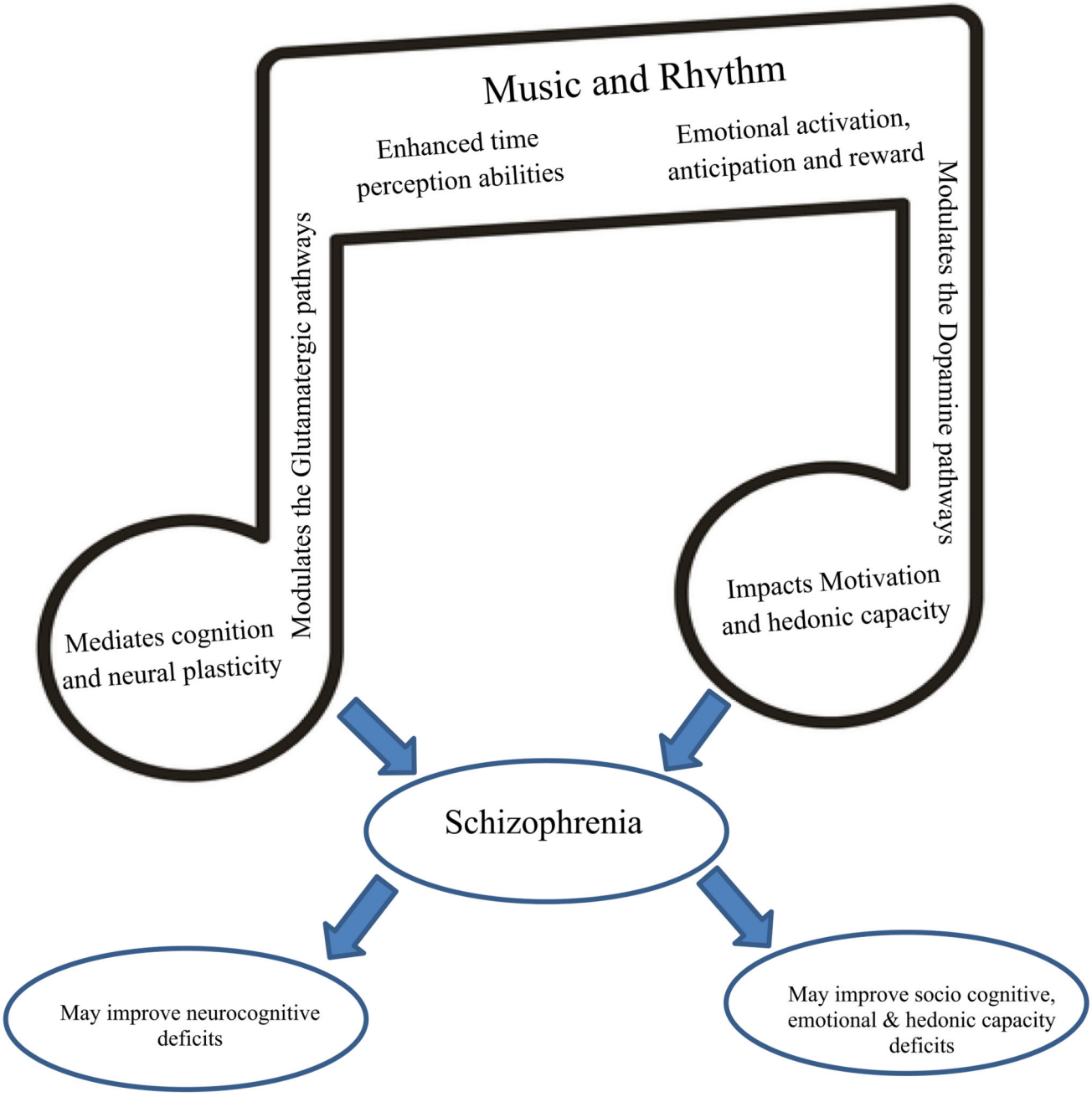

Fig. 1. Model proposing how music and rhythm-based assessments and interventions can help targeting various deficits in functioning observed in schizophrenia/schizophrenia like disorders.