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The neuromuscular basis of functional impairment in schizophrenia: A scoping review

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ABSTRACT

Patients with schizophrenia exhibit functional impairments in their locomotory tasks, which decreases their quality of life. Due to the limited current research, the neuromuscular mechanisms behind the functional impairments in patients is not fully understood. Thus, this review aims to summarize the neuromuscular mechanisms that underlie these deficits in daily functioning. These deficits are speculated to stem from abnormalities at various levels from neurons through to the skeletal muscles. The neurological abnormalities are exhibited as lower motor neuron dysfunction whereas the skeletal muscle pathology is shown as increased muscle fibre (type 1 and type 2) atrophy, reduction in maximal force generation, and increased strength loss per decade. Although antipsychotics effectively reduce positive symptoms, functional impairments remain unresolved. Both endurance and resistance training have shown potential benefits in alleviating deficits in daily functioning by increasing muscular strength, increasing fat-free mass, and preserving neuromuscular properties from degradation. In summary, the review elucidates various possible mechanisms for the onset of functional impairment experienced by patients with schizophrenia and highlights the potential utility of endurance and resistance training to alleviate these deficits in daily functioning.

1. Introduction

Schizophrenia is a complex and chronic psychiatric illness that is prevalent in 1 % of the world population (Mueser and Jeste, 2011). The pathogenesis of the illness remains unclear, but there are several lines of evidence from monozygotic twin studies showing a high concordance rate, suggesting a strong hereditary effect (Sullivan et al., 2003). Additionally, the overactivation of dopamine at D2 receptors may play a critical role in the pathophysiology of the illness (Seeman and Kapur, 2000). Schizophrenia is characterized by a multitude of symptoms, including positive symptoms, such as hallucinations and delusions, and negative symptoms, such as apathy, amotivation, and impaired cognition (Owen et al., 2016). Antipsychotics, the cornerstone treatment for schizophrenia, significantly relieve positive symptoms in most patients (Hazif-Thomas and Thomas, 2008; Kapur et al., 2006). However, antipsychotics are not efficacious in targeting other domains of dysfunction that play a key role in the development of long-term disability and functional impairment, leading to a reduction in quality of life (QoL) (Correll and Schooler, 2020). In this paper, functional impairment refers to limitations in a person's ability to perform physical tasks or activities typically expected in daily life, such as walking, lifting, or other motor skill-dependent actions. These limitations can be assessed using various methods, including self-report questionnaires, clinician-rated scales, and performance-based measures.

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1.1. Evidence of functional impairments

Patients with schizophrenia show impairments in balance, endurance, strength, and power, which can lead to a more significant exertional requirement in most everyday activities and poor QoL (Chang et al., 2019; Viertiö et al., 2008; Vancampfort et al., 2013a, 2013b). This may lead to reduced physical activity, which increases the risk factor for cardiovascular disease (Booth et al., 2017; Vancampfort et al., 2017).

Patients have reported functional impairment in daily tasks such as walking 2 km without rest, climbing stairs for one flight, and handgrip strength (Viertiö et al., 2008).

Additionally, functional performance has also been assessed in patients using the Medical Outcome Health Survey Short Form 36 (SF-36), in which a physical function score is a display of physical limitation independent of mood and mental status (Pukrop et al., 2003). Using the SF-36, patients with schizophrenia showed significantly impaired physical function (e.g., carrying groceries, using stairs, bending, lifting) due to lower SF-36 scores compared to the normative data. Specifically, young patients with schizophrenia showed SF-36 scores similar to individuals without schizophrenia 10–20 years older, with an increased deviation of patient scores from the normative scores with each successive age group (Chafetz et al., 2006). Next, reduced endurance capacity is highlighted in the examination of walking capacity in patients using the 6-min walk test (6MWT), in which patients walked significantly less distance relative to healthy control, suggesting an impairment in the patient's aerobic capacity (Vancampfort et al., 2013a). Although there is an increased prevalence of elevated BMI in individuals with schizophrenia, the functional impairments remain after controlling for BMI, age, and gender (Vancampfort et al., 2013a; Annamalai et al., 2017).

The same study by Vancampfort et al. (2013a) examined muscular power through standing broad jump and found a significant reduction between patients and healthy controls in the distance travelled, suggesting decreased lower limb muscular power. Furthermore, this diminished muscular power is also prevalent during the half sit-up test, in which the patients scored below the 50th percentile, indicating decreased core muscular strength and endurance (Gretchen-Doorly et al., 2011). Finally, patients have demonstrated a 73 % reduction in balance relative to healthy control when tested using the unipedal stance test with eyes closed (i.e., standing on one leg while arms are folded for a maximum of 60 s) after controlling for age, BMI, and sex, suggesting that patients with schizophrenia have impaired sensitivity to proprioceptive cues in the absence of visual stimuli (Nygård et al., 2019).

Neuromuscular mechanisms that might underlie functional deficits include the dysfunction of motor neurons, abnormalities in muscle fibers and a reduction in maximal muscle force generation (Flyckt et al., 2000a, 2000b; Nygård et al., 2019; Ozbulut et al., 2013).

However, there is limited understanding of the mechanisms behind the functional impairments seen in patients with schizophrenia. Therefore, this scoping review aimed to elucidate potential mechanisms behind these impairments and potential therapeutics. To investigate these mechanisms, we adopted a holistic approach, analyzing the entire motor action pathway from upper motor neurons to lower motor neurons and finally to skeletal muscles. This comprehensive examination was supported by conducting three distinct literature reviews focused on: 1) neurological abnormalities [i.e, upper motor neurons, lower motor neurons] 2) skeletal muscle impairments, and 3) exercise therapy.

2. Methods

Our protocol was developed using the scoping review methodological framework proposed by the Joanna Briggs Institute. The objectives, inclusion criteria, and methods for this scoping review were specified in advance and documented in a protocol.

2.1. Search strategy

Three separate comprehensive search strings were developed to individually address the three objectives of this review. The detailed search strings are provided in *Supplementary Table 1*.

Ovid MEDLINE, EMBASE and PsycINFO databases were searched for relevant articles written in the English language. A grey literature search was also performed by mining references from relevant review articles and review papers identified in the search. Vocabulary and syntax were adjusted across databases. There were no date or methodology restrictions.

2.2. Source of evidence screening and study selection

Article screening, including automatic duplicate removal, was completed using Covidence. Two authors independently screened each article for eligibility at both the title/abstract and full-text screening stages (VR and NS). Conflicts were resolved by discussions and consensus between the authors and in consultation with the senior authors. At all stages, screening decisions were made according to prespecified inclusion and exclusion criteria, as outlined below:

Population: Individuals diagnosed with schizophrenia spectrum disorders, including first-episode patients.

Intervention:

1. Neurological Abnormalities: neurological assessments (e.g., neuroimaging, neurophysiological tests), genetic and molecular studies.
2. Skeletal Muscle Impairments: studies assessing skeletal muscle function and morphology through various methods such as muscle biopsies, imaging techniques (MRI, CT scans), physiological tests (e.g., strength testing, electromyography), and assessments of muscle mass (e.g., fat-free mass).
3. Exercise Therapy: endurance training (i.e., structured programs involving large muscle groups in rhythmic activities over an extended period, such as running and cycling) or resistance training (i.e., exercises involving overcoming resistive loads through training modalities such as weight training).

Comparison: Comparisons between patients with schizophrenia and healthy controls, including age-matched and elderly controls to assess age-related changes, as well as comparisons within schizophrenia subgroups (i.e., medicated versus unmedicated, different antipsychotic treatments).

Outcomes:

1. Neurological Abnormalities: motor dysfunction outcomes, functional impairment related to motor dysfunction, neurological findings relating to motor dysfunction.
2. Skeletal Muscle Impairments: outcomes related to skeletal muscle function, including muscle strength (e.g., maximal force generation, rate of force development), muscle morphology (e.g., fibre type proportion, atrophy, pathological morphology such as split fibers, ring fibers, angulated fibers), fat-free mass (FFM) or body composition, or physical fitness parameters related to muscle function (e.g., balance, endurance).
3. Exercise Therapy: motor function improvements (i.e., increased motor cortex activation and grey matter volume, enhanced neuromuscular properties and preserved neuromuscular junctions, improved gait, balance, coordination and mobility, increased muscle strength and decreased psychotic symptoms, or improved functional test performance) or physical health improvements (i.e., increased aerobic capacity, improved body composition, including increased FFM).

Study design: All study designs that focus on quantitative or qualitative assessment of skeletal muscle in schizophrenia, such as cross-sectional, longitudinal, case-control, and experimental studies.

2.3. Data extraction/collection process

A standardized data extraction template was created to collect the following information from each included study: study title, authors, year of publication, study design, sample size, patient population characteristics, type of intervention, comparison group, and primary outcome/main study results.

2.4. Synthesis and presentation of results

Studies were summarized and presented according to their relevant section: (1) Studies describing neurological abnormalities related to motor function in schizophrenia, (2) studies describing skeletal muscle impairments in schizophrenia, and (3) potential therapeutic efficacy of endurance and resistance exercise in minimizing functional deficits in schizophrenia. Within each section, studies were further grouped according to common characteristics or themes. A narrative summary of each study is reported in its respective subsection, with overlap in other subsections if applicable. Where appropriate, tables were created to concisely summarize the characteristics of included studies and relevant findings.

3. Results

Three separate PRISMA (preferred reporting items for systematic review and meta-analyses) flow diagrams were created for each of the individual subsections (Figs. 1–3).

The results for each search will be reported in their respective sections.

3.1. Neurological abnormalities

Our search string resulted in 419 studies of which 23 studies met the inclusion criteria and examined neurological abnormalities and mechanisms underlying motor impairment in patients. Of these, 5 studies focused on frontal lobe/upper motor neuron abnormalities, while 18 studies examined neuromuscular and synaptic dysfunction in patients. The extracted information from all included studies is provided in *Supplementary Table 2*.

3.1.1. Frontal lobe abnormalities

The frontal lobe can be divided into several functional areas, including the motor cortex and the prefrontal cortex, which play critical roles in voluntary motor planning and execution (Levy and Wagner, 2011; Teka et al., 2017). Motor behaviour abnormalities have been reported in patients with schizophrenia, and abnormalities in the frontal lobe have been correlated with abnormalities in motor function. A study by Peralta et al. (2010) found that 66.5 % of drug-naive patients with schizophrenia spectrum disorders exhibited at least one motor sign, with 40.5 % displaying motor syndromes such as abnormal involuntary movements, hypokinesia, and catalepsy. This was further supported by the literature review conducted by Neves and Freitas (2015) and the study by Cuesta et al. (2014), which found neurological soft signs, psychomotor slowing, and spontaneous parkinsonism in antipsychotic-naive patients, suggesting that movement disorders are intrinsic to the pathophysiology of schizophrenia. The studies discussed a dysregulation of the cortical-basal ganglia-thalamo-cortical/cerebellar network connectivity as a possible mechanism.

Furthermore, a study by Chee et al. (2008) examined neurological soft signs and frontal executive function in patients with schizophrenia and their first-degree relatives and found significant differences in motor

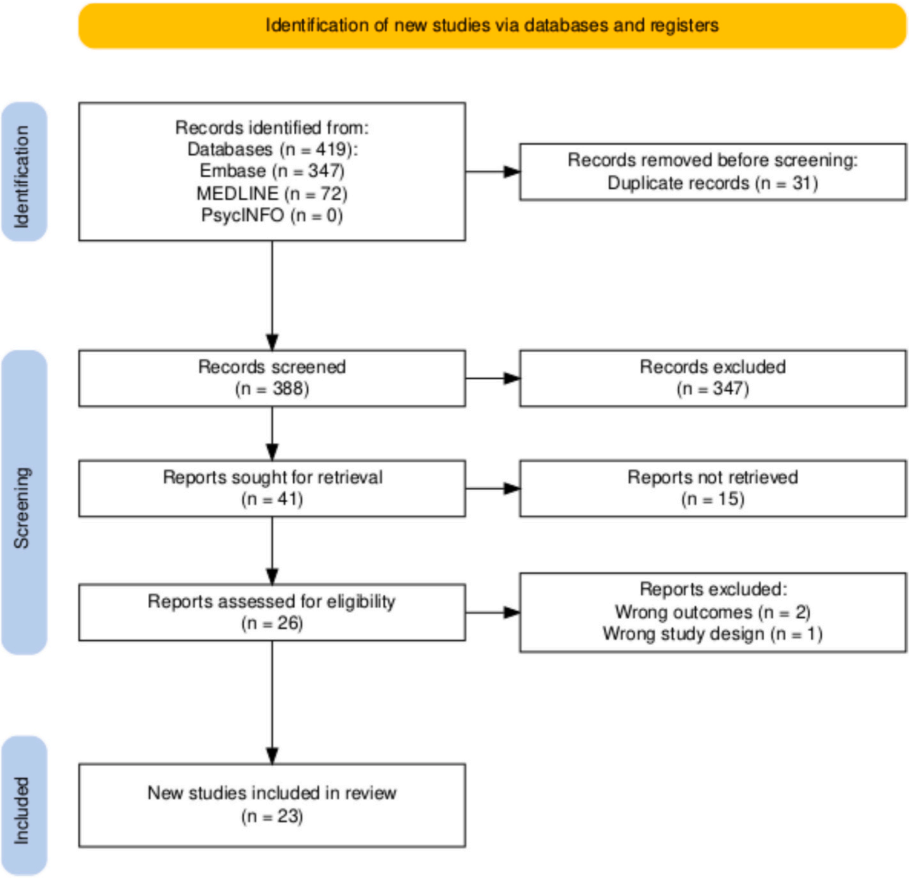

Fig. 1. PRISMA flowchart of the scoping review on neurological abnormalities.

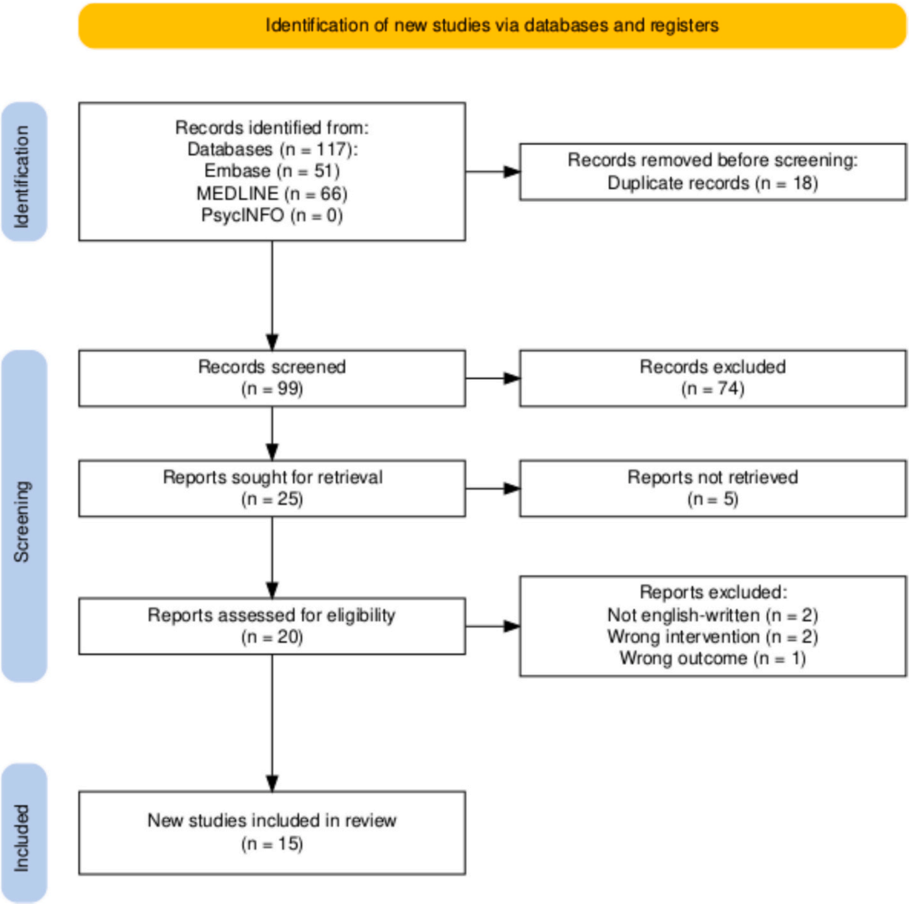

Fig. 2. PRISMA flowchart of the scoping review on skeletal muscle impairments.

coordination and sequencing of complex motor acts among patients, relatives, and controls. Patients with schizophrenia displayed the highest levels of motor coordination problems, followed by their first-degree relatives, which could potentially indicate a genetic or familial predisposition to these motor issues.

Readiness potential (RP) is a negative potential observed 1–2 s before the onset of motor movement according to electroencephalography (EEG), and it serves as a measure of motor planning and preparation (Wen et al., 2018). Interestingly, when examining the RP amplitude in patients with schizophrenia, it was significantly lower and delayed relative to healthy controls, suggesting delayed motor preparation and decision dysfunction (Dreher et al., 1999). Additionally, Wobrock et al. (2008) used transcranial magnetic stimulation (TMS) to measure cortical excitability and found significantly higher motor evoked potential (MEP) amplitudes in first-episode schizophrenia patients compared to healthy controls. This finding suggests reduced short-interval cortical inhibition (SICI), which is thought to be mediated by the neurotransmitter GABA, the primary inhibitory neurotransmitter in the brain. Thus, reduced SICI could indicate a GABAergic deficit, leading to reduced motor inhibitory control in patients. Furthermore, Yildiz et al. (2009) showed that cortical inhibition (CI) can be improved by antipsychotic treatment, highlighting a potential therapeutic mechanism for improving motor control in schizophrenia patients.

Impairment in motor preparation and motor planning was further corroborated when examining supplementary motor area (SMA) activation through functional magnetic resonance imaging while performing the neurological soft signs test “finger-to-thumb opposition.” Patients with schizophrenia showed decreased activation of the SMA (Schröder et al., 1997; Shibasaki et al., 1993). Additionally, when patients underwent a study examining their stop-signal reaction time (SSRT), those with higher levels of negative symptoms showed longer SSRT, indicating poor inhibitory action of motor control areas such as the SMA and premotor cortex (Bellgrove et al., 2005). A study by Ortuño et al. (2005) examining cerebral blood flow to the SMA during tasks engaging auditory attention and time estimation found significantly lower activation in the right SMA and right putamen in patients compared to controls.

Overall, individuals with schizophrenia exhibit a range of abnormalities in the motor cortex, including dysfunctional motor planning, motor execution, and motor inhibition. These impairments can manifest in various ways, such as difficulties in initiating or coordinating movements, slowed or uncoordinated motor responses, and challenges in suppressing involuntary movements. These motor abnormalities are not isolated; they likely contribute to the broader spectrum of functional impairments seen in patients, affecting their ability to perform daily activities.

3.1.2. *Neuromuscular and synaptic dysfunction*

Neuromuscular and synaptic dysfunctions are prevalent in patients with schizophrenia, suggesting both central and peripheral nervous system involvement. Studies have shown that these abnormalities are not solely attributable to medication effects. For example, Borg et al. (1987) and Crayton and Meltzer (1976) found impaired peripheral impulse propagation and significant structural alterations in motor endplates, including larger and more variable endplate areas, increased branching, and a lower synaptic index, in both treated and untreated schizophrenic patients. Similarly, Puri et al. (1999) found abnormal involuntary movements, particularly orofacial dyskinesia in antipsychotic naive patients. These findings suggest intrinsic neuromuscular abnormalities in schizophrenia.

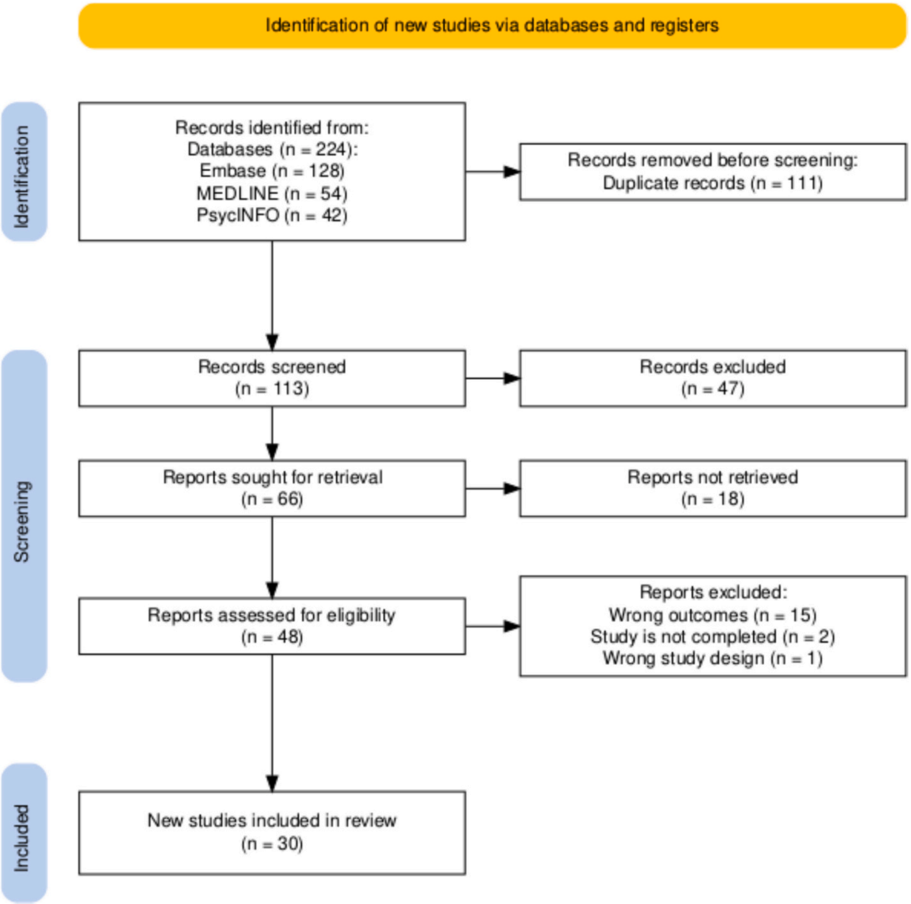

Fig. 3. PRISMA flowchart of the scoping review on exercise therapy.

Flyckt et al. (2000a, 2000b) conducted muscle biopsies and macro EMG assessments, revealing neuromuscular abnormalities in approximately 50 % of patients with schizophrenia. These included atrophic muscle fibers and pathological macro EMG recordings, suggesting disturbed cell membrane function in the neuromuscular system. Interestingly, Peters (1978) identified electrophysiological abnormalities in the motor units of schizophrenic patients and their first-degree relatives, suggesting a genetic predisposition to motor unit dysfunction in schizophrenia. Goode et al. (1977) also reported reduced motor unit estimates in chronic schizophrenic patients, indicating neuromuscular degeneration. Studies have consistently reported increased subterminal axonal branching and elevated serum creatine kinase (CK) activity, indicating muscle damage or stress (Meltzer, 1976; Meltzer and Crayton, 1974, 1975). Further supporting these findings, studies have observed extensive neuromuscular abnormalities in patients, including increased subterminal nerve branching and complex endplates thereby increasing fiber density (grouping due to reinnervation after denervation) (Crayton et al., 1977; Ross-Stanton et al., 1980). Increased subterminal axonal branching can lead to impaired motor control, resulting in tremors, muscle weakness, and poor coordination.

Studies have highlighted various aspects of functional asymmetry and its impact on motor functions in schizophrenia patients. Bennett (2009) discussed that approximately 30 % of synapses formed during childhood in the dorsolateral prefrontal cortex are lost during adolescence. However, in patients with schizophrenia, the synapse loss is about 60 %, which can significantly affect motor planning. This heightened synapse loss can lead to a range of motor impairments. Rains et al. (2012) highlighted sensory feedback dysfunction in patients with acute psychosis, noting increased activation in the left inferior parietal lobe (IPL) during motor tasks. This finding aligns with Gruzelier's (1999) study, which identified asymmetries in the Hoffman reflex, a neurological test indicative of sensory feedback dysfunction. The combined evidence suggests that these abnormalities contribute to reduced motoneuron excitability and slower motor responses, directly impacting motor coordination and control. Interestingly, Tan and Gürgen (1986) demonstrated that neuroleptic treatment can modulate spinal motor asymmetry, potentially improving motor neuron excitability. This finding suggests that medication can play a role in alleviating some of the motor deficits observed in schizophrenia patients by targeting underlying neurobiological dysfunctions.

Lastly, the study by Walker et al. (1994) used archival home movies of patients with schizophrenia to show that neuromotor dysfunction is present in infancy and may be a precursor to schizophrenia. Early developmental signs, including delayed motor milestones, poor coordination, and gait abnormalities, were all observed, suggesting that neuromotor impairment may be intrinsic to the pathophysiology of the illness.

Overall, existing literature suggests significant neuromuscular, synaptic, and sensory dysfunction in schizophrenia, implicating both central and peripheral nervous system involvement. These abnormalities were observed in both patients taking antipsychotics and those not taking them, highlighting the potential intrinsic neuromuscular issues rather than being solely medication-induced. Additionally, functional asymmetry and early motor dysfunction were observed. These findings highlight the need for further research to elucidate the extent to which these components contribute to the motor impairments seen in patients.

3.2. Skeletal muscles

Our search string resulted in 117 studies of which 15 studies met the inclusion criteria and examined skeletal muscle abnormalities and motor dysfunction in patients with schizophrenia. The extracted information from all included studies is provided in *Supplementary Table 3*.

Patients show subpar performance in several fitness parameters (e.g., strength, balance, and endurance) as outlined in the *Functional Impairment* section. There is a range of studies that showcase the significant muscle abnormalities and motor dysfunction in patients. Studies that examined muscle biopsies for acutely psychotic patients in which abnormalities such as architectural abnormalities and end-stage atrophic necrosis were correlated with elevated CK levels, suggesting an underlying myopathic process (Engel and Meltzer, 1970; Fischman et al., 1970). Similarly, various studies reported extensive morphologic abnormalities, including type I fibre atrophy, type II fibre hypertrophy, nemaline (rod) bodies, and sarcomere disruption in patients with schizophrenia (Meltzer et al., 1973; Flyckt et al., 2000a, 2000b; Ross-Stanton et al., 1980). The study by Ross-Stanton et al. (1980) also reported elevated serum CK activity, further corroborating ongoing muscle damage or stress in patients. The study by Bunkan et al. (2003) observed significant differences in muscle tone and rigidity between nonpatients and psychotic patients, with higher peripheral slackness and central hardness scores in the patient group. Interestingly, muscle strength has been reported to be lost at the rate of 8–10 % per decade after the age of 40 in healthy individuals, which is in contrast with patients with schizophrenia who have been shown to have a greater rate of loss at 20 % per decade after the age of 40 (Lindle et al., 1997). These studies reveal significant structural abnormalities in skeletal muscles, which may underlie the loss of strength observed in patients.

Elevation in serum CK levels has been reported in schizophrenia patients, indicating muscular damage and abnormality. CK is an enzyme found in skeletal muscles, and when muscle tissue is damaged, CK leaks into the bloodstream. Meltzer et al. (1996) reported marked elevations in serum CK activity associated with antipsychotic drug treatment in some patients, suggesting that these drugs might intermittently increase cell membrane permeability, especially in skeletal muscle. Furthermore, studies have found increased serum CK in a significant proportion of acute patients, indicating potential muscle damage during the acute phase of psychosis (Hatta et al., 1998; Butkus et al., 2022). This was also reflected in patients with chronic schizophrenia, who exhibited elevated levels of muscle enzymes such as lactate dehydrogenase and aspartate aminotransferase, as well as a reduction in monoamine oxidase, which may reflect underlying muscular stress and motor disturbances seen in these patients (Meltzer and Arora, 1980; Swartz and Breen, 1990). In the study by Hatta et al. (1998), patients were undergoing antipsychotic treatment within two weeks prior to admission, but none of them displayed neuroleptic malignant syndrome, suggesting that increased CK is likely not due to the influence of antipsychotic medication but rather other causes. Hermesh et al. (2001) and the case study by Butkus et al. (2022) observed elevated serum CK levels without myoglobinuria in acute psychotic patients, suggesting a non-traumatic pathophysiological mechanism for muscle damage.

Furthermore, Rapaport et al. (1997) found a strong correlation between increased serum-soluble interleukin-2 receptors (SIL-2Rs) and muscle force instability in schizophrenic patients, highlighting a relationship between immune activation and motor function disturbances. The study indicated that increased SIL-2R levels are correlated with muscle force instability, suggesting that immune activation may play a role in the motor dysfunction observed in schizophrenia.

Overall, these studies collectively indicate significant muscle abnormalities and motor dysfunction in patients with schizophrenia. These abnormalities include histochemical and morphological changes, increased CK levels, reduced muscle strength, and increased muscle rigidity. Antipsychotic medications may further exacerbate these issues. More research is needed to elucidate the underlying mechanisms.

3.3. *Exercise therapy*

Our search string resulted in 224 studies of which 30 studies met the inclusion criteria and examined aerobic, resistance training or both and its effect on motor impairment in patients. Of these 16 studies focused on aerobic exercise, 6 studies focused on resistance training and 8 examined the effects of combining aerobic and resistance training in patients. The extracted information from all included studies is provided in *Supplementary Table 4*.

3.3.1. *Exercise – endurance*

Endurance exercise is a structured program involving using large muscle groups for an extended period in rhythmic activities (Heath, 2005) such as running and cycling. As reported in the *Functional Impairment* section, impaired endurance capacity is a reported symptom of patients with schizophrenia. Studies examining endurance exercise as an intervention for these patients primarily focus on its benefits for aerobic capacity. The utility behind exercise training stems from the systematic stressing and rebuilding of the body, resulting in a positive adaptive response.

Brobakken et al. (2024) highlighted the importance of aerobic endurance in functional skills and performance. Their observational study found that aerobic endurance ($\dot{V}O_2$peak) was positively associated with the improvement of functional skills and physical functioning domains in patients with schizophrenia spectrum disorders. Similarly, Vancampfort et al. (2012) identified a significant positive correlation between functional exercise capacity (measured by the 6-min walk test) and global functioning in schizophrenia patients. Several studies have shown that exercise interventions, particularly aerobic and high-intensity interval training (HIIT), significantly improve muscle strength and activities of daily living (ADL) in patients with schizophrenia (Gallardo-Gómez et al., 2023; Leone et al., 2015). These studies underscore the importance of enhancing endurance capacity to alleviate the functional impairments observed in these patients.

Endurance training specifically has been explored in various studies. Keller-Varady et al. (2016) conducted a controlled interventional study comparing the effects of standardized aerobic endurance training on patients with schizophrenia and healthy controls. Both groups showed significant improvements in physical working capacity and maximal achieved power, although patients with schizophrenia exhibited less pronounced adaptations in energy metabolism, suggesting underlying physiological differences such as mitochondrial dysfunction. Similarly, Herbsleb et al. (2019) investigated continuous aerobic exercise in patients with multi-episode schizophrenia. This study found that patients had significantly higher baseline heart rates compared to healthy controls, indicating a need for tailored aerobic interventions to address cardiovascular abnormalities. Additionally, Malchow et al. (2015) took a comprehensive approach by combining endurance training with cognitive remediation. Their clinical trial demonstrated that this combination significantly improved global functioning, social activities, and household functioning, indicating that integrating physical and cognitive exercises can enhance overall functionality in schizophrenia patients.

In terms of neurobiological benefits, a literature review conducted by Maurus et al. (2019) emphasized the positive effects of aerobic exercise, noting improvements in negative and general symptoms, cognition, global functioning, and quality of life in schizophrenia patients. Structural MRI studies showed that aerobic exercise led to increases in hippocampal volume and cortical regions, supporting its role in enhancing brain health. This is consistent with the study by Falkai et al. (2023), which found that endurance training improved brain structures such as hippocampal volume and cortical thickness. Additionally, studies have demonstrated that endurance training increased grey matter volumes in the left temporal lobe and other cortical regions in schizophrenia patients, suggesting improvements in cognitive functions (Malchow, 2017; Malchow et al., 2016, 2018). These studies also highlighted the importance of continuous training, as many of the improvements were not maintained after a 3-month training-free period. Interestingly, a study by Papiol et al. (2019) found that aerobic exercise led to changes in the hippocampus, with the extent of these changes influenced by genetic factors. People with a higher genetic risk for schizophrenia saw less improvement in their hippocampus. Moreover, a qualitative critical review by Saviola et al. (2023) reviewed 21 studies on physical exercise in psychosis and found that while results varied, there were positive associations between physical activity and changes in brain structure, including increased cortical thickness and improved white matter integrity. These changes in brain structure can improve neural connectivity, learning capability, and spatial navigation, aiding in the improvement of patients' functional impairments. Furthermore, the significant improvement in endurance capacity highlights the potential for physical training to enhance overall functioning and quality of life, emphasizing the need for continuous intervention to sustain these benefits. This also underscores the importance of using activities that are feasible and enjoyable for patients.

Schmitt et al. (2018) reviewed the effects of aerobic exercise on metabolic syndrome, cardiorespiratory fitness, and overall symptoms in schizophrenia. HIIT and continuous aerobic training were particularly effective in improving $\dot{V}O_2$ max, reducing resting heart rates, and enhancing metabolic health. This finding was also consistent with the multicenter randomized wait-list controlled trial by García-Garcés et al. (2021), which found significant reductions in BMI and waist circumference with aerobic training.

In summary, the collective evidence from these studies highlights the significant impact of aerobic exercise on improving exercise/endurance capacity, which has been correlated with improved ADL. Furthermore, some studies have shown that aerobic exercise improves brain structure by increasing hippocampal volume and cortical thickness, which could play a role in alleviating some of the motor impairments seen in schizophrenia patients. This therapeutic intervention not only improves overall functioning and quality of life but is also very feasible for most patients, reducing barriers to accessibility and making it a vital component of comprehensive care for individuals with schizophrenia.

3.3.2. *Exercise – resistance training*

Resistance training refers to exercises that involve overcoming resistive loads during training modalities such as weight training (Faigenbaum et al., 2009). Several studies have collectively demonstrated that resistance training significantly enhances functional outcomes in patients with schizophrenia. A cross-sectional study by Brobakken et al. (2024) found that skeletal muscle strength (1RM) positively correlates with improved functional skills and physical functioning domains in patients with schizophrenia spectrum disorders. This highlights the potential of resistance training in enhancing daily functioning and alleviating motor impairments.

Similarly, a systematic review by Keller-Varady et al. (2018) evaluated various strength training interventions, including isolated strength training. The review highlighted that isolated strength training improved walking efficiency and muscle strength, although results for psychopathology and quality of life were mixed. Furthermore, in a pilot study, Heggelund et al. (2012) demonstrated that maximal strength training could significantly improve both maximal strength (1RM) and net mechanical efficiency of walking in patients with schizophrenia, reinforcing the importance of strength training in this population. Improving net mechanical efficiency is crucial as it enhances energy utilization during physical activities, reducing fatigue and improving overall functional mobility. Moreover, a clinical trial by Maurus et al. (2020) further supported these findings, showing significant improvements in general functioning (GAF scores) following a 12-week resistance training program.

A randomized controlled trial by Nygård et al. (2023) integrated strength training into the long-term care of patients with schizophrenia, resulting in substantial gains in leg press strength and power, as well as sit-to-stand performance. These findings were corroborated by another study by Nygård et al. (2021), which found that maximal strength training significantly restored muscle force-generating capacity in schizophrenia patients, bringing it to levels comparable to healthy references. Restoring muscle strength and functional capacity is essential for mitigating the physical impairments often associated with schizophrenia, thereby improving overall quality of life.

The effectiveness of resistance training was also evident in a blind, randomized controlled trial by Silva et al. (2015), where a 20-week resistance exercise program led to notable improvements in both positive and negative symptoms, physical role limitations, and muscle strength. The improvements were significant enough to suggest that resistance training can be a viable therapeutic option for enhancing physical and functional health in schizophrenia patients.

Overall, these studies collectively highlight the significant role of resistance training in improving physical and functional outcomes in patients with schizophrenia. Incorporating structured resistance training into the treatment regimen can enhance muscle strength, net mechanical efficiency, functional performance, and overall quality of life, offering a low-cost and effective intervention for managing schizophrenia.

3.3.3. *Exercise – combined aerobic and resistance training*

The combined approach of aerobic and resistance training has shown significant promise in improving various health outcomes for individuals with schizophrenia. This holistic method addresses not only physical fitness but also cognitive and functional health, providing a comprehensive benefit for this population.

In terms of physical health and fitness, studies have found that combined aerobic and resistance training led to significant improvements in physical strength, including leg, grip strength, flexibility etc. (Fogarty et al., 2004; Martin et al., 2017; Maurus et al., 2022). These findings are further supported by Kim et al. (2014), who reported that a combined exercise program consisting of resistance exercises using elastic bands and moderate walking significantly improved body composition, cardiovascular fitness, balance, and serum brain-derived neurotrophic factor (BDNF) levels. The increase in BDNF suggests enhanced neuroplasticity and overall brain health. Lavratti et al. (2017) also highlighted the benefits of concurrent aerobic and resistance training, showing significant reductions in body mass, BMI, and abdominal circumference. Additionally, they observed reductions in histone H4 acetylation levels and inflammatory cytokines, indicating a potential mechanism through which exercise may reduce inflammation and improve physical health.

Bredin et al. (2022) conducted a meta-analysis comparing various exercise modalities and found that combined aerobic and resistance training led to significant improvements in physical health metrics, including $\dot{V}O_2$ max, body weight, and negative symptoms measured by the PANSS scores. This underscores the comprehensive benefits of combined exercise interventions on psychiatric symptoms and overall health. Similarly, a systematic review and meta-analysis by Korman et al. (2023) found moderate improvements in global functioning and daily living skills. Furthermore, the study by Strassnig et al. (2015) examined the utility of high-velocity circuit resistance training as a combined modality, in which participants showed significant improvements in their strength, power, and cognitive performance after an 8-week intervention, while also showing a reduction in negative symptoms.

In terms of cognitive and brain health, Sommer and Kahn (2015) conducted a literature review that highlighted the potential of exercise, particularly concurrent aerobic and resistance training, to improve brain structure and function. The review noted increased integrity of white matter connections and improved fibre integrity in the motor circuit among patients who engaged in regular exercise, compared to those who did not. This suggests that exercise can mitigate some of the cognitive and neurological deterioration associated with schizophrenia. However, the review also discussed the challenges of implementing exercise interventions in this population, such as low motivation, side effects from medication, and lack of energy.

These studies highlight the utility of combined aerobic and resistance training in improving physical, cognitive, and functional outcomes in patients with schizophrenia. Incorporating structured exercise programs that integrate both aerobic and resistance training can enhance muscle strength, cardiovascular fitness, cognitive function, and overall quality of life. This holistic approach offers a low-cost method to address some of the functional impairments seen in patients. It is also important to emphasize the inclusion of exercise programs that are feasible for patients to see sustained benefits.

4. Conclusions and limitations

Patients with schizophrenia suffer from functional impairments (i.e., physical limitations due to disease symptoms) that affect their ability to carry out daily tasks (Fig. 4). These impairments may stem from underlying issues with balance, endurance, strength, and power. Abnormalities have been noted in the motor cortex, which is involved in the planning, execution, and inhibition of motor movements. These abnormalities translate to greater exertional requirements when performing motor tasks. The neural pathological features that contribute to the development of functional impairment can produce downstream effects on the skeletal muscle and lower motor neurons. Patients show reduced motor neurons and excessive axonal sprouting, contributing to weakness and reduced motor-unit excitability. Additionally, skeletal muscles in patients show decreased maximal force-generating capacity and increased muscle atrophy, which is consistent with evidence highlighting lower motor neuron pathology.

Exercise can function as a therapeutic intervention to alleviate patients' functional impairments (Fig. 4). Resistance training has been correlated with increased muscular strength, increased FFM, and improved walking efficiency. Increased muscular strength can counteract the weakness and muscular atrophy experienced by patients, while increased FFM and improved walking efficiency can alleviate various functional impairments that stem from physical inactivity. Aerobic exercise has been shown to improve exercise/endurance capacity, which has been correlated with improved ADL. Endurance exercise has also been shown to improve hippocampal volume and cortical thickness, which can play a role in alleviating motor impairments. Combining aerobic and resistance modalities has shown great benefits, as it combines many of the benefits seen in each modality alone. Given this, it is also important to consider the feasibility of the exercise protocol, as the benefits of these therapies are not maintained if patients discontinue the activity. There are few studies that investigate the neuromuscular mechanisms associated with the functional impairments experienced by patients, and many of these studies have various limitations. One of the limitations is the lack of control for antipsychotic usage and physical activity levels in many studies. While most antipsychotics function by reducing dopamine, they each have unique side effects and pharmacodynamics that can impact the results of the studies.

5. Future consideration

This scoping review has uncovered evidence of mechanisms contributing to the increased functional impairments prevalent in patients. Due to the limited research examining the neuromuscular properties of functional impairments in patients, it is vital to examine further the mechanisms that were elucidated in this review. Furthermore, future research should aim to uncover to what degree these functional impairments are attributed to inactivity and schizophrenia pathophysiology. Finally, further research is needed to determine the optimal combination, type, duration, and intensity of exercise to maximize the

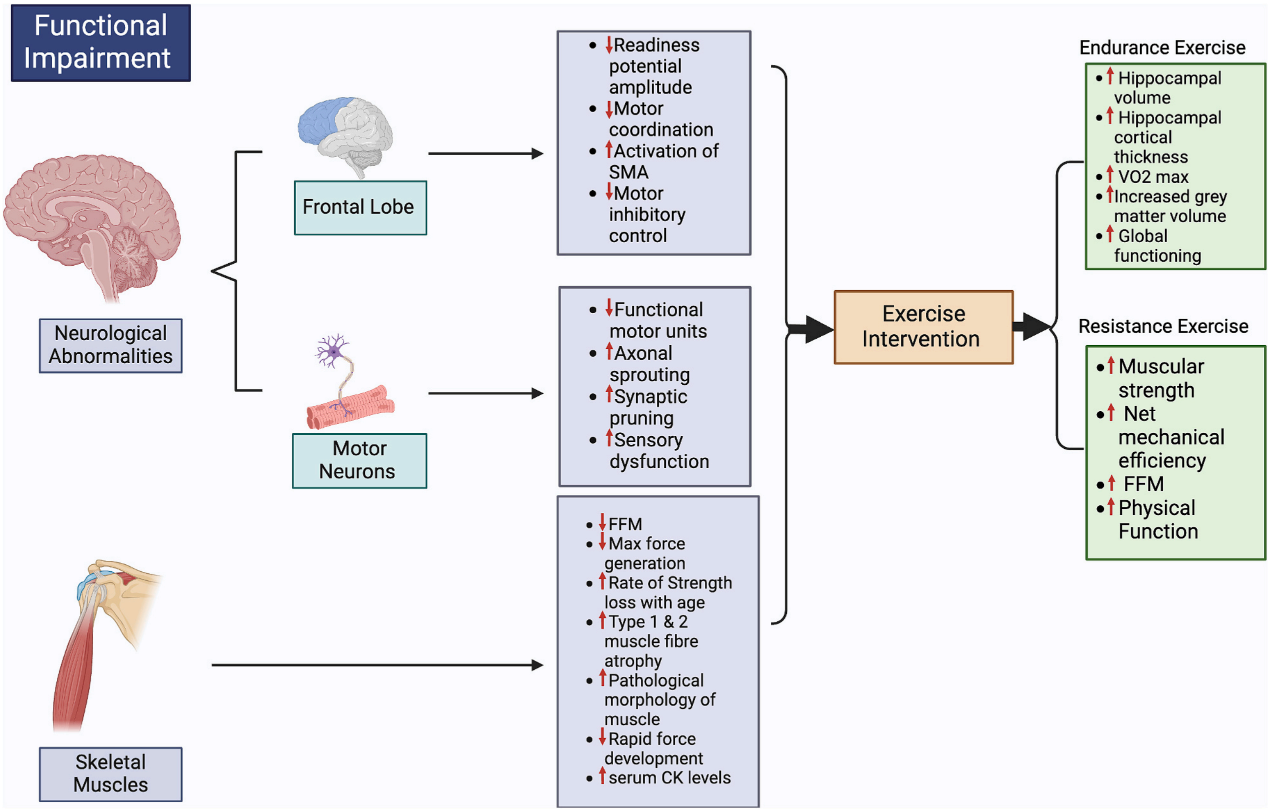

Fig. 4. Summary of the mechanisms that underlie the functional impairments afflicting patients with schizophrenia. The mechanisms are broadly categorized as abnormalities in neurology and skeletal muscle. Neurological abnormalities have shown specific pathologies from the frontal lobe and motor neurons. Many of the pathological mechanisms outlined have the potential to be alleviated through exercise intervention (aerobic and resistance training).

exercise-induced adaptations in patients in schizophrenia to counteract the functional impairments.

Authorship contribution statement

V.R. and A.J.C. conceptualized this review, V.R., N.S., and A.J.C. drafted this manuscript, V.R., N.S., S.M.A, and A.J.C., revised versions of this manuscript.

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CRediT authorship contribution statement

Vijai Raj: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Nicolette Stogios:** Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Sri Mahavir Agarwal:** Formal analysis, Investigation, Methodology, Resources, Supervision, Validation, Writing – review & editing. **Arthur J. Cheng:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing.

Declaration of generative AI and AI-assisted technologies in the writing process

No AI or AI-assisted technologies were used in the writing of this manuscript.

Declaration of competing interest

All authors declare no conflict of interest.

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Appendix A. Supplementary data

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